Australian Government
Department of Health

The Australian Immunisation Handbook

10th Edition 2013 (updated January 2014)

IMMUNISATION

CONTACT DETAILS FOR AUSTRALIAN, STATE AND TERRITORY GOVERNMENT HEALTH AUTHORITIES

Australian Government health authorities	
Australian Government Department of Health	**02 6289 1555** **Freecall: 1800 671 811** **www.immunise.health.gov.au**
State and territory government health authorities	
Australian Capital Territory	**02 6205 2300** **Immunisation Enquiry Line**
New South Wales	**1300 066 055** (to connect to your local Public Health Unit)
Northern Territory	**08 8922 8044** **Centre for Disease Control**
Queensland	**13 HEALTH (13 4325 84)** **Contact your local Public Health Unit, details at www.health.qld.gov.au/cdcg/contacts.asp**
South Australia	**1300 232 272 (8.30 am to 5.00 pm)** **Email: CDCB@health.sa.gov.au** **www.sahealth.sa.gov.au**
Tasmania	**03 6222 7666 or 1800 671 738**
Victoria	**1300 882 008** **Email: immunisation@health.vic.gov.au** **www.health.vic.gov.au/immunisation**
Western Australia	**08 9388 4868** **08 9328 0553 (after hours Infectious Diseases Emergency)** **Email: cdc@health.wa.gov.au**

For changes introduced in the 10th edition of the *Handbook*, see 1.4 *What's new*

INFORMATION SHEET – ADVERSE EVENTS FOLLOWING IMMUNISATION

Side effects following immunisation for vaccines used in the National Immunisation Program (NIP) schedule

Common adverse events following immunisation are usually mild and temporary (occurring in the first few days after vaccination, unless otherwise stated). Specific treatment is not usually required (see below).

If the adverse event following immunisation is unexpected, persistent and/or severe, or if you are worried about your or your child's condition, see your doctor or immunisation nurse as soon as possible, or go directly to a hospital. Adverse events that occur following immunisation may be reported to the Therapeutic Goods Administration (TGA) (www.tga.gov.au) or to the Adverse Medicines Events line on 1300 134 237, or discuss with your immunisation provider as to how reports are submitted in your state or territory.

Diphtheria-tetanus-pertussis (acellular) DTPa-containing vaccines and dTpa (reduced antigen) vaccines	*Haemophilus influenzae* type b vaccine (Hib)	Hepatitis A vaccine (HepA)	Hepatitis B vaccine (HepB)
• Localised pain, redness and swelling at injection site • Occasionally, an injection-site nodule; may last many weeks; no treatment needed • Low-grade temperature (fever) In children, the following may also occur: • Irritable, crying, unsettled and generally unhappy • Drowsiness or tiredness	• Localised pain, redness and swelling at injection site • Occasionally, an injection-site nodule; may last many weeks; no treatment needed • Low-grade temperature (fever)	• Localised pain, redness and swelling at injection site • Low-grade temperature (fever)	• Localised pain, redness and swelling at injection site • Occasionally, an injection-site nodule; may last many weeks; no treatment needed • Low-grade temperature (fever)
Human papillomavirus vaccine (HPV)	**Influenza vaccine**	**Measles-mumps-rubella vaccine (MMR, MMRV – see also varicella)**	**Meningococcal C conjugate vaccine (MenCCV)**
• Localised pain, redness and swelling at injection site • Low-grade temperature (fever) • Mild headache • Mild nausea	• Drowsiness or tiredness • Muscle aches • Localised pain, redness and swelling at injection site • Occasionally, an injection-site nodule; may last many weeks; no treatment needed • Low-grade temperature (fever)	• Occasionally, an injection-site nodule; may last many weeks; no treatment needed Seen 7–10 days after vaccination: • Temperature (fever, can be >39.4˚C), lasting 2–3 days, faint red rash (not infectious), head cold and/or runny nose, cough and/or puffy eyes • Drowsiness or tiredness • Swelling of salivary glands	• Irritable, crying, unsettled and generally unhappy • Loss of appetite • Headache (usually observed in adolescents/adults) • Localised pain, redness and swelling at injection site • Occasionally, an injection-site nodule; may last many weeks; no treatment needed • Low-grade temperature (fever)
Pneumococcal vaccines (conjugate 13vPCV and polysaccharide 23vPPV)	**Inactivated poliomyelitis vaccine (IPV) and IPV-containing vaccines**	**Rotavirus vaccine**	**Varicella vaccine (VV)**
• Localised pain, redness and swelling at injection site • Occasionally, an injection-site nodule; may last many weeks; no treatment needed • Low-grade temperature (fever)	• Muscle aches • Localised pain, redness and swelling at injection site • Occasionally, an injection-site nodule; may last many weeks; no treatment needed • Low-grade temperature (fever)	• Vomiting and diarrhoea can occur up to 7 days following vaccination	• Localised pain, redness and swelling at injection site • Occasionally, an injection-site nodule; may last many weeks; no treatment needed • Temperature (fever, can be >39˚C) Seen 5–26 days after vaccination: • Pustular rash (2–5 lesions), usually at injection site, occasionally elsewhere

Key to table

DTPa	diphtheria-tetanus-pertussis acellular (infant/child formulation)	**MenCCV**	meningococcal C conjugate vaccine
dTpa	diphtheria-tetanus-pertussis acellular (reduced antigen content formulation)	**MMR**	measles-mumps-rubella vaccine
HepA	hepatitis A vaccine	**MMRV**	measles-mumps-rubella-varicella vaccine
HepB	hepatitis B vaccine	**13vPCV**	pneumococcal conjugate vaccine (13 serotypes)
Hib	*Haemophilus influenzae* type b vaccine	**23vPPV**	pneumococcal polysaccharide vaccine (23 serotypes)
HPV	human papillomavirus vaccine	**Rotavirus**	rotavirus vaccine
Influenza	influenza or flu vaccine	**VV**	varicella vaccine
IPV	inactivated poliomyelitis vaccine		

How to manage injection site discomfort	Managing fever after immunisation	Concerns
Many vaccine injections may result in soreness, redness, itching, swelling or burning at the injection site for 1 to 2 days. Paracetamol might be required to ease the discomfort. Sometimes a small, hard lump (nodule) at the injection site may persist for some weeks or months. This should not be of concern and requires no treatment.	Give extra fluids to drink. Do not overdress the baby if hot. Although routine use of paracetamol after vaccination is not recommended, if fever is present, paracetamol can be given. The dose of paracetamol for a child up to 12 years of age is 15 mg/kg/dose, every 4 to 6 hours, up to four times a day. Adults and children aged ≥12 years can receive 500 to 1000 mg every 4 to 6 hours. Paracetamol should not be given for more than 48 hours without seeking medical advice.	If you are worried about yourself or your child's condition after a vaccination, see your doctor or immunisation nurse as soon as possible, or go directly to a hospital. It is also important to seek medical advice if you or your child are unwell, as this may be due to other illness rather than because of the vaccination.

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Department of Health

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10th Edition 2013

(updated January 2014)

IMMUNISATION

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These guidelines were approved by the Chief Executive Officer (CEO) of the National Health and Medical Research Council (NHMRC) on 25/01/2013 (with minor amendments approved by the CEO on 19/12/2013), under Section 14A of the *National Health and Medical Research Council Act 1992*. In approving these guidelines the NHMRC considers that they meet the NHMRC standard for clinical practice guidelines. This approval is valid for a period of five years.

NHMRC is satisfied that they are based on the systematic identification and synthesis of the best available scientific evidence and make clear recommendations for health professionals practising in an Australian health care setting. The NHMRC expects that all guidelines will be reviewed no less than once every five years.

This publication reflects the views of the authors and not necessarily the views of the Australian Government.

THE AUSTRALIAN IMMUNISATION HANDBOOK 10TH EDITION (UPDATED JANUARY 2014)

WHAT'S NEW IN THE 2014 UPDATE

The 2014 update of the 10th edition of *The Australian Immunisation Handbook* contains minor amendments to the version published in February 2013. There has been no change to any vaccine recommendations. Page numbering, sectioning and indexing remain the same.

Changes made between the 9th and 10th editions of *The Australian Immunisation Handbook* are listed in a separate section in this *Handbook* (see 1.4 *What's new*).

Changes in this update

A summary of the changes made in this update is provided below.

A more detailed description of these changes is available on the Immunise Australia website (www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook10-home).

Summary of changes

- Updated details of where to find information on smallpox (page 7)
- Updated link to the new (2nd) edition of the *National vaccine storage guidelines: Strive for 5* (page 25)
- Correction of the age for which children only need 1 dose of Hib vaccine as catch-up (pages 42 and 195)
- Correction of the minimum interval between doses of MenCCV in Table 2.1.5 (page 47)
- Correction of the minimum acceptable age for the 1st dose of DTPa vaccine in Table 2.1.5 footnote (†) (page 48)
- Correction and new format of Table 2.1.8 to more clearly present catch-up recommendations for Hib vaccination for children <5 years of age (pages 54–55)
- Clarification of the text outlining how to use palm placement to identify the ventrogluteal injection site in conjunction with Figure 2.2.7 (page 81)
- Updated value for the estimated excess number of intussusception cases attributable to rotavirus vaccination(pages 93 and 382)
- Correction of the INR cut-off for deferral of intramuscular vaccination (page 168)
- Clarification on the exposures that increase the risk of hepatitis B among certain occupations(pages 170, 223 and 225)

- Updated upper age limit for which refugees may have been offered MMR vaccine as part of a pre-departure health check (page 174)
- Clarification of the recommended timing of the 3rd dose of hepatitis B vaccine (not including birth dose) in infants born to mothers who are HBsAg-positive in Table 4.5.3 (page 229)
- Clarification on the acceptable minimum age for the 1st dose of MMR vaccine (page 272), to be consistent with footnote in Table 2.1.5
- Updated age range for which 13vPCV (Prevenar 13) is registered in children (pages 323 and 336)
- Corrections of minor editorial issues, including grammatical, typographical and formatting issues

Any future updates of the 10th edition of *The Australian Immunisation Handbook* will be made online and notified through immunisation provider networks. Online updates can be accessed via the Immunise Australia website: www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook10-home

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PART 1 INTRODUCTION TO *THE AUSTRALIAN IMMUNISATION HANDBOOK*

1.1 BACKGROUND

For more than 200 years, since Edward Jenner first demonstrated that vaccination offered protection against smallpox, the use of vaccines has continued to reduce the burden of many infectious diseases. Vaccination has been demonstrated to be one of the most effective and cost-effective public health interventions. Worldwide, it has been estimated that immunisation programs prevent approximately 2.5 million deaths each year.[1] The global eradication of smallpox in 1997, near elimination of poliomyelitis and global reduction in other vaccine-preventable diseases, are model examples of disease control through immunisation.

Vaccination not only protects individuals, but also protects others in the community by increasing the overall level of immunity in the population and thus minimising the spread of infection. This concept is known as 'herd immunity'. It is vital that healthcare professionals take every available opportunity to vaccinate children and adults. Australia has one of the most comprehensive publicly funded immunisation programs in the world. As a result of successful vaccination programs in Australia, many diseases, for example, tetanus, diphtheria, *Haemophilus influenzae* type b and poliomyelitis, do not occur now or are extremely rare in Australia.[2]

The purpose of *The Australian Immunisation Handbook* is to provide clinical guidelines for health professionals on the safest and most effective use of vaccines in their practice. These recommendations are developed by the Australian Technical Advisory Group on Immunisation (ATAGI) and were considered for approval by the National Health and Medical Research Council (NHMRC) (under section 14A of the *NHMRC Act 1992*).

The *Handbook* provides guidance based on the best scientific evidence available at the time of publication from published and unpublished literature. Further details regarding the *Handbook* revision procedures are described below in 1.2 *Development of the 10th edition of the Handbook*. The reference lists for all chapters are included in the electronic version of the *Handbook*, which is available via the Immunise Australia website (www.immunise.health.gov.au).

The information contained within this *Handbook* was correct as at October 2012. However, the content of the *Handbook* is reviewed regularly. The 10th edition of *The Australian Immunisation Handbook* will remain current unless amended electronically via the Immunise Australia website or until the 11th edition of the *Handbook* is published.

Information is provided in the *Handbook* for all vaccines that are available in Australia at or near the time of publication. These include many vaccines that are funded under the National Immunisation Program (NIP). A copy of the current NIP schedule is provided with the hard copy of the *Handbook*. However, the NIP schedule may also be updated regularly; immunisation service providers should consult the Immunise Australia website (www.immunise.health.gov.au) for changes. A number of vaccines included in this *Handbook* are not part of the routine immunisation schedule; these vaccines may be given to, for example, persons travelling overseas, persons with a medical condition placing them at increased risk of contracting a vaccine-preventable disease, or those at occupational risk of disease.

Electronic updates to the 10th edition of
The Australian Immunisation Handbook will be available at:
www.immunise.health.gov.au

References

A full reference list is available on the electronic *Handbook* or website www.immunise.health.gov.au

1.2 DEVELOPMENT OF THE 10TH EDITION OF THE *HANDBOOK*

The 10th edition of the *Handbook* has been developed by the Australian Technical Advisory Group on Immunisation (ATAGI), which provides advice to the Federal Minister for Health on the Immunise Australia Program and other vaccine-related issues. In addition to technical experts from many fields, the ATAGI's membership includes a consumer representative and general practitioners. Staff of the National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases (NCIRS) provided the technical support to the ATAGI to develop the *Handbook*.

It is important to note that recommendations contained within the *Handbook* do not formally address the cost-effectiveness of different vaccines or different vaccine schedules. Since January 2006, the cost-effectiveness of vaccines is assessed by the Pharmaceutical Benefits Advisory Committee (PBAC), which advises government on the funding of vaccines under the National Immunisation Program and/or Pharmaceutical Benefits Scheme (PBS). Most, but not all, of the recommendations made within the *Handbook* will be funded under the NIP, PBS or via other means, such as through special schemes and state- or territory-based programs.

1.2.1 Process of developing *Handbook* recommendations

The *Handbook* is designed as a general guide to inform clinicians on the safest and most effective vaccination strategies, using the highest quality evidence available. In the absence of high-quality evidence, such as well-conducted randomised controlled trials and meta-analyses, the ATAGI based its recommendations on less rigorous studies, such as uncontrolled clinical trials, case-series and/or other observational studies. Where clinical guidelines were available on specific topics, these were also consulted to help frame recommendations, if relevant, in the Australian setting. Further details on literature search strategies utilised for the production of this edition can be found in Appendix 2. The ATAGI also consulted immunisation handbooks produced by comparable countries. When published sources were inadequate, recommendations were based on expert opinion. However, limitations and challenges to developing recommendations continue to exist when there are unaddressed scientific questions, complex medical practice issues and continuous new information, as well as differences in expert opinion. Despite these limitations, the ATAGI has sought to provide clear and relevant recommendations wherever possible.

The 1st edition of *The Australian Immunisation Handbook* was published in 1975. Due to its longevity, scope and complexity, the *Handbook* does differ from other NHMRC guidelines. As such, recommendations contained in the *Handbook* do not contain formal levels or grades of evidence or evidence tables. The grades of evidence assigned to recommendations for the three newly vaccine-preventable diseases (human papillomavirus [HPV], rotavirus and herpes zoster) that were included in the 9th edition *Handbook* (and its electronic amendments) have now

been removed and replaced with an evidence statement for consistency with other chapters in the 10th edition of the *Handbook*. The ATAGI has developed new recommendations for the *Handbook* after considering clinical questions, reviewing available evidence, as described above, and through extensive consultation with other experts (described below). Evidence statements for recommendations, with cross reference to other relevant sections of the *Handbook*, have been included wherever possible.

1.2.2 Consultation and input into the draft 10th edition *Handbook*

Prior to completion of the draft 10th edition *Handbook*, the ATAGI sought expert review of individual chapters by leading Australian experts. These reviewers, who are acknowledged in the front of this *Handbook*, provided input to further refine each chapter. The ATAGI also, where relevant, consulted members of each of its current disease-based Working Parties. Other peak advisory groups, in particular the National Immunisation Committee, were also consulted and provided valuable input into the development of this revised edition. The draft 10th edition of the *Handbook* was available for public consultation over a 4-week period during July–August 2012. The ATAGI reviewed all public comments received and, where necessary, incorporated these as changes to the *Handbook*. The NHMRC was also consulted throughout the development of the 10th edition of the *Handbook*, prior to the *Handbook* being proposed for submission to the NHMRC for consideration of approval (under section 14A of the *NHMRC Act 1992*).

1.2.3 Implementation of recommendations in the 10th edition *Handbook*

The 10th edition of the *Handbook* is disseminated directly to all registered medical practitioners in Australia. Additional hard copies are distributed to other immunisation service providers via their state or territory health authority. An electronic version of the *Handbook* is freely accessible on the Immunise Australia Program website (www.immunise.health.gov.au). Implementation of the recommendations as stated in the *Handbook* is undertaken by immunisation service providers in conjunction with their state or territory health authority and the Immunise Australia Program of the Australian Government Department of Health.

1.3 HOW TO USE THE 10TH EDITION *HANDBOOK*

The following information provides an overview of how information is presented in this 10th edition of *The Australian Immunisation Handbook*, to guide the reader in how to best use this resource.

The *Handbook* is divided into five major parts. Part 1 contains information on the development process for the *Handbook*, a summary of changes from the 9th edition *Handbook*, and an overview of the general principles of immunisation, including both active and passive immunisation, vaccine efficacy and vaccine safety. Part 2 of the *Handbook* is divided into three chapters, which describe the processes and procedures involved around a vaccination encounter: pre-vaccination requirements; a detailed discussion of the administration of vaccines; and information on post-vaccination considerations. In Part 3 of the *Handbook*, there are three chapters, each dedicated to vaccinations for different special risk groups, including Aboriginal and Torres Strait Islander people, international travellers, and other special risk categories (e.g. immunocompromised persons, pregnant women and others).

Part 4 of the *Handbook* contains 24 chapters, each dealing with an individual disease for which a vaccine, or vaccines, are currently available in Australia. These chapters all follow the same format and are divided into various sections describing:

- the biology, clinical features and epidemiology of the disease
- information on vaccines, with those available, or soon to be available, in Australia highlighted in a shaded box (for more information see also the Therapeutic Goods Administration, www.tga.gov.au, for the latest vaccine product information document provided by the manufacturer and 1.5.3 *Active immunisation*)
- recommendations for vaccine use
- use in pregnancy and breastfeeding
- contraindications, precautions and advice on adverse events following immunisation specific to the vaccine(s) (for more information see 1.5.5 *Vaccine safety and adverse events following immunisation*)
- information on the public health management of each disease; this is only given in detail where there are specific additional recommendations for vaccine use in the context of disease control and/or post-exposure prophylaxis
- variations from product information.

Variations from product information

In some instances, the ATAGI recommendations in the *Handbook* may differ from information provided by the manufacturer in the vaccine product information document (PI); these differences may be recommendations that are in addition to or instead of those listed in the PI. Where indicated, variations from the PI are detailed in each relevant vaccine chapter under the heading 'Variations from product information'. ***Where a variation exists, the ATAGI recommendation should be considered best practice.***

The reader is encouraged to seek additional information on communicable disease surveillance, prevention and control, including published guidelines, from the Communicable Diseases Network Australia (CDNA) via the Australian Government CDNA website (www.health.gov.au/cdnasongs).

Part 5 of the *Handbook* pertains to passive immunisation using immunoglobulin preparations and provides an overview of the available products and their intended use.

There are a number of appendices, including contact details for state and territory health departments (Appendix 1); the literature search strategies used for the 10th edition of the *Handbook* (Appendix 2); components used in the vaccines available via the National Immunisation Program (Appendix 3); some commonly asked questions (Appendix 4); a glossary of terms used in the *Handbook* (Appendix 5); abbreviations used in the *Handbook* (Appendix 6); and a list of dates when various vaccines became available in Australia (Appendix 7).

1.4 WHAT'S NEW

All chapters have been updated and revised, where necessary, from the 9th edition. The 10th edition introduces new vaccines, changes to the schedules and recommendations, and changes to the presentation of the *Handbook*.

1.4.1 New chapters and chapters that no longer appear in the *Handbook*

- Layout of the *Handbook* differs from the previous edition. The *Handbook* is now in 5 parts: Part 1 *Introduction to The Australian Immunisation Handbook*; Part 2 *Vaccination procedures*; Part 3 *Vaccination for special risk groups*; Part 4 *Vaccine-preventable diseases*; and Part 5 *Passive immunisation*.
- Part 1 now includes the development process for the *Handbook* (previously in Appendix 2) and information on the fundamentals of immunisation, including passive and active immunisation, vaccine efficacy and vaccine safety.
- The new Part 5 *Passive immunisation* contains information previously contained in Chapter 3.8 of the 9th edition, *Immunoglobulin preparations*.
- The chapter on Australian bat lyssavirus and rabies is now listed under *Rabies and other lyssaviruses (including Australian bat lyssavirus)* in the alphabetical list of diseases in Part 4.
- The chapter on zoster (herpes zoster) is now included as a disease chapter in Part 4 in this printed version of the 10th edition. It had previously been available as an online update to the 9th edition.
- The chapter on smallpox has been deleted. For information on smallpox, see the *Guidelines for smallpox outbreak, preparedness, response and management* on the Department of Health website www.health.gov.au.
- Some appendices contained in the 9th edition have been deleted:
  - *Products registered in Australia but not currently available* (previously Appendix 3); information regarding such products can be sought from the Therapeutic Goods Administration (www.tga.gov.au)
  - *Definitions of adverse events following immunisation* (previously Appendix 6); some common adverse events are now defined in the glossary of technical terms and an expanded section on adverse events following immunisation is now provided in Part 2 (2.3.2)
  - *Summary table – procedures for a vaccination encounter* (previously Appendix 10); this information is now incorporated throughout Part 2.

1.4.2 Changes to the format of disease chapters in Part 4

- Where relevant, information on reconstitution and stability of reconstituted vaccines has been included in the 'Transport, storage and handling' section of disease chapters.

- Where relevant, information on co-administration with other vaccines and interchangeability of vaccines is now included in the 'Dosage and administration' section of disease chapters.
- A 'Pregnancy and breastfeeding' section has been added to all disease chapters.
- Information on the public health management of each disease is only given in detail where there are specific additional recommendations for vaccine use in the context of disease control and/or post-exposure prophylaxis. The reader is referred to published guidelines from the Communicable Diseases Network Australia (CDNA), where available.
- The Evidence Grades assigned in the 9th edition to recommendations contained within three chapters – *Human papillomavirus*, *Rotavirus* and *Zoster* (online only) – have been removed (see discussion in 1.2 *Development of the 10th edition of the Handbook* regarding *Handbook* development).

1.4.3 Overview of major changes to recommendations

The following list summarises major changes to recommendations and other important information that have occurred in each part of the 10th edition of the *Handbook*.

Part 2 Vaccination procedures

2.1 Pre-vaccination

- The checklist summarising activities required for optimal storage of vaccines has been deleted; readers are referred to the *National vaccine storage guidelines: Strive for 5*.
- The table (Table 2.1.5) containing information on the minimum acceptable age for the 1st vaccine doses in infants now provides advice on action required in case of early administration.
- Catch-up recommendations and tables are now for children aged <10 years (previously <8 years).
- Catch-up guidelines have been included for new vaccines (MMRV, Hib-MenCCV, 13vPCV and 10vPCV).
- Updated pneumococcal catch-up tables (Tables 2.1.9, 2.1.10 and 2.1.11) provide recommendations for use of pneumococcal vaccines up to the age of 5 years.
- Information is provided on the HALO (health, age, lifestyle, occupation) principle for use when considering catch-up vaccination for adults.
- Additional vaccines (MenCCV, 13vPCV, 23vPPV, zoster) have been added to the catch-up table (Table 2.1.12) for adolescents and adults and this table now applies to persons ≥10 years of age (previously 8 years).

2.2 Administration of vaccines

- Advice is now provided on the use of vaccines in multi-dose vials.
- Advice is provided on what to do if a vaccine is inadvertently administered via a route (e.g. intramuscular [IM] or subcutaneous [SC]) other than for which it is recommended.
- Information is now provided on vaccinating children with congenital limb malformation, children in spica casts, patients undergoing treatment for breast cancer, and patients with lymphoedema.
- The section on administration of multiple vaccine injections at the same visit now includes advice on the order in which to give sequential vaccines and advice on simultaneous injections by two providers.

2.3 Post-vaccination

- The section on adverse events following immunisation has been enhanced and expanded, including use of adrenaline autoinjectors for anaphylaxis treatment and more information on reporting of adverse events following immunisation.
- Contact details are provided for obtaining HPV vaccination history from the National HPV Vaccination Program Register (NHVPR, or the 'HPV Register').
- The section on documentation of vaccination has been expanded to include updated details for reporting to the ACIR, and information on the National HPV Vaccination Program Register and other registers.

Part 3 Vaccination for special risk groups

3.1 Vaccination for Aboriginal and Torres Strait Islander people

- Information on the burden of influenza in Indigenous children, and the rationale for vaccination of those, especially ≥6 months to <5 years of age, has been included.
- It is now recommended that Aboriginal and Torres Strait Islander people have their risks and vaccination status for hepatitis B reviewed, be offered testing for previous hepatitis B infection, and be offered vaccination if non-immune.
- Information on the importance of ensuring immunity to rubella, especially among rural and remote Indigenous women of child-bearing age, has been added.
- A new table (Table 3.1.1) has been added summarising additional vaccines recommended for Aboriginal and Torres Strait Islander people.

3.2 Vaccination for international travel

- This section has been updated and expanded and information on recommended vaccines is now divided into routinely recommended vaccines (that are not specifically related to travelling overseas) and selected vaccines that are recommended based on travel itinerary, activities and likely risk of disease exposure.
- Information on more vaccines, including new vaccines, has been added to the tables outlining the dose and routes of administration (Table 3.2.1) and recommended lower age limits (Table 3.2.2) for vaccines for travellers.

3.3 Groups with special vaccination requirements

- The section on vaccination of persons with a prior adverse event following immunisation has been expanded. Advice is provided on vaccination of persons with allergies, including egg allergy.
- The section on vaccination of women who are planning pregnancy, pregnant or breastfeeding, and preterm infants has been updated and expanded.
- The table of recommendations for vaccination in pregnancy (Table 3.3.1) has been updated to include new vaccines.
- dTpa vaccine can be given during the third trimester of pregnancy as an alternative to post-partum or pre-conception vaccination.
- The section on vaccination of immunocompromised persons, including transplant recipients and oncology patients, has been updated and expanded.
- All immunocompromised persons, irrespective of age, who receive influenza vaccine for the first time are now recommended to receive 2 vaccine doses, at least 4 weeks apart, and 1 dose annually thereafter.
- The tables of recommendations for vaccinations in solid organ transplant (Table 3.3.2) and haematopoietic stem cell transplant (Table 3.3.3) recipients have been updated to include new vaccines.
- Information on recommendations for persons infected with human immunodeficiency virus (HIV) now discusses both children and adults and includes rotavirus, HPV, varicella and zoster vaccines.
- The section on vaccination of persons with functional and anatomical asplenia has been updated to include new vaccines, and now includes a table (Table 3.3.5) summarising vaccine recommendations in this group.
- The section on vaccination of persons with autoimmune diseases has been expanded to include those undergoing treatment with immunosuppressive agents and those with Guillain-Barré syndrome and other chronic conditions (hypopituitarism and metabolic diseases).
- The section on vaccination of recent recipients of normal human immunoglobulin and other blood products has been expanded.

- The section on vaccination of persons with bleeding disorders has been updated to include new recommendations for when IM injections should be deferred and advice regarding vaccination of persons with haemophilia.
- The table of recommended vaccinations for persons at risk of occupationally acquired vaccine-preventable diseases (Table 3.3.7) has been updated to include new occupational groups and recommendations.
- The section on vaccination of migrants to Australia has been expanded.
- A new section has been added to provide recommendations for vaccination for sex industry workers.

Part 4 Vaccine-preventable diseases

4.1 Cholera

- If the interval between primary immunisation and booster dose is more than 6 months in children aged 2–6 years, or more than 2 years in adults and children aged >6 years, primary immunisation must be repeated.

4.2 Diphtheria, 4.19 Tetanus and 4.12 Pertussis

- The 1st dose of DTPa-containing vaccines due at 2 months of age can be given as early as 6 weeks of age.
- Advice is provided that an additional dose of pertussis-containing vaccine can be given in the 2nd year of life (e.g. at 18 months of age) if parents wish to minimise the likelihood of their child developing pertussis.
- The booster dose of DTPa-containing vaccine recommended at 4 years of age can be given as early as 3.5 years.
- DTPa-containing vaccines can be used for primary or booster doses in children aged <10 years (previously 8 years). Unvaccinated or partially vaccinated contacts of pertussis cases should be offered DTPa-containing vaccines up to their 10th birthday (previously 8th); dTpa should be offered to those aged ≥10 years.
- The 2nd booster dose recommended for adolescents (using dTpa) should preferably be given between 11 and 13 years of age.
- Adults aged ≥65 years should be offered a single dTpa booster if they have not received one in the previous 10 years.
- For adults who are in certain risk categories for acquiring pertussis, or transmitting it to vulnerable persons, revaccination with dTpa is recommended 10 years after receipt of a prior pertussis-containing vaccine. This interval can be shortened to 5 years in the context of pregnancy.
- Information is provided on maternal vaccination with dTpa during the third trimester of pregnancy as an alternative to post-partum or pre-conception vaccination.

- For persons undertaking high-risk travel, a 5-yearly booster dose with dT or dTpa should be considered for protection against tetanus. In other travellers, a booster dose of tetanus-containing vaccine should be provided if 10 years have elapsed since the previous dose.
- More information on the definition of 'tetanus-prone wounds' is provided, and the table (Table 4.19.1) on wound management has been updated to include recommendations for use of tetanus immunoglobulin (TIG) in immunocompromised persons.
- Information on diphtheria antitoxin is now contained in Part 5 of the *Handbook*.

4.3 *Haemophilus influenzae* type b

- Combination Hib-meningococcal C vaccine (Hib-MenCCV) included.
- Hib vaccination recommendations apply to all children, including Aboriginal and Torres Strait Islander children, as only PRP-T Hib vaccines have been in use in recent years.

4.4 Hepatitis A

- The section on serological testing for hepatitis A prior to vaccination has been expanded, and more detail provided as to rationale for vaccination of certain groups.
- Hepatitis A vaccination is recommended in preference to NHIG for use in post-exposure prophylaxis in immunocompetent persons ≥12 months of age.

4.5 Hepatitis B

- Different schedules for hepatitis B vaccination, including minimum intervals between doses, have been described in more detail.
- Advice is provided regarding the validity of a hepatitis B vaccine schedule used for children born overseas, who were vaccinated at birth, 1 month and 6 months of age.
- Information is provided on checking for infection/immunity to hepatitis B in infants born to mothers with chronic hepatitis B infection 3 to 12 months after the primary vaccine course.
- It is now recommended that Aboriginal and Torres Strait Islander people have their risks and vaccination status for hepatitis B reviewed, be offered testing for previous hepatitis B infection, and be offered vaccination if non-immune.
- Migrants from hepatitis B endemic countries should be offered testing for hepatitis B, and vaccination if appropriate.
- The section on serological testing for hepatitis B prior to vaccination has been expanded, and more detail provided as to rationale for testing and/or vaccination of certain groups, including hepatitis B vaccine non-responders.

4.6 Human papillomavirus

- HPV vaccination is now recommended for girls at the optimal age for vaccination of 11–13 years.
- HPV vaccination is now not routinely recommended for women aged 19–26 years. A risk-benefit assessment should be conducted when contemplating vaccination of women in this and older age groups.
- Recommendations for use of HPV in males have been included. HPV vaccination is recommended for males aged 9–18 years, with the optimal age for vaccination being 11–13 years.
- Specific recommendations regarding the use of HPV vaccine in immunocompromised persons and men who have sex with men are now included.

4.7 Influenza

- Intradermal influenza vaccines are included.
- Ages for which different brands of influenza vaccine are registered have been specified.
- Readers are referred to the Immunise Australia website (www.immunise.health.gov.au) to check annual statements on influenza vaccine availability and recommendations for use.
- Information on the disease burden and benefits of influenza vaccination in pregnancy and in children aged ≥6 months and <5 years has been expanded.
- The list of persons at increased risk of complications from influenza infection has been expanded to include persons with significant obesity and persons with Down syndrome. Alcoholism has been added to the list of chronic illnesses increasing the risk of complications from influenza infection.
- Immunocompromised persons, irrespective of age, who receive influenza vaccine for the first time are now recommended to receive 2 vaccine doses, at least 4 weeks apart, and 1 dose annually thereafter.
- Influenza vaccination is now also recommended for staff working in early childhood education and care and for persons working in the pork industry.

4.8 Japanese encephalitis

- Two new JE vaccines are included.
- Advice on booster doses and information on adverse events have been updated.

4.9 Measles, 4.11 Mumps, 4.18 Rubella and 4.22 Varicella

- Recommendations for MMRV vaccines are updated, and changed from the recommendations provided in the 9th edition. It is stated that MMRV vaccines will be available in Australia from July 2013.

- MMR vaccine is to be used for the 1st dose at 12 months of age. MMRV is *not* recommended for use as the 1st dose of MMR-containing vaccine in children <4 years of age.
- The recommended age for administration of the 2nd dose of measles-containing vaccine will be moved from 4 years of age to 18 months of age (from July 2013).
- MMRV vaccine can be used as the 2nd dose of MMR-containing vaccine and to provide a single dose of varicella vaccine at 18 months of age (from July 2013).
- MMRV vaccines are not recommended in persons ≥14 years of age.
- A new table has been included in the *Measles* (Table 4.9.1) and *Varicella* (Table 4.22.1) chapters summarising the different recommendations before and after the introduction of MMRV vaccines in July 2013.
- The table describing post-exposure prophylaxis for measles (Table 4.9.2) has been revised and expanded to include more specific age ranges, MMR vaccination history and advice regarding persons who are immunocompromised.
- More information on serological testing and revaccination of women of child-bearing age who are non-immune to rubella is included.

4.10 Meningococcal disease

- Combination Hib-meningococcal C vaccine (Hib-MenCCV) has been included.
- Quadrivalent meningococcal conjugate vaccines (4vMenCV) have been included.
- 4vMenCV is preferred over the quadrivalent meningococcal polysaccharide vaccine (4vMenPV) for use in persons aged ≥9 months who are at increased risk of meningococcal disease.
- For young children with medical risk factors for meningococcal disease, meningococcal C conjugate vaccine (MenCCV) is recommended in those aged 6 weeks to <12 months; thereafter 4vMenCV is recommended in a 2-dose schedule at approximately 12 and 18 months of age.
- 5-yearly booster doses of 4vMenCV are recommended for persons at ongoing high risk of meningococcal infection.
- For persons at ongoing risk of meningococcal infection who have previously received 4vMenPV, a booster dose of 4vMenCV should be given 3 years after the 4vMenPV and then every 5 years.

4.13 Pneumococcal disease

- 10-valent (10vPCV) and 13-valent (13vPCV) pneumococcal conjugate vaccines are included.

- For Aboriginal and Torres Strait Islander children living in the Northern Territory, Queensland, South Australia or Western Australia, a booster dose of 13vPCV at 12–18 months of age replaces the booster dose of 23vPPV at 18–24 months of age.
- The list of conditions associated with increased risks of invasive pneumococcal disease (IPD) (List 4.13.1) has been revised to include both adults and children, and is now divided into two categories: those conditions posing the *highest* increased risk of developing IPD and those associated with an increased risk of IPD.
- The table (Table 4.13.3) summarising recommendations for vaccination of adults with 23vPPV has been revised.
- Recommendations for the use of a single dose of 13vPCV in adults and children >5 years of age with conditions associated with the highest increased risk of IPD (and who have not previously received a 13vPCV dose) are included.
- Information on the use of 23vPPV in persons >5 years of age at increased risk of IPD has also been more clearly presented.

4.14 Poliomyelitis

- The 1st dose of IPV-containing combination vaccine due at 2 months of age can be given as early as 6 weeks of age.
- A booster dose of IPV-containing vaccine is recommended at 4 years of age, but can be given as early as 3.5 years.

4.15 Q fever

- Q fever vaccination and skin testing training is now undertaken via an educational module available online.
- Information on the Australian Q Fever Register, which lists Q fever immunisation service providers and records of Q fever vaccinations given to some persons, is included.
- Q fever vaccination is now also recommended for professional dog and cat breeders, and wildlife and zoo workers who have contact with at-risk animals, including kangaroos and bandicoots.

4.16 Rabies and other lyssaviruses (including Australian bat lyssavirus)

- The terms PEP (post-exposure prophylaxis) and PreP (pre-exposure prophylaxis) are used throughout the chapter.
- Information and recommendations on management of all potential lyssavirus exposures, including lyssavirus infection from exposure to bats in non-rabies-enzootic countries, is now included.
- A 4-dose PEP schedule is now recommended for immunocompetent persons. A 5-dose schedule is only recommended for persons who are immunocompromised.

- A table (Table 4.16.1) summarising World Health Organization (WHO) categories of lyssavirus exposure, for guidance in use of post-exposure prophylaxis, has been added.
- Algorithms are provided with details of the recommended management pathways for post-exposure prophylaxis for rabies and other lyssaviruses (including Australian bat lyssavirus), and for booster doses for persons at ongoing risk of exposure to rabies and other lyssaviruses.
- Advice regarding the completion of post-exposure prophylaxis commenced overseas has been expanded, including the addition of a summary table (Table 4.16.2).
- Persons who have completed a primary course of a currently available cell culture-derived rabies vaccine no longer routinely require booster doses if travelling or living in an area of high risk.
- Information on the role of serological testing has been more clearly presented.

4.17 Rotavirus

- The upper age limits for each dose of rotavirus vaccines are more clearly defined.
- Contraindications to rotavirus vaccination now include previous history of intussusception (IS) and severe combined immunodeficiency in infants.
- Information on the safety of rotavirus vaccines in infants with underlying conditions and infants who are immunocompromised has been updated.
- Information on adverse events following rotavirus vaccination has been updated and expanded, including new information on the low, but increased, risk of IS occurring following the 1st or 2nd dose of either rotavirus vaccine.

4.20 Tuberculosis

- Bacille Calmette-Guérin (BCG) vaccination is no longer routinely recommended for neonates weighing <2.5 kg.
- Generalised septic skin disease, skin conditions such as eczema, dermatitis and psoriasis, and significant febrile illness are no longer contraindications to BCG vaccination but, if present, vaccination should be deferred.

4.23 Yellow fever

- Yellow fever vaccine is not recommended in women who are breastfeeding infants aged <9 months.
- More detail is provided on how to access the WHO information regarding areas of high yellow fever activity and requirements for travel.

4.24 Zoster

- Information on the efficacy of vaccination in persons aged 50–59 years has been included.

Part 5 Passive immunisation

- Information regarding the use of intravenous immunoglobulins as treatment for disease conditions (such as Kawasaki disease) or as replacement therapy for immunodeficient individuals is no longer included in the *Handbook*. Readers are referred to National Blood Authority guidelines.

1.5 FUNDAMENTALS OF IMMUNISATION

1.5.1 Overview

Vaccines are complex biological products designed to induce a protective immune response effectively and safely. Vaccines contain one or more antigens (or immunogens) that stimulate an active immune response. These are generally protein- or polysaccharide (sugar)-based substances. The number and derivation of the antigen(s) contained in each vaccine vary. Most vaccines work by inducing B-lymphocytes to produce antibodies that bind to and inhibit pathogenic organisms or their toxins. Generation of T-cell-mediated (cellular) immunity is also important for some vaccines.

Vaccines, like all medicines, are regulated in Australia by the Therapeutic Goods Administration (TGA). Before they are made available for use they are rigorously tested in human clinical trials to confirm that they are safe and that they stimulate protective immune responses. Vaccines are also evaluated to ensure compliance with strict manufacturing and production standards. This testing is required by law and is usually conducted both during the vaccine's development and after its registration. In addition, once they are in use, the safety of vaccines is monitored by the TGA and other organisations using different methods, including passive and active surveillance for adverse events following immunisation (see 1.5.5 *Vaccine safety and adverse events following immunisation*).

1.5.2 Passive immunisation

Passive immunity is the direct transfer or administration of antibodies to a non-immune person to provide immediate protection. One example of passive immunisation is the transfer of maternal antibodies to the fetus, which provides some short-lived protection of the newborn infant against certain infections.[1,2] Another example is the administration of a product containing antibodies (or immunoglobulins, IgG) pooled from blood donors, in order to provide temporary protection to a non-immune person who has recently been exposed to infection.[3] The protection afforded is immediate, but lasts for only a few weeks as the half-life of IgG is approximately 3 to 4 weeks. Regular immunoglobulin infusions are also indicated for some immunocompromised persons who are deficient in antibody. A separate use of immunoglobulins is in the treatment of a number of specific immune-mediated conditions in order to modulate the disease course. For further information regarding the use of intravenous immunoglobulin for this purpose, refer to *Criteria for the clinical use of intravenous immunoglobulin in Australia* (www.nba.gov.au/ivig/index.html).

For more information on passive immunisation see Part 5 *Passive immunisation*.

1.5.3 Active immunisation

Active immunisation involves the use of vaccines to stimulate the immune system to produce a protective immune response. Vaccines usually induce an immune response that mimics the host's response to natural infection, but

without the harmful consequences of the infection itself. In addition to antibody responses, many vaccines also stimulate cell-mediated immunity. Immunity following active immunisation generally lasts for months to many years, depending on the nature of the vaccine as well as host factors.[4,5] Protective immunity is induced by antigen(s) contained within the vaccine. This may be a toxoid (a bacterial toxin that has been rendered non-toxigenic, e.g. for tetanus or diphtheria); killed or inactivated bacteria or viruses, such as hepatitis A vaccines; live attenuated bacteria or viruses, such as measles, mumps and rubella vaccines; or subunit components of a pathogen that only contain the antigen(s) of interest, such as the hepatitis B vaccine.[4,5]

In addition to containing the immunising antigen(s), vaccines may also contain the following:

- Adjuvants, which enhance the immune response to an antigen; an example is aluminium hydroxide.
- Preservatives, which reduce the risk of contamination; some examples are 2-phenoxyethanol, which is also used in many cosmetics and pharmaceuticals, and thiomersal, which is used in the Q fever vaccine but is not present in any of the vaccines on the National Immunisation Program for young children.
- Stabilisers, which improve the shelf-life and help to protect the vaccine from adverse conditions; examples are sucrose, mannitol, lactose and gelatin. Stabilisers are also used in most confectionery and many pharmaceuticals.
- Emulsifiers or surfactants, which alter the surface tension of the liquid vaccine; examples are polysorbate-80 and sorbitol. Emulsifiers are added to most ice creams and many pharmaceuticals.
- Residuals, which are minute or trace amounts of substances that remain after the manufacture of the vaccine; examples of residuals detectable in some vaccines are formaldehyde, antibiotics such as neomycin or polymyxin, and egg proteins.

Further details of a particular vaccine's constituents can be found in either the product information (PI) or the consumer medicines information (CMI) for individual vaccines. This information is presented in the shaded box for each vaccine under the disease-specific chapters in Part 4 of this *Handbook* (current June 2012); however, it is important to note that PIs and CMIs are updated periodically. The most current versions of the PI (and CMI) for vaccines (and other medicines) are available from the TGA website (www.tga.gov.au).

In addition, information on the components contained in vaccines that are available under the Australian National Immunisation Program is provided in Appendix 3 of this *Handbook*, and further details on vaccine composition can be found in Appendix 4 *Commonly asked questions about vaccination*.

The recommended number of doses and age of administration vary for each vaccine. These recommendations are based on the type of vaccine, disease epidemiology (the age-specific risk for infection and for complications), and the anticipated immune response of the recipient (including whether transplacental transfer of maternal antibodies will inhibit the immune response in an infant).[4,5] Several doses of a vaccine may be required to induce protective immunity, particularly in younger children.

Homeopathic preparations do not induce immunity and are never an alternative to vaccination (see Appendix 4 *Commonly asked questions about vaccination*).

Detailed information on the background, available vaccines and recommendations for vaccines used in active immunisation are provided in the disease-specific chapters in Part 4 of this *Handbook*.

1.5.4 Vaccine efficacy, vaccine effectiveness and vaccine failure

The terms vaccine efficacy and vaccine effectiveness are often used interchangeably. However, in general terms, vaccine *efficacy* refers to estimates of protection obtained under the idealised conditions of a randomised controlled trial (RCT). It is usually expressed as the percentage reduction in a person's risk of disease if vaccinated compared to the risk if not vaccinated. Vaccine *effectiveness* refers to estimates of protection obtained under 'real world' rather than trial conditions, for example, in immunisation programs after vaccine registration. Sometimes vaccine effectiveness is also taken to include the broader impact of a vaccination program on overall disease incidence in the population, including any additional herd protection conferred to unvaccinated individuals.[4,6]

The extent and duration of protection provided by vaccination varies and is influenced by many factors. For example, some vaccines, such as the pneumococcal and meningococcal polysaccharide vaccines, provide protection for a few years only. This is because polysaccharide antigens induce antibodies without the involvement of T-lymphocytes (T-cell independent response). T-cell lymphocyte involvement is needed for long-term immune memory; without it, protection is relatively short-lived and immunity wanes, sometimes requiring revaccination. In addition, polysaccharide vaccines are less immunogenic in children aged <2 years.[4] The process of conjugating (or linking) capsular polysaccharides to a protein carrier creates conjugate vaccines that can induce antibody production with the help of T-lymphocytes (T-cell dependent response). This results in higher-quality and longer-term immunity, including in children <2 years of age.[4] Conjugated vaccines are available for *Haemophilus influenzae* type b, *Neisseria meningitidis* (serogroups A, C, W_{135} and Y) and pneumococcal disease.

Vaccination failure can be due to either vaccine failure or failure to vaccinate (i.e. that an indicated vaccine was not administered appropriately for any reason). Sometimes a vaccinated person may develop infections despite being vaccinated

(vaccine failure). Often such infections result in a milder or more attenuated form of disease, for example, chickenpox developing despite varicella vaccination or whooping cough developing after 2 or more doses of pertussis vaccine. Vaccine failure can be categorised in two ways. 'Primary' vaccine failure occurs when a fully vaccinated person does not form an adequate immune response to that vaccine. This might occur because a vaccine is defective due to a manufacturing fault or, more typically, because of inadequate storage (e.g. breakage of the cold chain) or expiry of the shelf-life. Primary vaccine failure may also occur because the recipient's immune response is ineffective, which may be relatively specific for that vaccine or part of a broader immunodeficiency. 'Secondary' vaccine failures occur when a fully vaccinated person becomes susceptible to that disease over time, usually because immunity following vaccination wanes over time. As discussed above, the duration of the protective effect of vaccination varies depending on the nature of the vaccine and the type of immune response elicited, the number of doses received, and host factors. Some vaccinated persons may get further immune stimulation from natural infection or colonisation, which aids in maintaining ongoing protection.

1.5.5 Vaccine safety and adverse events following immunisation

What is an adverse event following immunisation?

The term 'adverse event following immunisation' (AEFI) refers to any untoward medical occurrence that follows immunisation, whether expected or unexpected, and whether triggered by the vaccine or only coincidentally occurring after receipt of a vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.[7]

Adverse events following immunisation (AEFI) should be reported promptly, either according to relevant state or territory protocols or directly to the TGA (for detailed information on reporting and management of AEFI, see 2.3 *Post-vaccination*).

The safety of vaccines is very important as vaccines are given to prevent disease and target all or many members of the population, most of whom are healthy. All vaccines available in Australia must pass stringent safety testing before being approved for use by the TGA. This testing is required by law and is usually done over many years during the vaccine's development. In addition, the TGA monitors the safety of vaccines once they are registered.

From the time a vaccine comes into use, there is ongoing review of both vaccine safety and efficacy through a variety of mechanisms, such as further clinical

trials and surveillance of disease and vaccine adverse events. One important component of ensuring that vaccines are safe is to monitor the occurrence of AEFI. In Australia, there are regional and national surveillance systems that collect reports of any adverse events following immunisation. All AEFI reported are added to the national Adverse Drug Reactions System (ADRS) database, which is operated by the TGA. (See also 2.3 *Post-vaccination*.) Each year, reports presenting data and analysis of AEFI in Australia are published in the journal *Communicable Diseases Intelligence*, accessible via the Australian Government Department of Health website (www.health.gov.au/internet/main/publishing.nsf/content/cda-pubs-cdi-cdiintro.htm).

In some cases, other specific studies will be conducted to ensure that vaccine safety is closely monitored once a vaccine is in use. For example, the risk of intussusception (IS) following rotavirus vaccines has been closely monitored in Australia and elsewhere because of the association of a previously licensed vaccine with an unacceptably high risk of IS.

Adverse reactions to vaccines (also known as 'vaccine side effects') do sometimes occur. It is usually not possible to predict which individuals may have a mild or, rarely, a serious reaction to a vaccine. However, by following guidelines regarding when vaccines should and should not be used, the risk of adverse events can be minimised. As vaccines are usually given to healthy people, any adverse event that follows soon after immunisation may be perceived as due to the vaccine. The fact that an adverse event occurs after an immunisation does not prove the vaccine caused the event. A causal association is rarely certain, but is most likely when the AEFI is both typical (even if very rare) and when there is no other plausible explanation, for example, an injection site reaction occurring a day after vaccination or typical anaphylaxis occurring within minutes of vaccination. Many AEFIs are less specific and/or have plausible alternative explanations, including coincidence. Such associations can only be assessed by large-scale epidemiological studies or specific tests, for example, in the case of allergy, by allergy testing or challenge. Even when an AEFI is typical, it may be nonetheless unrelated to vaccination (see 2.3 *Post-vaccination*).

Vaccine adverse events fall into two general categories: local or systemic. Local reactions are defined as reactions occurring at the site of vaccine administration (usually pain, redness or swelling at the injection site) and are generally the least severe and most frequently occurring AEFI. Systemic reactions most commonly include fever, headache and lethargy.[8,9] Allergic reactions can also occur, although anaphylaxis, the most severe form of an allergic response, is rarely caused by vaccination. It is not possible to completely predict which individuals may have a reaction to a vaccine.

Each chapter in the *Handbook* indicates under which circumstances vaccine administration is contraindicated or where precautions are required. A contraindication to vaccination usually occurs when a person has a pre-existing condition that significantly increases the chance that a serious adverse event

will occur following receipt of a specific vaccine. A contraindication may also occur when there is insufficient safety data regarding a vaccine's use and there is a theoretical risk of harm. In general, vaccines should not be given where a contraindication exists, except under advice from your local state or territory health department (Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*).

A precaution is a condition that may increase the chance of an adverse event following immunisation or one that may compromise the ability of the vaccine to produce immunity. When a precaution exists, there may still be circumstances when the benefits of giving the vaccine outweigh the potential risks; however, special care and the provision of appropriate advice to the vaccine recipient may be required (see 3.3.1 *Vaccination of persons who have had an adverse event following immunisation*).

In 2010, a national review of the management of adverse events that occurred following influenza vaccine administration was performed.[10] The review made a number of recommendations to further improve the monitoring of vaccine safety in Australia. Any changes to the system(s) for monitoring or reporting of AEFI in Australia will be reflected in future updates to the *Handbook* and will also be available from the Immunise Australia website (www.immunise.health.gov.au).

References

A full reference list is available on the electronic *Handbook* or website www.immunise.health.gov.au

PART 2 VACCINATION PROCEDURES

In Australia, vaccination is undertaken predominantly through general practices, but in some jurisdictions vaccines may be given through local council clinics, community centres or through school-based immunisation programs. In some situations, vaccinations may also be given in travel medicine clinics, public hospitals, staff occupational health clinics and aged care facilities. State or territory legislation outlines who can access and administer vaccines. All vaccines must be administered in accordance with the relevant legislation, best practice and the following *Handbook* guidelines and recommendations.

2.1 PRE-VACCINATION

The following sections discuss steps and procedures that should occur before a vaccination encounter.

2.1.1 Preparing an anaphylaxis response kit

The availability of protocols, equipment and drugs necessary for the management of anaphylaxis should be checked before each vaccination session. An anaphylaxis response kit should be on hand at all times and should contain:

- adrenaline 1:1000 (minimum of three ampoules – check expiry dates)
- minimum of three 1 mL syringes and 25 mm length needles (for intramuscular [IM] injection)
- cotton wool swabs
- pen and paper to record time of administration of adrenaline
- laminated copy of adrenaline doses (Table 2.3.2 or back cover of this *Handbook*)
- laminated copy of 'Recognition and treatment of anaphylaxis' (back cover of this *Handbook*).

See 2.3.2 *Adverse events following immunisation* for details on recognition and treatment of adverse events following immunisation (in particular, see 'Use of adrenaline' and 'Use of adrenaline autoinjectors for anaphylaxis treatment' in that section).

2.1.2 Effective cold chain: transport, storage and handling of vaccines

The cold chain is the system of transporting and storing vaccines within the temperature range of +2°C to +8°C from the place of manufacture to the point of administration.[1] Maintenance of the cold chain is essential for maintaining vaccine potency and, in turn, vaccine effectiveness. This is vital, not only for those vaccines provided as part of the National Immunisation Program, but also for vaccines purchased by the patient via prescription from a pharmacist. In such

cases, both the doctor issuing the prescription and the pharmacist dispensing the vaccine must inform the patient of the need for maintaining, and how to maintain, the cold chain for the vaccine they have purchased.

All immunisation service providers must be familiar with, and adhere to, the *National vaccine storage guidelines: Strive for 5* (2nd edition).[1] This publication can be accessed free of charge from www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/IMM77-cnt

The *National vaccine storage guidelines: Strive for 5* contains specific details on setting up the infrastructure for a vaccination service, and immunisation service providers should refer to this document to ensure that satisfactory equipment and procedures are in place before commencing vaccination services.[1]

These guidelines also provide instructions on how best to transport vaccines from the main storage facility to outreach or external clinics. Purpose-built vaccine refrigerators (PBVR) are the preferred means of storage for vaccines. Domestic refrigerators are not designed for the special temperature needs of vaccine storage.

Cold chain breaches

Despite best practices, cold chain breaches sometimes occur. It is important to report any cold chain breaches so that revaccination of patients or recall of unused vaccines can be undertaken, if required.

Do not discard or use any vaccines exposed to temperatures below +2°C or above +8°C without obtaining further advice. Isolate vaccines and contact the state/territory health authorities (see Appendix 1) for advice on the National Immunisation Program vaccines and the manufacturer/supplier for privately purchased vaccines. ***Recommendations for the discarding of vaccines may differ between health authorities and manufacturers.***

2.1.3 Valid consent

Valid consent can be defined as the voluntary agreement by an individual to a proposed procedure, given after sufficient, appropriate and reliable information about the procedure, including the potential risks and benefits, has been conveyed to that individual.[2-6] As part of the consent procedure, persons to be vaccinated and/or their parents/carers should be given sufficient information

(preferably written) on the risks and benefits of each vaccine, including what adverse events are possible, how common they are and what they should do about them[7] (the table inside the front cover of this *Handbook*, *Side effects following immunisation for vaccines used in the National Immunisation Program (NIP) schedule*, can be used for this purpose).

For consent to be legally valid, the following elements must be present:[6,8]

1. It must be given by a person with legal capacity, and of sufficient intellectual capacity to understand the implications of being vaccinated.
2. It must be given voluntarily in the absence of undue pressure, coercion or manipulation.
3. It must cover the specific procedure that is to be performed.
4. It can only be given after the potential risks and benefits of the relevant vaccine, risks of not having it and any alternative options have been explained to the individual.

The individual must have sufficient opportunity to seek further details or explanations about the vaccine(s) and/or its administration. The information must be provided in a language or by other means the individual can understand. Where appropriate, an interpreter and/or cultural support person should be involved.

Consent should be obtained before each vaccination, once it has been established that there are no medical condition(s) that contraindicate vaccination. Consent can be verbal or written. Immunisation providers should refer to their state or territory's policies on obtaining written consent (see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*).

Consent on behalf of a child or adolescent

In general, a parent or legal guardian of a child has the authority to consent to vaccination of that child; however, it is important to check with your state or territory authority where any doubt exists.[2,5] A child in this context is defined as being under the age of 18 years in Tasmania, Victoria and Western Australia; under the age of 14 years in New South Wales; and under the age of 16 years in the Australian Capital Territory, South Australia and the Northern Territory. Queensland follows common law principles.

For certain procedures, including vaccination, persons younger than the ages defined above may have sufficient maturity to understand the proposed procedure and the risks and benefits associated with it, and thus may have the capacity to consent under certain circumstances. Refer to the relevant state or territory immunisation service provider guidelines for more information.

Should a child or adolescent refuse a vaccination for which a parent/guardian has given consent, the child/adolescent's wishes should be respected and the parent/guardian informed.[2]

Consent on behalf of an adult lacking capacity

A careful assessment should be made of an adult's capacity to give valid consent to a vaccination. If the adult lacks capacity, practitioners should refer to relevant state and territory laws relating to obtaining consent from a substitute decision-maker. For example, this may occur for influenza vaccination of an elderly person with dementia. Refer to the enduring guardianship legislation appropriate for your state or territory for further advice.

Resources to help communicate the risks and benefits of vaccines

Plain language should be used when communicating information about vaccines and their use. The person to be vaccinated (or their parent/guardian) must be encouraged and allowed to ask for further information and have sufficient time to make a decision about whether to consent or not.[9,10]

It is preferable that printed information is available to supplement any verbal explanations.[11] The summary table *Comparison of the effects of diseases and the side effects of NIP vaccines* inside the back cover of this *Handbook* provides some basic information necessary to communicate the risks and benefits of vaccination. The table can be photocopied and used freely as required.

More detailed information concerning vaccines and their use is available from the following sources:

- www.immunise.health.gov.au

  The Immunise Australia website includes the booklet *Understanding childhood immunisation*, which contains frequently asked questions and links to state and territory health department websites. Several of these sites offer multilingual fact sheets.

- www.ncirs.edu.au

  The National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases website includes fact sheets related to specific vaccines, vaccine-preventable diseases and vaccine safety. The website also hosts online decision aids to assist patients in deciding whether to vaccinate or not.

See also Appendix 4 *Commonly asked questions about vaccination*.

Evidence of consent

General practice or public immunisation clinics

Consent may be given either in writing or verbally, according to the protocols of the health facility, but it must meet the criteria for valid consent. Evidence of verbal consent should be documented in the clinical records. If a standard procedure is routinely followed in a practice or clinic, then a stamp, a sticker

or a provider's signature indicating that the routine procedure has been followed may be used. For paperless medical records, a typed record of verbal consent may be made in the patient's file, or a copy of written consent scanned into the file.

Explicit verbal consent is required before administration of any vaccine, even when written consent has been given at previous vaccination encounters for the same vaccine. Verbal consent should be documented in the patient's file each time it is given.

School-based vaccination programs

Consent is required for provision of individual vaccines or a vaccine course offered in school-based vaccination programs.

In school-based, and other large-scale, vaccination programs, the parent or guardian usually does not attend with the child on the day the vaccination is given, and written consent from the parent or guardian is desirable in these circumstances. However, if written consent is not able to be provided, or if further clarification is required, verbal consent may be sought by telephone from the parent or guardian by the immunisation service provider. This should be clearly documented on the child's consent form. In some jurisdictions, older adolescents *may* be able to provide their own consent for vaccinations offered through school-based vaccination programs.[12] Consent requirements and vaccines offered in these programs vary between jurisdictions. Refer to the relevant state or territory school-based vaccination program guidelines for more information.

2.1.4 Pre-vaccination screening

Immunisation service providers should perform a comprehensive pre-vaccination health screen of all persons to be vaccinated. For some individuals, alterations to the routinely recommended vaccines may be necessary to either eliminate or minimise the risk of adverse events, to optimise an individual's immune response, or to enhance the protection of a household contact against vaccine-preventable diseases.

Providers should:

- ensure that they have the right person to be vaccinated
- ensure which vaccine(s) are indicated, including any previously missed vaccine doses
- consider whether alternative or additional vaccines should be given
- check if there are any contraindications or precautions to the vaccines that are to be given
- ensure that the patient to be vaccinated is the appropriate age for the vaccines to be given

- check that the correct time interval has passed since any previous vaccine(s) or any blood products were given.

See also 2.1.5 *Catch-up* and relevant disease chapters for further details.

Steps for pre-vaccination screening

Follow these steps to complete the pre-vaccination screening process:

- Provide the person to be vaccinated or the parent/carer with the *Pre-vaccination screening checklist* (Table 2.1.1).
  - » Some of the questions in this checklist are deliberately non-specific so as to elicit as much important information as possible.
  - » The checklist may be photocopied and handed to the person to be vaccinated or the parent/carer just before vaccination.
  - » The checklist may also be photocopied and displayed in the clinic/surgery for easy reference for the immunisation service provider.
- For vaccination of adults, seek additional information about the occupation and lifestyle factors that may influence vaccination requirements. This is discussed in more detail in 2.1.5 *Catch-up* below under 'Catch-up schedules for persons ≥10 years of age'.
- If you identify the presence of a condition or circumstance indicated on the pre-vaccination screening checklist, refer to Table 2.1.2, which lists the specific issues pertaining to such condition(s) or circumstances and provides the appropriate action with a rationale.
- Where necessary, seek further advice from a specialist immunisation clinic, a medical practitioner with expertise in vaccination, the immunisation section within your state or territory health authority, or your local Public Health Unit (see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*).

Table 2.1.1: Pre-vaccination screening checklist

Pre-vaccination screening checklist
This checklist helps decide about vaccinating you or your child today. Please fill in the following information for your doctor/nurse. Name of person to be vaccinated _____ Date of birth _____ Age today _____ Name of person completing this form _____ Please indicate if the person to be vaccinated: ☐ is unwell today ☐ has a disease that lowers immunity (e.g. leukaemia, cancer, HIV/AIDS) or is having treatment that lowers immunity (e.g. oral steroid medicines such as cortisone and prednisone, radiotherapy, chemotherapy) ☐ has had a severe reaction following any vaccine ☐ has *any* severe allergies (to anything) ☐ has had any vaccine in the past month ☐ has had an injection of immunoglobulin, or received any blood products or a whole blood transfusion within the past year ☐ is pregnant ☐ has a past history of Guillain-Barré syndrome ☐ was a preterm infant ☐ has a chronic illness ☐ has a bleeding disorder ☐ identifies as an Aboriginal or Torres Strait Islander ☐ does not have a functioning spleen ☐ is planning a pregnancy or anticipating parenthood ☐ is a parent, grandparent or carer of a newborn ☐ lives with someone who has a disease that lowers immunity (e.g. leukaemia, cancer, HIV/AIDS), or lives with someone who is having treatment that lowers immunity (e.g. oral steroid medicines such as cortisone and prednisone, radiotherapy, chemotherapy) ☐ is planning travel ☐ has an occupation or lifestyle factor(s) for which vaccination may be needed (discuss with doctor/nurse) Please specify:_____

Note: Please discuss this information or any questions you have about vaccination with your doctor/nurse before the vaccines are given.

Before any vaccination takes place, your doctor/nurse should ask you:

☐ Did you understand the information provided to you about vaccination?

☐ Do you need more information to decide whether to proceed?

☐ Did you bring your/your child's vaccination record card with you?

It is important for you to receive a personal record of your or your child's vaccinations. If you do not have a record, ask your doctor/nurse to give you one. Bring this record with you every time you or your child visit for vaccination. Make sure your doctor/nurse records all vaccinations on it.

Conditions or circumstances identified using the pre-vaccination screening checklist

The recommended responses for immunisation service providers to make if any conditions or circumstances are identified by using the pre-screening checklist are summarised in Table 2.1.2.

Note: Only vaccines recommended on the NIP schedule are included in Table 2.1.2. For information on other vaccines, refer to the relevant disease-specific chapter in Part 4 of this *Handbook* or to vaccine product information.

For reference, Table 2.1.3 provides a list of live attenuated vaccines.

Table 2.1.2: Responses to relevant conditions or circumstances identified through the pre-vaccination screening checklist

Condition or circumstance of person to be vaccinated	Action	Rationale[13-15]
Is unwell today: • acute febrile illness (current T ≥38.5°C) • acute systemic illness	Defer all vaccines until afebrile. *Note*: Children with minor illnesses (without acute systemic symptoms/signs) should be vaccinated.	To avoid an adverse event in an already unwell child, or to avoid attributing symptoms to vaccination

Condition or circumstance of person to be vaccinated	Action	Rationale[13-15]
Has a disease that lowers immunity or is receiving treatment that lowers immunity	Refer to 3.3.3 *Vaccination of immunocompromised persons*. In some cases, expert advice may need to be sought before vaccination (see Appendix 1). *Note*: Persons living with someone with lowered immunity should be vaccinated, including with live viral vaccines (see below).	The safety and effectiveness of the vaccine may be suboptimal in persons who are immunocompromised. Live attenuated vaccines may be contraindicated.
Has had anaphylaxis following a previous dose of the relevant vaccine	Do not vaccinate. Seek further medical advice to confirm causality and to assist with other vaccinations. See also 'Contraindications to vaccination' below.	Anaphylaxis to a previous dose of vaccine is a contraindication to receiving the same vaccine.
Has a severe allergy to a vaccine component	Refer to Appendix 3 for a vaccine component checklist. Do not vaccinate but seek specialist advice (see Appendix 1). The patient may still be able to be vaccinated, dependent on the allergy.	Anaphylaxis to a vaccine component is generally a contraindication to receiving the vaccine.
Has received a live attenuated viral parenteral vaccine* or BCG vaccine in past 4 weeks	Delay live attenuated viral parenteral vaccines by 4 weeks.	The immune response to a live attenuated viral vaccine (given parenterally) may interfere with the response to a subsequent live viral vaccine given within 4 weeks of the first.

Condition or circumstance of person to be vaccinated	Action	Rationale[13-15]
Has had any blood product in the past 7 months, or has had IM or IV immunoglobulin in the past year	Check which product the person received and the interval since administration. Refer to Table 3.3.6 *Recommended intervals between either immunoglobulins or blood products and MMR, MMRV or varicella vaccination*. If not eligible, make a return appointment for this vaccination, and send a reminder later if necessary.	Antibodies in these products may interfere with the immune response to MMR, MMRV and varicella vaccines. The recommended interval to vaccination varies depending on the immunoglobulin or blood product administered.
Is planning a pregnancy or anticipating parenthood	Ensure women planning pregnancy and household members have received vaccines recommended for their age group. For example, 2nd dose of MMR† (if born after 1966); varicella; dTpa;‡ and/or have had appropriate pre-conception serological testing. See 3.3.2 *Vaccination of women who are planning pregnancy, pregnant or breastfeeding, and preterm infants*. Advise women not to become pregnant within 28 days of receiving live viral vaccines.*	Vaccinating before pregnancy may prevent maternal illness, which could affect the infant, and may confer passive immunity to the newborn.

Condition or circumstance of person to be vaccinated	Action	Rationale[13-15]
Is pregnant	Refer to Table 3.3.1 *Recommendations for vaccination in pregnancy*. Influenza vaccine is recommended for all pregnant women. Live vaccines* should be deferred until after delivery. Vaccination of household contacts of pregnant women should be completed according to the NIP schedule.	There is insufficient evidence to ensure the safety of administering live vaccines during pregnancy. Inactivated vaccines are generally not contraindicated in pregnancy.
Has a history of Guillain-Barré syndrome (GBS)	See 3.3.3 *Vaccination of immunocompromised persons* and 4.7 *Influenza*. Risks and benefits of influenza vaccine should be weighed against the potential risk of GBS recurrence (seek further advice as per Appendix 1).	Persons with a history of GBS may be at risk of recurrence of the condition following influenza vaccine.
Was born preterm	See 3.3.2 *Vaccination of women who are planning pregnancy, pregnant or breastfeeding, and preterm infants*. Preterm infants born at <28 weeks gestation and/or with chronic lung disease require extra pneumococcal vaccinations (see 4.13 *Pneumococcal disease*). Preterm infants born at <32 weeks gestation and/or <2000 g birth weight may require an extra dose of hepatitis B vaccine (see 4.5 *Hepatitis B*).	Preterm infants may be at increased risk of vaccine-preventable diseases (e.g. invasive pneumococcal disease), and may not mount an optimal immune response to certain vaccines (e.g. hepatitis B).

Condition or circumstance of person to be vaccinated	Action	Rationale[13-15]
Has a severe or chronic illness	See 3.3 *Groups with special vaccination requirements*. These persons should receive recommended vaccines such as pneumococcal vaccine and annual influenza vaccination. If there is significant immunocompromise, they should not receive live vaccines* (see above).	Persons with a severe or chronic illness may be at increased risk of vaccine-preventable diseases (e.g. invasive pneumococcal disease), but may not mount an optimal immune response to certain vaccines. The safety and effectiveness of some vaccines may be suboptimal in persons who are immunocompromised (see above).
Has a bleeding disorder	See 3.3.5 *Vaccination of persons with bleeding disorders*. The subcutaneous route could be considered as an alternative to the intramuscular route; seek specialist advice (see Appendix 1).	Intramuscular injection may lead to haematomas in patients with disorders of haemostasis.
Identifies as an Aboriginal or Torres Strait Islander	See 3.1 *Vaccination for Aboriginal and Torres Strait Islander people*. See the National Immunisation Program for specific recommendations for Aboriginal and Torres Strait Islander people.	Some Indigenous persons are at increased risk of some vaccine-preventable diseases, such as influenza, pneumococcal disease and hepatitis A.
Does not have a functioning spleen	See 3.3.3 *Vaccination of immunocompromised persons*, 'Persons with functional or anatomical asplenia'. Check the person's vaccination status for pneumococcal, meningococcal, influenza and Hib vaccinations.	Persons with an absent or dysfunctional spleen are at an increased risk of severe bacterial infections, most notably invasive pneumococcal disease.

Condition or circumstance of person to be vaccinated	Action	Rationale[13-15]
Is a parent, grandparent or carer of an infant ≤6 months of age	Ensure parents, grandparents and carers of infants up to 6 months of age have been offered all vaccines recommended for their age group, including dTpa.‡	Persons in close contact are the most likely sources of vaccine-preventable diseases, in particular pertussis, in the newborn.
Lives with someone who is immunocompromised	Ensure all recommended vaccines (in particular MMR, varicella and influenza vaccines) have been offered to household members of immunocompromised persons. See above and 3.3.3 *Vaccination of immunocompromised persons*.	Household members are the most likely sources of vaccine-preventable diseases among immunocompromised persons (who often are unable to be vaccinated, especially with live viral vaccines).
Is planning travel	See 3.2 *Vaccination for international travel*	Travellers may be at increased risk of certain vaccine-preventable diseases.
Has certain occupation or lifestyle factors	See 3.3 *Groups with special vaccination requirements*, and 'Catch-up schedules for persons ≥10 years of age' in 2.1.5 *Catch-up* below.	Workers in certain occupations (e.g. healthcare workers and persons working in early childhood education and care), and those with certain lifestyle factors (e.g. persons who inject drugs) may be at increased risk of certain vaccine-preventable diseases.

* Live attenuated vaccines are classified in Table 2.1.3 below.
† See 4.9 *Measles*, 4.11 *Mumps* or 4.18 *Rubella* for further information.
‡ See 4.2 *Diphtheria*, 4.12 *Pertussis* or 4.19 *Tetanus* for further information.

Table 2.1.3: Live attenuated parenteral and oral vaccines

Live attenuated parenteral vaccines		Live attenuated oral vaccines	
Viral	Bacterial	Viral	Bacterial
Japanese encephalitis (Imojev) Measles-mumps-rubella (MMR) Measles-mumps-rubella-varicella (MMRV) Varicella Yellow fever Zoster	BCG	Oral rotavirus vaccine	Oral typhoid vaccine

Contraindications to vaccination

There are only two absolute contraindications applicable to *all* vaccines:

- anaphylaxis following a previous dose of the relevant vaccine
- anaphylaxis following any component of the relevant vaccine.

There are two further contraindications applicable to live (both parenteral and oral) vaccines:

- Live vaccines (see Table 2.1.3) should not be administered to persons who are significantly immunocompromised, regardless of whether the immunocompromise is caused by disease or treatment. The exception is that, with further advice, MMR, varicella and zoster vaccines can be administered to HIV-infected persons in whom immunocompromise is mild. (See 3.3.3 *Vaccination of immunocompromised persons*, and individual disease-specific chapters.)
- In general, live vaccines should not be administered during pregnancy, and women should be advised not to become pregnant within 28 days of receiving a live vaccine (see Table 3.3.1 *Recommendations for vaccination in pregnancy* in 3.3 *Groups with special vaccination requirements*).

False contraindications to vaccination

No-one should be denied the benefits of vaccination by withholding vaccines for inappropriate reasons.

Conditions listed in Table 2.1.4 below are *not* contraindications to vaccination. Persons with these conditions should be vaccinated with all recommended vaccines.

Table 2.1.4: False contraindications to vaccination

The following conditions are *not* contraindications to any of the vaccines in the National Immunisation Program schedule:

- mild illness without fever (T <38.5ºC)
- family history of any adverse events following immunisation
- past history of convulsions
- treatment with antibiotics
- treatment with locally acting (inhaled or low-dose topical) steroids
- replacement corticosteroids
- asthma, eczema, atopy, hay fever or 'snuffles'
- previous pertussis-like illness, measles, rubella, mumps, varicella, herpes zoster or meningococcal disease
- prematurity (vaccination should not be postponed and can be given if the infant is medically stable). See also 3.3.2 *Vaccination of women who are planning pregnancy, pregnant or breastfeeding, and preterm infants*.
- history of neonatal jaundice
- low weight in an otherwise healthy child
- neurological conditions, including cerebral palsy and Down syndrome
- contact with an infectious disease
- child's mother is pregnant
- child to be vaccinated is being breastfed
- woman to be vaccinated is breastfeeding
- recent or imminent surgery (see also 3.3.6 *Vaccination before or after anaesthesia/surgery*)
- poorly documented vaccination history.

2.1.5 Catch-up

Every opportunity should be taken to review a person's vaccination history and to administer the appropriate vaccine(s). If the person has not had documented receipt of vaccines scheduled in the NIP appropriate for his/her age, plan and document a catch-up schedule and discuss this with the person to be vaccinated or their parent/carer. The assessment of vaccination status should be based on the schedule for the state or territory in which the person to be vaccinated is residing.

The objective of catch-up vaccination is to complete a course of vaccination and provide optimal protection as quickly as possible. The information and tables below will assist in planning a catch-up schedule.

An online 'catch-up calculator' for NIP vaccines is hosted by South Australia Health (at immunisationcalculator.sahealth.sa.gov.au) and is available to assist in determining appropriate catch-up schedules for children ≤7 years of age across Australia. When using such resources, also check the accuracy of information provided by referring to your current state/territory immunisation schedule and the current edition of the *Handbook*.

If still uncertain about how to plan the catch-up schedule, or for more complicated catch-up scenarios, seek further advice (see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*).

For recently arrived migrants, the World Health Organization website (www.who.int/countries/en) lists immunisation schedules provided by other countries, which may supplement information regarding which vaccines a child/adult arriving from overseas may have received (see also 3.3.8 *Vaccination of migrants to Australia*).

Confirmation of vaccination history

The most important requirement for assessment of vaccination status is to have written documentation of vaccination. The approach of immunisation service providers to the problem of inadequate records should be based on the age of the person to be vaccinated, whether previous vaccines have been given in Australia or overseas, and the vaccines being considered for catch-up.

Detailed information on the vaccine registers used in Australia and how to obtain vaccination records is provided in 2.3.4 *Immunisation registers*, but is also described briefly below.

Children <7 years of age

The Australian Childhood Immunisation Register (ACIR) commenced on 1 January 1996 and holds records of all vaccinations given since then to children (between birth and their 7th birthday). Details of a child's immunisation history can be obtained via the ACIR Enquiry Line (1800 653 809) or website (www.humanservices.gov.au/customer/services/medicare/australian-childhood-immunisation-register). If a child's parent/carer states that vaccines not recorded on the ACIR have been given, every effort should be made to contact the relevant immunisation service provider. If confirmation from the nominated provider or the ACIR cannot be obtained, and no written records are available, the vaccines should be considered as not received, and the child should be offered catch-up vaccination appropriate for their age.

Older children and adolescents <18 years of age

No vaccination information is recorded on the ACIR after a child turns 7 years of age, but any information already held is retained. The information will relate only to vaccines received between birth and the 7th birthday. Records held for

a person who is now ≥7 years of age can be made available to an immunisation service provider or parent/carer.

The National HPV Vaccination Program Register (NHVPR, also referred to as the 'HPV Register') holds details of human papillomavirus (HPV) vaccinations reported to the Register since the commencement of the HPV Vaccination Program in April 2007. The NHVPR initially only recorded vaccinations for females, but from 2013 will also record vaccinations given to males. Details of HPV vaccinations held by the NHVPR can be obtained by phoning the Register on 1800 478 734 (1800 HPV REG). (See also 2.3.4 *Immunisation registers*.)

In older children and adolescents, alternative sources of documentation (such as personal health records) will be needed, but are less likely to be available with increasing age. Persons who do not have personal vaccination records may seek evidence of past vaccination from their parents, their past and present healthcare providers or immunisation service providers. Those born after 1990 may have some vaccinations recorded on the ACIR (see 2.3.4 *Immunisation registers*).

Information on how to obtain records of vaccines received through school-based vaccination programs can be obtained from state and territory government health departments (see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*).

Adults (≥18 years of age)

In adults, patient-held and/or provider-held documentation of previous vaccination history may not be available. In some cases, information may be available from other sources, such as the National HPV Vaccination Program Register and the Australian Q Fever Register. (See also 2.3.4 *Immunisation registers*.)

Incomplete documentation of prior vaccination

If receipt of prior vaccination cannot be confirmed via the above methods, it should generally be assumed that the vaccine(s) required have not been given previously. All efforts should be made to confirm and ensure appropriate documentation of prior receipt of vaccines.

For most vaccines (except Q fever), there are no adverse events associated with additional doses if given to an already immune person. In the case of diphtheria-, tetanus- and pertussis-containing vaccines and pneumococcal polysaccharide vaccines, frequent additional doses may be associated with an increase in local adverse events; however, the benefits of protection may outweigh the risk of an adverse reaction, for example, protection against pertussis from a booster dose of dTpa. (See also 4.2 *Diphtheria*, 4.12 *Pertussis*, 4.13 *Pneumococcal disease* or 4.19 *Tetanus*.) Additional doses of MMR, varicella, inactivated poliomyelitis (IPV) or hepatitis B vaccines are rarely associated with significant adverse events.

Use of serological testing to guide catch-up vaccination

In some instances, serological testing for immunity from prior vaccination and/or infection may be useful to guide the need for catch-up vaccination, such as for measles, hepatitis B and rubella. However, it is important to note that serological testing is not reliable for vaccine-induced immunity in all instances and is specifically *not* recommended to be used to guide the need for catch-up vaccination for certain diseases/vaccines (e.g. pertussis, pneumococcal disease and meningococcal disease). In most circumstances, and for most vaccines, it is more practical to offer vaccination, rather than serological testing. See also recommendations regarding serological testing before and after vaccination in various disease chapters (4.4 *Hepatitis A*, 4.5 *Hepatitis B*, 4.9 *Measles*, 4.11 *Mumps*, 4.18 *Rubella*, 4.22 *Varicella*, 4.24 *Zoster*).

Interpretation of the results of serological testing may be enhanced by discussion with the laboratory that performed the test, ensuring that relevant clinical information is provided.

Determining when a vaccine dose is valid according to age and interval since last dose

A 'valid' vaccine dose is a dose that is considered immunogenic (and safe) given the age and health status of the recipient and the interval since the recipient's last dose of the same vaccine. For children who are vaccinated at an age younger than that routinely recommended, or for children and adults in whom the interval between vaccine doses is shorter than the usual recommended interval, information regarding both the minimum acceptable age for the 1st dose of an infant vaccine (Table 2.1.5) and the minimum acceptable intervals between vaccine doses (Tables 2.1.7 to 2.1.12) can be used to determine whether additional vaccine doses and/or catch-up vaccination is required. For more details see the following sections.

Planning catch-up vaccination

This and the following two sections are dedicated to planning catch-up vaccination. In the following two sections information is presented by age of the vaccine recipient (children aged <10 years and persons aged ≥10 years). A number of tables and figures are provided to help plan a catch-up schedule:

- Figure 2.1.1 is a worksheet for calculating and recording which vaccines are required in children aged <10 years, the number of doses outstanding and the timing of these doses (see 'Using the catch-up worksheet (Figure 2.1.1) for children <10 years of age' below).
- Table 2.1.5 lists the minimum acceptable ages for the 1st dose of scheduled vaccines in infants.

- Table 2.1.6 can be used to assess the number of doses a child should have received if they were on schedule. Check under the current age of the child to see how many doses they should have already received and use that number of doses as the starting point for calculating a catch-up schedule. For example, a child who is 18 months old now should have received 3 doses of DTPa, 3 doses of IPV, etc.
- Table 2.1.7 lists the minimum acceptable interval between doses under special circumstances, such as catch-up vaccination. Vaccine doses should not be administered at less than the acceptable minimum interval.[16] In the majority of instances, doses administered earlier than the minimum acceptable interval should not be considered as valid doses and should be repeated, as appropriate, using Table 2.1.6.
- Tables 2.1.8 to 2.1.11 are for calculating catch-up for *Haemophilus influenzae* type b (Hib) and pneumococcal vaccination of children.
- Table 2.1.12 can be used to calculate a catch-up schedule for persons aged ≥10 years.

In addition, the following principles should generally be applied when planning catch-up vaccination:

- When commencing the catch-up schedule, the standard scheduled interval between doses may be reduced or extended, and the numbers of doses required may reduce with age. For example, from 16 months of age, only 1 dose of (any) Hib vaccine is required.
- As a child gets older, the recommended number of vaccine doses may change (or even be omitted from the schedule), as the child becomes less vulnerable to specific diseases.
- For incomplete or overdue vaccinations, build on the previous documented doses. In almost every circumstance, it is advisable to not start the schedule again, regardless of the interval since the last dose, but to count previous doses. One exception to this rule is for oral cholera vaccine (see 4.1 *Cholera*).
- If more than one vaccine is overdue, 1 dose of each due or overdue vaccine should be given at the first catch-up visit. Further required doses should be scheduled after the appropriate minimum interval (see Table 2.1.7).
- A catch-up schedule may require multiple vaccinations at a visit. Give all the due vaccines at the *same* visit – do not defer. See 2.2.9 *Administering multiple vaccine injections at the same visit*.
- The standard intervals and ages recommended in the NIP schedule should be used once the child or adult is up to date with the schedule.
- Some persons will require further doses of antigens that are available only in combination vaccines. In general, the use of the combination vaccine(s) is acceptable, even if this means the number of doses of another antigen administered exceeds the required number.

- For some vaccines, catch-up vaccination is not recommended. For example, rotavirus vaccination is not recommended if the 1st (and subsequent) vaccine doses are not able to be provided within the prescribed upper age limits (see 'Catch-up guidelines for individual vaccines for children <10 years of age' below).

Using the catch-up worksheet (Figure 2.1.1) for children <10 years of age

A catch-up schedule for a child <10 years of age should be planned by taking into account the guidelines above in conjunction with the catch-up tables (listed above). The catch-up worksheet (Figure 2.1.1) provides a method of recording these steps.

To use the catch-up worksheet:

1. Record the child's details, including date of birth and current age in the top left corner of the worksheet.
2. For each vaccine, determine how many doses have been received and the date that the last dose was given. Record this in the 'Last dose given' column of the worksheet. If documentation is adequate, include previous vaccinations given in another country (receipt of these vaccines should be entered onto the ACIR for a child <7 years of age – see 2.3.4 *Immunisation registers*).
3. Refer to Table 2.1.6 to check how many doses of each vaccine are required for the child's current age. Enter this number in the 'Number of doses required at current age' column of the worksheet.
4. Assess other factors that may affect the type or number of vaccines required. These should have been ascertained during pre-vaccination screening (see 2.1.4 *Pre-vaccination screening* above, the pre-vaccination screening check list [Table 2.1.1] and table of responses [Table 2.1.2]) and may include:
   - » anaphylaxis to any vaccine or one of its components (that vaccine is contraindicated)
   - » immunocompromise due to disease or treatment (see 3.3 Groups with special vaccination requirements)
   - » children identifying as Aboriginal or Torres Strait Islander (see 3.1 Vaccination for Aboriginal and Torres Strait Islander people)
   - » children with underlying medical risk condition(s) that predisposes them to invasive pneumococcal disease (see 4.13 Pneumococcal disease)
   - » preterm infants born at <32 weeks gestation (see 'Hepatitis B vaccine' and 'Pneumococcal conjugate vaccines (13vPCV and 10vPCV)' in 'Catch-up guidelines for individual vaccines for children <10 years of age' below).

   Record any factors that affect the schedule in the 'Comments' column beside the relevant vaccine.

5. If any variations to the schedule are necessary due to recorded factors (e.g. a child who is immunocompromised may require different vaccines), adjust the 'number of doses required' accordingly.
6. For each vaccine, compare the number of doses received, as recorded in the 'Last dose given' column, with the number of doses required for the child's current age.
7. If the child has already received the number of doses required for a particular vaccine, cross through the relevant 'Dose number due now' and 'Further doses' columns. Ensure that the minimum acceptable interval has been observed for all doses previously received, particularly if the child commenced their vaccination program overseas.
8. If the number of doses received, as recorded in the 'Last dose given' column, is less than the number of doses required, administer a dose of the relevant vaccine now, and record this in the 'Dose number due now' column. If this dose still does not complete the required doses, enter the further dose numbers in the 'Further doses' column.
9. To schedule the next dose at the most appropriate time (usually at the earliest opportunity), refer to Table 2.1.7 for the minimum acceptable interval required between doses. Record when the next dose is due in the 'Further doses' column.
10. Convert this information into a list of proposed appointment dates, detailing vaccines and dose number needed at each visit on the 'Catch-up appointments' section of the worksheet.
11. Record this catch-up schedule in your provider records and provide a copy to the child's parent/carer.
12. Once a child has received relevant catch-up vaccines, give the remaining scheduled vaccines as per the recommended NIP schedule. For example, for a 12-month-old child who is brought up to date with all vaccines including the 12-month vaccinations, the 2nd dose of MMR-containing vaccine should be given at 18 months of age, not 4 weeks after the last received dose.

Figure 2.1.1: Catch-up worksheet for children <10 years of age for NIP vaccines

This worksheet can be used in conjunction with Tables 2.1.6 and 2.1.7.

CATCH-UP WORKSHEET					
Name: ***DOB:*** ***Age:***	***Last dose given*** ***Dose number and date***	***Number of doses required at current age****	***Dose number due now***	***Further doses*** ***Interval or date***	***Comments***
DTPa					
Poliomyelitis (IPV)					
Hepatitis A					
Hepatitis B					
Hib†					
Pneumococcal (13vPCV)‡§					
Pneumococcal (23vPPV)‡					
MenCCV					
MMR					
Rotavirus					DO NOT give after upper age limits for each dose. See 4.17 *Rotavirus*, Table 4.17.1.
Varicella					

CATCH-UP APPOINTMENTS			
Date	***Vaccines and dose number***	***Interval to next dose***	***Comments***

* Refer to Table 2.1.6 *Number of vaccine doses that should have been administered by the current age of the child* and Table 2.1.7 *Minimum acceptable dose intervals for children <10 years of age.*
† See Table 2.1.8 for Hib vaccine catch-up recommendations.
‡ See Tables 2.1.9, 2.1.10 and 2.1.11 for pneumococcal vaccine catch-up recommendations.
§ Previous doses of pneumococcal conjugate vaccine may have been given using 7-valent (7vPCV) or 10-valent (10vPCV) vaccine(s).

Table 2.1.5: Minimum acceptable age for the 1st dose of scheduled vaccines in infants in special circumstances*

Vaccine	Minimum age for 1st dose in special circumstances*	Action if a vaccine dose is inadvertently administered prior to the recommended minimum age[17]
DTPa	6 weeks	If the 1st dose of DTPa-containing vaccine was administered at ≤28 days of age, it is recommended that the dose is repeated. This repeat dose should be given at 2 months of age. The NIP schedule should be followed thereafter, with the next dose of DTPa-containing vaccine given at 4 months of age.†‡ If the 1st dose of DTPa-containing vaccine was administered between >28 days and <42 days (6 weeks) of age, it does not necessarily need to be repeated. Limited data suggest that administration at this age will still be safe and immunogenic. The NIP schedule should be followed thereafter, with the next dose of DTPa-containing vaccine given at 4 months of age.†
Poliomyelitis (IPV)	6 weeks	See DTPa-containing vaccines above.
Hib	6 weeks	See DTPa-containing vaccines above.
Hepatitis B§	6 weeks§ (*Note*: this excludes birth dose of hepatitis B vaccine)§	See DTPa-containing vaccines above.
Pneumococcal (13vPCV or 10vPCV)	6 weeks	If the 1st dose of PCV was administered at ≤28 days of age, it is recommended that the dose is repeated. This repeat dose should be given at 2 months of age. The NIP schedule should be followed thereafter, with the next dose of PCV given at 4 months of age.† If the 1st dose of PCV was administered between >28 days and <42 days (6 weeks) of age, it does not necessarily need to be repeated. Limited data suggest that administration at this age will still be safe and immunogenic. The NIP schedule should be followed thereafter, with the next dose of PCV given at 4 months of age.†

Vaccine	Minimum age for 1st dose in special circumstances*	Action if a vaccine dose is inadvertently administered prior to the recommended minimum age[17]
Rotavirus	6 weeks	If the 1st dose of rotavirus vaccine was administered at ≤28 days of age, it is recommended that the dose is repeated. This repeat dose should be given at 2 months of age. The NIP schedule should be followed thereafter, with the next dose of rotavirus vaccine given at 4 months of age. If the 1st dose of rotavirus vaccine was administered between >28 days and <42 days (6 weeks) of age, it does not necessarily need to be repeated. Limited data suggest that administration at this age will still be safe and immunogenic. The NIP schedule should be followed thereafter, with the next dose of rotavirus vaccine given at 4 months of age. For all doses of rotavirus vaccine it is important to ensure the upper age limits for dose administration are not exceeded (see 4.17 *Rotavirus*, Table 4.17.1).
MenCCV	6 weeks	If any MenCCV doses are given before 12 months of age, then a booster dose of MenCCV should be given at 12 months of age or 8 weeks after the last dose, whichever is later. *Note*: MenCCV is routinely recommended at 12 months of age, although recommendations for children at increased risk of meningococcal disease differ (see 4.10 *Meningococcal disease*).
Hepatitis A (Indigenous children in NT, Qld, SA and WA only)	12 months	If the 1st dose of hepatitis A vaccine is administered at <12 months of age, and ongoing protection against hepatitis A is required, the 1st dose should be repeated.
MMR¶	12 months	MMR vaccine may be given from 9 months of age, in certain circumstances, such as for post-exposure prophylaxis for measles (see 4.9 *Measles*), but it is recommended that the 1st dose be repeated if it was given at <12 months of age.# See note on MMRV below.¶
Varicella**	12 months	If a varicella-containing vaccine is administered at <12 months of age, the dose should be repeated, preferably at 18 months of age. See note on MMRV below.¶

* Special circumstances may include infants/children being vaccinated during an outbreak of a certain disease, before overseas travel, or opportunistic vaccination following early attendance to a provider. These ages *will often* differ from routinely recommended ages of administration under the NIP schedule. In some instances, these ages will also result in the dose not being considered by the Australian Childhood Immunisation Register (ACIR) as 'valid' for the purpose of calculating immunisation status. If the ACIR age requirement differs from the minimum ages in this table, this is noted.

† If the need to repeat the 1st dose of vaccine is not recognised until the infant is older (e.g. a 4-month-old infant presents for vaccination and has only previously received 1 dose of DTPa-hepB-IPV-Hib or 13vPCV vaccines both at age ≤28 days), repeat these vaccines now (and count these as dose 1), then proceed with subsequent schedule as per NIP and/or catch-up recommendations for these vaccines described in this chapter.

‡ The minimum age from which the combination vaccine DTPa-hepB-IPV-Hib (or the antigens contained within it) is considered a valid dose on the ACIR is 1 month (>28 days) of age.[17]

§ Monovalent hepatitis B vaccine should be given at birth (up to 7 days of age). However, for subsequent doses where hepatitis B-containing combination vaccine is given at 2, 4 and 6 months of age, the minimum age for the 1st dose (scheduled at age 2 months) is 6 weeks of age. If an infant has not received a birth dose within the first 7 days of life, a primary 3-dose course of a hepatitis B-containing combination vaccine should be given at 2, 4 and 6 months of age; catch-up of the birth dose is not necessary.

¶ MMRV vaccine is recommended as the 2nd (not 1st) dose of MMR-containing vaccine in children <4 years of age. However, if MMRV has been inadvertently given as the 1st dose of MMR-containing vaccine, that MMR-containing dose does not need to be repeated, unless it was provided at <12 months of age (as per MMR and monovalent varicella vaccines).

Note: The ACIR will record MMR vaccine given at ≥11 months of age as a valid dose, for purposes of calculating immunisation status. There is some evidence that a dose provided at ≥11 months (but before 12 months) of age is sufficiently immunogenic, especially in infants born to mothers with measles antibody derived from vaccination rather than natural infection. As such, doses given in this timeframe may not need to be repeated in all circumstances.[17]

** One monovalent varicella vaccine, Varilrix, is registered for use from 9 months of age, and can be provided from ≥9 months of age in special circumstances, for example, prior to travel. However, if a dose has been provided at <12 months of age, it should be repeated.

Table 2.1.6: Number of vaccine doses that should have been administered by the current age of the child

This table can be used in conjunction with Figure 2.1.1 Catch-up worksheet for children <10 years of age for NIP vaccines.

Vaccine	Current age						
	0 to <2 months	2 to <4 months	4 to <6 months	6 to <12 months	12 to 18 months	>18 months to <4 years	4 years to <10 years
DTPa*		1	2	3	3	3	4
Poliomyelitis (IPV)		1	2	3	3	3	4†
Hepatitis A‡					1‡	2‡	2‡
Hepatitis B§		1	2	3	3	3	3
Hib	Complex – see Table 2.1.8 for Hib vaccine catch-up						
Pneumococcal (13vPCV and 23vPPV)	Complex – see Tables 2.1.9, 2.1.10 and 2.1.11 for pneumococcal vaccine catch-up						
MenCCV					1	1	1
MMR¶					1	2¶	2¶
Rotavirus#	There are specific age limits as per 4.17 *Rotavirus*, Table 4.17.1			NO CATCH-UP			
Varicella¶						1¶	1¶

* Some children may have received 4 doses of DTP by 18 months of age, especially if arrived from overseas. These children will require a 5th dose of DTPa at 4 years of age.

† If the 3rd dose of IPV is given after 4 years of age, a 4th dose is not required. However, if using a combination vaccine it is acceptable to give a 4th dose.

‡ Indigenous children resident in the Northern Territory, Queensland, South Australia and Western Australia only. Dependent on jurisdiction, the 1st dose is given at 12–18 months of age, followed by the 2nd dose 6 months later at 18–24 months of age. Consult relevant state/territory health authorities for advice regarding catch-up in children >2 years of age.

§ A birth dose of monovalent hepatitis B vaccine is recommended for all infants; however, if this was not given, a catch-up birth dose is not necessary. Where the birth dose was given, in the usual circumstances where hepatitis B-containing combination vaccines for children are used for catch-up, a further 3 doses of hepatitis B-containing vaccine are required. In the unusual circumstance where a child requires catch-up only for hepatitis B vaccination, the standard monovalent hepatitis B vaccination schedule of 0, 1, 6 months can be adopted to work out the remaining number of doses required and intervals of the catch-up schedule (see 4.5 *Hepatitis B*).

¶ MMRV can be given as the 2nd dose of MMR-containing vaccine where both MMR and varicella are required (see 4.9 *Measles* and 4.22 *Varicella*).

There is *no catch-up* for rotavirus vaccine (see 4.17 *Rotavirus*).

Table 2.1.7: Minimum acceptable dose intervals for children <10 years of age

This table can be used in conjunction with Figure 2.1.1 Catch-up worksheet for children <10 years of age for NIP vaccines and Table 2.1.6 Number of vaccine doses that should have been administered by the current age of the child.

Note: These are *not* the routinely recommended intervals between vaccine doses. These minimum intervals are only to be used under special circumstances, such as when catch-up vaccination is required until a child is back on schedule for their age. These intervals may differ from the routinely recommended intervals between doses under the NIP schedule.

Vaccine		Minimum interval between dose 1 and 2	Minimum interval between dose 2 and 3	Minimum interval between dose 3 and 4
DTPa*		4 weeks	4 weeks	6 months
Poliomyelitis (IPV)		4 weeks	4 weeks	4 weeks†
Hepatitis A‡		6 months		
Hepatitis B§		1 month§	2 months§	
Hib		See Table 2.1.8 for Hib vaccine catch-up		
Pneumococcal (13vPCV and 23vPPV)		See Tables 2.1.9, 2.1.10 and 2.1.11 for pneumococcal vaccine catch-up		
MenCCV¶				
MMR#		4 weeks		
Rotavirus**	Rotarix	4 weeks		
	RotaTeq	4 weeks	4 weeks	
Varicella#††		4 weeks		

* If DTPa is only available in combination with other antigens (e.g. DTPa-IPV or DTPa-hepB-IPV-Hib), these formulations can be used where necessary for primary course or catch-up doses in children <10 years of age.

† If the 3rd dose of IPV is given after 4 years of age, a 4th dose is not required. However, if using a combination vaccine, it is acceptable to give a 4th dose.

‡ Indigenous children resident in the Northern Territory, Queensland, South Australia and Western Australia only.

§ This excludes the birth dose. The minimum interval between the birth dose (which can be regarded as dose 0 [zero] for the purposes of this table) and the next hepatitis B-containing dose (usually given as DTPa-hepB-IPV-Hib at 2 months of age) is 4 weeks. For the 3 hepatitis B-containing doses (usually given as DTPa-hepB-IPV-Hib at 2, 4 and 6 months of age) the minimum intervals in this table apply. The minimum interval required between dose 1 and dose 3 is 4 months and the minimum age for administration of dose 3 is 24 weeks (see 4.5 *Hepatitis B*).

¶ The routine schedule is a single dose given at 12 months of age. Alternative schedules are available for children <12 months of age (see 4.10 *Meningococcal disease*).

MMR is recommended as the 1st dose of MMR-containing vaccine in children <4 years of age (see 4.9 *Measles*). MMRV is recommended to be given as the 2nd dose of MMR-containing vaccine. MMRV can be given 4 weeks following the 1st catch-up dose of MMR vaccine or as catch-up for the 2nd dose of MMR where varicella is also required.

** Refer to 4.17 *Rotavirus*, Table 4.17.1 for upper age limits for administration of rotavirus vaccines. Catch-up is *not* recommended.

†† Two doses of varicella-containing vaccine are not routinely recommended in children <14 years of age; however, a 2nd dose can be provided to offer increased protection against varicella (see 4.22 *Varicella*).

Catch-up guidelines for individual vaccines for children <10 years of age

DTPa vaccine

Monovalent pertussis vaccine is not available in Australia. If a child has received previous doses of diphtheria-tetanus (DT) vaccines and requires pertussis catch-up, then DTPa or DTPa-combination vaccines can be used, provided that no more than 6 doses of diphtheria and tetanus toxoids are given before the 10th birthday (see 4.12 *Pertussis*).

If a DTPa-hepatitis B-containing combination vaccine is used, there should be a *minimum interval* of 8 weeks between doses 2 and 3, as per the minimum interval requirements for the hepatitis B vaccine.

Hepatitis B vaccine

The birth dose hepatitis B vaccine is only scheduled for infants up to 7 days of age. If this dose was not given, a catch-up birth dose is not necessary. Where the birth dose was given, and where hepatitis B-containing combination vaccines for children are used (for routine vaccination or for catch-up), a further 3 doses of hepatitis B-containing vaccine are required (see 4.5 *Hepatitis B*).

In the unusual circumstance where a child requires catch-up vaccination only for hepatitis B, but not any other components in the hepatitis B-containing combination vaccines, the standard monovalent hepatitis B vaccination schedule of 0, 1, 6 months can be used for the remaining dose(s) if required (see 4.5 *Hepatitis B*).

In preterm (<32 weeks gestation) or low-birth-weight infants (<2000 g birth weight) it is recommended to give hepatitis B vaccine at birth, 2, 4 and 6 months of age, followed by either serological testing for anti-HBs or a booster at 12 months of age. For details, see 3.3.2 *Vaccination of women who are planning pregnancy, pregnant or breastfeeding, and preterm infants* and 4.5 *Hepatitis B*.

Hib vaccine

The recommended number of doses and intervals for Hib vaccines vary with the vaccine type and age of the child. For catch-up recommendations see Table 2.1.8.

PRP-OMP is the Hib formulation contained in Liquid PedvaxHIB. PRP-T is the Hib formulation contained in the other Hib-containing vaccines: Act-HIB, Hiberix, Infanrix hexa, Menitorix and Pediacel. Where possible, the same brand of Hib-containing vaccine should be used for all primary doses. If different Hib vaccines (i.e. PRP-OMP and PRP-T vaccines) are used in the primary series, then 3 doses (of any Hib vaccine) are required for the primary series, at 2, 4 and 6 months of age, with a booster of a Hib-containing vaccine at 12 months of age.

For extremely preterm and/or low-birth-weight infants (<28 weeks gestation or <1500 g birth weight), 4 doses of a Hib-containing vaccine (irrespective of the brand used) should be given, at 2, 4, 6 and 12 months of age (see 3.3.2 *Vaccination of women who are planning pregnancy, pregnant or breastfeeding, and preterm infants*).

See also 4.3 *Haemophilus influenzae type b*.

MMR vaccine, MMRV vaccine and varicella vaccine

If no previous documented doses have been given, catch-up for MMR vaccine consists of 2 doses of MMR-containing vaccine, given at least 4 weeks apart (see 4.9 *Measles*). If no previous documented varicella vaccination has been given, a single dose of varicella-containing vaccine is recommended in children aged <14 years (see 4.22 *Varicella*).

If a child receives varicella vaccine at <12 months of age, a further dose should be given at 18 months of age. In this circumstance MMRV vaccine may be given where the 2nd dose of MMR vaccine and a dose of varicella vaccine are both required (see below and 4.22 *Varicella*).

MMRV vaccines should only be administered as the 2nd dose of MMR-containing vaccine in children <4 years of age. If no previous doses of MMR vaccine have been administered in a child aged >12 months and <4 years, MMR vaccine should be administered as the 1st dose and then MMRV vaccine can be administered 4 weeks later as the 2nd dose of MMR-containing vaccine. MMRV can be used as the 1st dose of MMR-containing vaccine in children ≥4 years of age, up to age 14 years (see 4.9 *Measles* and 4.22 *Varicella*).

Meningococcal C conjugate vaccine

Meningococcal C conjugate vaccine (MenCCV) is recommended on the NIP as a single dose for children at 12 months of age. If no dose was received at ≥12 months of age (or if dose(s) were received at <12 months of age), a single dose of any meningococcal conjugate vaccine is recommended (see 4.10 *Meningococcal disease*). Additional MenCCV doses and 4vMenCV doses are recommended for certain children at increased risk of meningococcal disease (see 'Persons with functional or anatomical asplenia' in 3.3.3 *Vaccination of immunocompromised persons*, and 4.10 *Meningococcal disease*).

Menitorix (combined Hib-MenCCV) can be administered when a booster dose of *Haemophilus influenzae* type b (Hib) and primary vaccination for meningococcal C is required (see 4.3 *Haemophilus influenzae type b* and 4.10 *Meningococcal disease*).

Pneumococcal conjugate vaccines (13vPCV and 10vPCV)

The number of doses and recommended intervals of 13vPCV required for catch-up vaccination vary with the age of the child, their health and Indigenous status, and the state or territory of residence (see Tables 2.1.9, 2.1.10 and 2.1.11 below).

Table 2.1.9 is for children who are not at increased risk of invasive pneumococcal disease (IPD) (including Indigenous children living in the Australian Capital Territory, New South Wales, Victoria and Tasmania). Table 2.1.10 is for Indigenous children residing in the Northern Territory, Queensland, South Australia and Western Australia. Table 2.1.11 provides catch-up details for children with a medical condition(s) associated with an increased risk of IPD. (See also 4.13 *Pneumococcal disease*.)

If 13vPCV is not available, and 10vPCV is being used, 10vPCV is recommended in a 4-dose schedule. (See also 4.13 *Pneumococcal disease*.) If catch-up is required for 10vPCV, vaccination can be done according to the information provided in Table 2.1.10.

Children aged ≥5 years who are not at increased risk of invasive pneumococcal disease (including Indigenous children aged ≥5 years) do *not* require catch-up doses of PCV.

Preterm infants born at <28 weeks gestation should receive extra doses of pneumococcal vaccines, in accordance with the schedule for those at increased risk of IPD (see 4.13 *Pneumococcal disease* and 3.3.2 *Vaccination of women who are planning pregnancy, pregnant or breastfeeding, and preterm infants*).

Poliomyelitis vaccine

If no previous doses of poliomyelitis vaccine have been given, give 3 doses of IPV or IPV-containing vaccines at least 4 weeks apart (see 4.14 *Poliomyelitis*). (Previous doses of OPV are interchangeable with IPV.)

If the 3rd dose of IPV is administered before 4 years of age, give the 4th (booster) dose at either the 4th birthday or 4 weeks after the 3rd dose, whichever is later. If the 3rd dose is given after the 4th birthday, a 4th dose is not required. However, if the use of combination vaccines is necessary, a further IPV-containing dose may be given.

Rotavirus vaccine

Catch-up rotavirus vaccination of older infants or children is *not* recommended. Infants should commence the course of rotavirus vaccination within the recommended age limits for the 1st dose; that is, the 1st dose of RotaTeq should be given between 6 and 12 weeks of age (i.e. before turning 13 weeks old), and the 1st dose of Rotarix should be given between 6 and 14 weeks of age (i.e. before turning 15 weeks old). It is recommended that vaccine doses are not given beyond the upper age limits specified in Table 4.17.1 (see 4.17 *Rotavirus*).

Table 2.1.8: Catch-up schedule for *Haemophilus influenzae* type b (Hib) vaccination for children <5 years of age*

Number of Hib doses given previously	Current age	Age when previous dose(s) of Hib vaccine given			Recommendations	
		1st dose	2nd dose	3rd dose	Number of further primary dose(s) required†	Number of booster doses required at age ≥12 months‡
No previous doses	<7 months	–	–	–	3§	1
	7–11 months	–	–	–	2	1
	12–15 months	–	–	–	1	1
	16–59 months	–	–	–	1	Not needed¶
1 previous dose	<7 months	<7 months	–	–	2§	1
	7–11 months	<7 months	–	–	2§	1
		7–11 months	–	–	1	1
	12–15 months	<12 months	–	–	1	1
		≥12 months	–	–	Not needed	1
	16–59 months	<16 months	–	–	Not needed	1
		≥16 months	–	–	Not needed	Not needed¶
2 previous doses	<12 months	<7 months	<12 months	–	1§	1
		7–11 months	7–11 months	–	Not needed	1
	12–59 months	<7 months	<12 months	–	1§	1
			12–15 months	–	Not needed	1
		7–11 months	7–15 months	–	Not needed	1
		12–15 months	12–15 months	–	Not needed	Not needed
		Any age	≥16 months	–	Not needed	Not needed¶

Number of Hib doses given previously	Current age	Age when previous dose(s) of Hib vaccine given			Recommendations	
		1st dose	2nd dose	3rd dose	Number of further primary dose(s) required †	Number of booster doses required at age ≥12 months‡
3 previous doses	7–11 months	Any age	Any age	Any age	Not needed	1
	12–59 months	<7 months	<12 months	<12 months	Not needed	1
				12–15 months	Not needed	1#
			12–15 months	12–15 months	Not needed	Not needed
		7–11 months	7–15 months	12–15 months	Not needed	Not needed
		Any age	Any age	≥16 months	Not needed	Not needed¶

* Recommendations for vaccination of haematopoietic stem cell transplant (HSCT) recipients differ; see Table 3.3.3 *Recommendations for revaccination following haematopoietic stem cell transplant (HSCT) in children and adults, irrespective of previous immunisation history*.

† This column lists the number of further primary doses that should be scheduled for the child, based on their current age. The recommended interval between primary doses for catch-up is 1 month. Where possible, it is recommended to schedule the required remaining primary doses to be given prior to 12 months of age. If there are further delays in the scheduled catch-up primary dose(s), the number of doses required should be checked again against the child's age at each presentation.

‡ This column lists the number of booster doses that should be scheduled for the child, based on their current age. Booster doses are to be given at age 12 months or 2 months after the last dose of Hib vaccine, whichever is later.

§ One less dose is required if PRP-OMP is to be used for the entire primary course, or if PRP-OMP has already been given for all previous doses. If PRP-T has been given as one or more of the doses in the primary course, plan for the number of doses as specified in this table. PRP-OMP is the Hib formulation contained in Liquid PedvaxHIB. PRP-T is the Hib formulation contained in the other Hib-containing vaccines: ACT-Hib, Hiberix, Infanrix hexa, Menitorix and Pediacel.

¶ A booster dose is not needed if the last previous dose was given at ≥16 months of age.

This booster dose is not required if PRP-OMP was used for both the 1st and the 2nd (primary) doses of Hib vaccine in infancy, since the 3rd dose of Hib vaccine received at age 12–15 months would have served as the booster dose for these children.

Table 2.1.9: Catch-up schedule for 13vPCV (Prevenar 13) for non-Indigenous children, and Indigenous children residing in the Australian Capital Territory, New South Wales, Tasmania and Victoria, who do not have any medical condition(s) associated with an increased risk of invasive pneumococcal disease (IPD), aged <5 years

Number of doses given previously	Age at presentation	Age when previous dose of any PCV* was given			Number of further dose(s) required†
		1st dose	2nd dose	3rd dose	
No previous doses	<7 months	–	–	–	3
	7–11 months	–	–	–	2
	12–59 months	–	–	–	1
1 previous dose	<7 months	<7 months	–	–	2
	7–11 months	<7 months	–	–	2
		7–11 months	–	–	1
	12–59 months	<12 months	–	–	1
		≥12 months	–	–	Not needed
2 previous doses	<12 months	<7 months	<12 months	–	1
		7–11 months	7–11 months	–	Not needed
	12–23 months	<7 months	<12 months	–	1
			≥12 months	–	Not needed
		≥7 months	Any age	–	Not needed
	24–59 months	Any age	Any age	–	Not needed
3 previous doses	7–59 months	Any age	Any age	Any age	Not needed

* Prior PCV doses may have been given as 7vPCV (e.g. from overseas), 10vPCV or 13vPCV. Use 13vPCV as the vaccine formulation for further catch-up doses required, regardless of which formulation of PCV the child received previously.

† Recommended interval between primary doses for catch-up is 1–2 months. Where possible, it is recommended to align doses with the standard schedule points at 4 months and 6 months of age for infants aged <7 months. The minimum interval between dose(s) is 1 month if aged <12 months, and 2 months if aged ≥12 months.

Table 2.1.10: Catch-up schedule for 13vPCV* (Prevenar 13) for Indigenous children residing in the Northern Territory, Queensland, South Australia or Western Australia ONLY, who do not have any medical condition(s) associated with an increased risk of invasive pneumococcal disease (IPD), aged <5 years

Number of doses given previously	Age at presentation	Age when previous dose of any PCV† was given			Recommendations	
		1st dose	2nd dose	3rd dose	Number of further primary dose(s) required‡	Number of booster 13vPCV doses required§
No previous doses	<7 months	–	–	–	3	1
	7–11 months	–	–	–	2	1
	12–23 months	–	–	–	1	1
	24–59 months	–	–	–	1	Not needed
1 previous dose	<7 months	<7 months	–	–	2	1
	7–11 months	<7 months	–	–	2	1
		7–11 months	–	–	1	1
	12–23 months	<12 months	–	–	1	1
		≥12 months	–	–	Not needed	1
	24–59 months	<12 months	–	–	1	Not needed
		≥12 months	–	–	Not needed	Not needed

Number of doses given previously	Age at presentation	Age when previous dose of any PCV† was given			Recommendations	
		1st dose	2nd dose	3rd dose	Number of further primary dose(s) required‡	Number of booster 13vPCV doses required§
2 previous doses	<12 months	<7 months	<12 months	–	1	1
		7–11 months	7–11 months	–	Not needed	1
	12–23 months	<7 months	<12 months	–	1	1
			≥12 months	–	Not needed	1
		7–11 months	Any age	–	Not needed	1
		≥12 months	≥12 months	–	Not needed	Not needed
	24–59 months	Any age	Any age	–	Not needed	Not needed
3 previous doses	7–11 months	Any age	Any age	Any age	Not needed	1
	12–23 months	<7 months	<12 months	Any age	Not needed	1
			≥12 months	≥12 months	Not needed	Not needed
		7–11 months	7–11 months	≥12 months	Not needed	Not needed
	24–59 months	Any age	Any age	Any age	Not needed	Not needed

* If 13vPCV is not available, and 10vPCV is being used for all/any children, 10vPCV is recommended in a 4-dose schedule for infants (i.e. at ages 2, 4, 6 and 12–18 months). If catch-up is required for 10vPCV, vaccination can be done according to the information provided in this Table. (See also 4.13 *Pneumococcal disease*.)

† Prior PCV doses may have been given as 7vPCV (e.g. from overseas), 10vPCV or 13vPCV. 13vPCV should be used as the vaccine formulation for further catch-up doses required, regardless of which formulation of PCV the child received previously.

‡ Recommended interval between primary doses for catch-up is 1–2 months. Where possible, it is recommended to align doses with the standard schedule points at 4 months and 6 months of age for infants aged <7 months. The minimum interval between dose(s) is 1 month if aged <12 months, and 2 months if aged ≥12 months.

§ A minimum interval of 2 months is required after the last dose of 13vPCV in the primary course.

Table 2.1.11: Catch-up schedule for 13vPCV (Prevenar 13) and 23vPPV (Pneumovax 23) in children with a medical condition(s) associated with an increased risk of invasive pneumococcal disease (IPD),* presenting at age <2 years

For children with a medical condition(s) associated with an increased risk of IPD presenting at age ≥2 years, see recommendations in 4.13 Pneumococcal disease and Table 4.13.2.†

Number of doses given previously	Age at presentation	Age when previous dose of any PCV‡ was given			Recommendations		
		1st dose	2nd dose	3rd dose	Number of further primary dose(s) of 13vPCV required§	Number of booster doses of 13vPCV required at age ≥12months¶	Number of doses of 23vPPV required at age 4–5 years
No previous doses	<7 months	–	–	–	3	1	1
	7–11 months	–	–	–	2	1	1
	12–23 months	–	–	–	1	1	1
1 previous dose	<7 months	<7 months	–	–	2	1	1
	7–11 months	<7 months	–	–	2	1	1
		7–11 months	–	–	1	1	1
	12–23 months	<12 months	–	–	1	1	1
		≥12 months	–	–	Not needed	1	1

Number of doses given previously	Age at presentation	Age when previous dose of any PCV‡ was given			Recommendations		
		1st dose	2nd dose	3rd dose	Number of further primary dose(s) of 13vPCV required§	Number of booster doses of 13vPCV required at age ≥12months¶	Number of doses of 23vPPV required at age 4–5 years
2 previous doses	<12 months	<7 months	<12 months	–	1	1	1
		7–11 months	7–11 months	–	Not needed	1	1
	12–23 months	<7 months	<12 months	–	1	1	1
			≥12 months	–	Not needed	1	1
		7–11 months	Any age	–	Not needed	1	1
		≥12 months	≥12 months	–	Not needed	Not needed	1
3 previous doses	7–11 months	Any age	Any age	Any age	Not needed	1	1
	12–23 months	<7 months	<12 months	Any age	Not needed	1	1
			≥12 months	≥12 months	Not needed	Not needed	1
		7–11 months	7–11 months	≥12 months	Not needed	Not needed	1

* Refer to List 4.13.1 in 4.13 *Pneumococcal disease* for the list of specified conditions.

† Recommendations for vaccination of haematopoietic stem cell transplant (HSCT) recipients differ; see Table 3.3.3 *Recommendations for revaccination following HSCT in children and adults, irrespective of previous immunisation history*.

‡ Prior PCV doses may have been given as 7vPCV (e.g. from overseas), 10vPCV or 13vPCV. 13vPCV should be used as the vaccine formulation for further catch-up doses required, regardless of which formulation of PCV the child received previously.

§ Recommended interval between primary doses for catch-up is 1–2 months. Where possible, it is recommended to align doses with the standard schedule points at 4 months and 6 months of age for infants aged <7 months. The minimum interval between dose(s) is 1 month if age <12 months, and 2 months if age ≥12 months.

¶ The booster dose of 13vPCV should be given at the earliest opportunity after the child reaches 12 months of age, but a minimum interval of 2 months is required after the last dose of 13vPCV in the primary course.

Catch-up schedules for persons ≥10 years of age

Catch-up is much less commonly required for this age group than for young children. Nevertheless, issues surrounding booster doses or revaccinations are common, particularly in adults. Persons who did not have natural infection as children but were not vaccinated remain at unnecessary risk of vaccine-preventable diseases.

In general, the same principles for catch-up vaccination apply as for younger children. For example, if a vaccine course is incomplete, do not start the course again, regardless of the interval since the last dose. One exception to this rule is for oral cholera vaccine (see 4.1 *Cholera*).

Catch-up vaccination for adults can be less straightforward than for children and adolescents. A useful principle to consider when planning which vaccines to give to adults is the HALO principle, which allows for assessment of vaccines needed depending on risk factors:

- **H**ealth
- **A**ge
- **L**ifestyle
- **O**ccupation

The schedule for each individual adult may differ because of the risk factors identified when applying the HALO principle. Some examples of how the HALO principle can be used:

- **H**ealth: the person to be vaccinated has a medical condition(s) that places them at increased risk of acquiring a particular vaccine-preventable disease or experiencing complications from that disease, for example, influenza.
- **A**ge: older age groups may require extra vaccines, such as influenza or pneumococcal vaccination, or certain age groups may be targeted for immunisation against a particular vaccine-preventable disease, such as HPV. Another example is young to middle-aged adults who may have missed out on vaccine doses due to schedule changes, such as the 2nd dose of MMR vaccine.
- **L**ifestyle: the person may have missed vaccines because they moved location of residence, may require extra vaccines because they travel frequently, or have other lifestyle risk factors that increase their risk of acquiring a vaccine-preventable disease, for example, smoking or injecting drugs.
- **O**ccupation: the person may be employed in an occupation for which certain vaccines are recommended because of the increased risk of acquiring a vaccine-preventable disease and/or transmitting it to others, such as in healthcare or early childhood education and care.

The HALO principle is also incorporated, to some extent, into questions used in the pre-vaccination screening checklist (see Tables 2.1.1 and 2.1.2).

Table 2.1.12 contains information on vaccine doses and intervals between doses for persons aged ≥10 years in whom catch-up vaccination is required. This table only contains information on vaccines that are recommended at a population level, and for which catch-up is required if doses have been missed earlier in life. The table does not include information on all vaccines required for adults. Recommended vaccines and catch-up vaccination that might be required when assessed using the HALO principle above and/or by using the pre-vaccination screening checklist (see Tables 2.1.1 and 2.1.2) are discussed in 3.3 *Groups with special vaccination requirements*.

Table 2.1.12 can be used as follows:

- determine how many doses of a particular vaccine a person should have received to be considered completely vaccinated (see 'Doses required' column)
- deduct any previous doses of the vaccine from the number in the 'Doses required' column
- check the appropriate 'Minimum interval' column to schedule further doses
- refer to the relevant disease-specific chapter(s) in Part 4, 3.1 *Vaccination for Aboriginal and Torres Strait Islander people*, 3.2 *Vaccination for international travel*, and 3.3 *Groups with special vaccination requirements*, for additional recommendations, as required.

For example, a 32-year-old woman (**A**ge) is returning to nursing (**O**ccupation) but has only ever had 1 dose of hepatitis B vaccine, 4 doses of the oral poliomyelitis vaccine, 1 dose of MMR vaccine and 2 doses of DTPw vaccine as a child and recently had a splenectomy (**H**ealth) following an accident. This person would require:

- 1 dose of dTpa
- 2 adult doses of hepatitis B; 1 dose given now and a further dose in 2 months
- no further doses of poliomyelitis vaccine (is fully vaccinated against poliomyelitis)
- 1 dose of MMR vaccine
- 2 doses of varicella vaccine if non-immune; 1 dose given now and a further dose in 4 weeks
- 1 dose of influenza vaccine, and 1 dose annually thereafter
- pneumococcal vaccine: 1 dose of 13vPCV, followed by 23vPPV approximately 2 months later (because of splenectomy)
- 1 dose of Hib vaccine (because of splenectomy)
- 2 doses of 4vMenCV; 1 dose given now and a further dose in 8 weeks (because of splenectomy).

For additional details on these recommendations, see 3.3.7 *Vaccination of persons at occupational risk*; 'Persons with functional or anatomical asplenia' in 3.3.3 *Vaccination of immunocompromised persons*, and relevant disease-specific chapters in Part 4.

Where several vaccines are required for an adolescent or adult – for example, dTpa, hepatitis B and poliomyelitis vaccines – childhood combination vaccines (recommended for use in those <10 years of age) should not be used as their antigen content differs and there may be an increased risk of adverse event(s), such as injection site reactions. *The childhood combination vaccines are not registered for use in children aged ≥10 years, adolescents or adults.*

Table 2.1.12: Catch-up schedule for persons ≥10 years of age (for vaccines recommended on a population level)

Vaccine		Doses required	Minimum interval between dose 1 and 2	Minimum interval between dose 2 and 3
dT (dTpa*)		3 doses	4 weeks	4 weeks
Hepatitis B	Aged 10–19 years	3 paediatric doses	1 month	2 months†
Hepatitis B	Aged 11–15 years only	2 adult doses	4 months	Not required
Hepatitis B	Aged ≥20 years	3 adult doses	1 month	2 months†
Poliomyelitis (IPV)		3 doses	4 weeks	4 weeks
Human papillomavirus		3 doses	4 weeks	12 weeks
MMR		2 doses	4 weeks	Not required
MenCCV‡		1 dose	Not required	Not required
Pneumococcal (13vPCV and 23vPPV)		Depends on age of person, Indigenous status and if they have medical condition(s) associated with an increased risk of invasive pneumococcal disease (see Table 4.13.3 in 4.13 *Pneumococcal disease*, and 3.3 *Groups with special vaccination requirements*)		
Varicella vaccine§¶		At least 1 dose if aged <14 years	If 2nd dose given, a 4-week interval is required§	Not required
		2 doses if aged ≥14 years	4 weeks	Not required

Vaccine	Doses required	Minimum interval between dose 1 and 2	Minimum interval between dose 2 and 3
Zoster vaccine	1 dose if aged ≥60 years	Not required	Not required

* One of the doses should be given as dTpa (or dTpa-IPV if poliomyelitis vaccination is also needed) and the course completed with dT. In the unlikely event that dT is *not* available, dTpa or dTpa-IPV may be used for all 3 primary doses *but this is not routinely recommended as there are no data on the safety, immunogenicity or efficacy of dTpa for primary vaccination* (see also 4.12 *Pertussis*).

† For hepatitis B vaccine, the minimum interval between dose 1 and dose 3 is 4 months (see 4.5 *Hepatitis B*).

‡ 4vMenCV is indicated for those at increased risk of meningococcal disease; see recommendations in 4.10 *Meningococcal disease* and 3.3 *Groups with special vaccination requirements*).

§ Varicella vaccine is recommended for all non-immune persons. At least 1 dose should be given to those aged <14 years, and all persons aged ≥14 years should receive 2 doses. (See also 4.22 *Varicella*.)

¶ MMRV is suitable to provide varicella vaccination in children aged <14 years. This vaccine is not recommended for use in persons ≥14 years of age. (See also 4.22 *Varicella*.)

References

A full reference list is available on the electronic *Handbook* or website www.immunise.health.gov.au

2.2 ADMINISTRATION OF VACCINES

2.2.1 Occupational health and safety issues

Standard occupational health and safety guidelines should always be followed during a vaccination. This will minimise the risk of needle-stick injury.[1]

Work practices should include the use of standard infection control precautions to minimise exposure to blood and body fluids (refer to National Health and Medical Research Council's *Australian guidelines for the prevention and control of infection in healthcare*).[1] If exposure does occur, guidelines for post-exposure prophylaxis should be followed. Gloves are not routinely recommended for immunisation service providers, unless the person administering the vaccine is likely to come into contact with body fluids or has open lesions on the hands.

A new, sterile, disposable syringe and needle must be used for each injection. Disposable needles and syringes must be discarded into a clearly labelled, puncture-proof, spill-proof container that meets Australian standards in order to prevent needle-stick injury or re-use.[1] Always keep sharps containers out of the reach of children. All immunisation service providers should be familiar with the handling and disposal of sharps according to the National Health and Medical Research Council's *Australian guidelines for the prevention and control of infection in healthcare*.[1]

2.2.2 Equipment for vaccination

Preparing for vaccination

Depending on the vaccine(s) that are to be administered, and the age and size of the person to be vaccinated, decide on the appropriate injection site and route, and the injection equipment required (e.g. syringe size, needle length and gauge).

The equipment chosen will vary depending on whether the vaccine is a reconstituted vaccine, a vaccine from an ampoule or vial, or a vaccine in a pre-filled syringe.

Equipment may include:

- medical waste (sharps) container
- vaccine, plus diluent if reconstitution is required
- 2 or 3 mL syringe (unless vaccine is in pre-filled syringe)
- appropriate drawing-up needle (19 or 21 gauge needle if required, to draw up through rubber bung and for reconstitution of vaccine)
- appropriate injecting needle (see Table 2.2.2 *Recommended needle size, length and angle for administering vaccines*)
- clean cotton wool and hypoallergenic tape to apply to injection site after vaccination
- a rattle or noisy toy for distraction after the injection.

Preparing the vaccine

- Ensure that the minimum/maximum thermometer displays temperatures within the +2°C to +8°C range before removing vaccine from the refrigerator.
- Ensure that the correct vaccine is taken from the refrigerator and that it is within the expiry date.
- Check that there is no particulate matter or colour change in the vaccine.
- Ensure that the diluent container is not damaged and potentially contaminated.
- Wash hands with soap and water or use a waterless alcohol-based hand rub.[2]
- Prepare the appropriate injection equipment for the vaccine to be administered.

Injectable vaccines that do not require reconstitution

- If the vaccine is in a vial, remove the cap carefully to maintain sterility of the rubber bung. There is no need to wipe the rubber bung of single-dose vials with an alcohol swab if it is visibly clean. If there is visible contamination, the bung should be cleaned with a single-use swab, allowing time to dry before drawing up the contents.[3]
- Use a 19 or 21 gauge needle to draw up the recommended dose through the bung (or through the top of the ampoule), if required.
- Change the needle after drawing up from a vial with a rubber bung or ampoule, before giving the injection. If using a safety needle system, once the vaccine has been drawn up, draw back on the syringe to ensure as much vaccine as possible is removed from the tip of the needle, and then eliminate any air to the tip of the syringe without re-priming the needle.

Injectable vaccines that require reconstitution

- Reconstitute the vaccine as needed immediately before administration.
- Use a sterile 21 gauge needle for reconstitution and a separate 23 or 25 gauge needle, 25 mm in length, for administration of the vaccine in most circumstances.
- Use only the diluent supplied with the vaccine; do not use sterile water for injection instead of a supplied diluent. Ensure that the diluent and vaccine are completely mixed.[4]
- Check reconstituted vaccines for signs of deterioration, such as a change in colour or clarity.
- Administer reconstituted vaccines as soon as practicable after they have been reconstituted as they may deteriorate rapidly. Refer to individual vaccine product information for recommended times from vaccine reconstitution to administration.

- Never freeze a vaccine after it has been reconstituted.

For all injectable vaccines

- Do not extrude small air bubbles through the needle for injection. However, in the rare instance of a large air bubble in a pre-filled syringe, first draw back on the needle to ensure no vaccine is expelled along with the air, and then expel the air through the needle, taking care not to prime the needle with any of the vaccine, as this can lead to increased local reaction.
- *Never* mix other vaccines together in the one syringe (unless that is the manufacturer's registered recommendation, e.g. Infanrix hexa).[4]
- *Never* mix a local anaesthetic with a vaccine.[4]

Vaccines in multi-dose vials

Multi-dose vials are not routinely used in Australia. The current exception is bacille Calmette-Guérin (BCG) vaccine (see 4.20 *Tuberculosis*). Single-dose preparations are now available for all other vaccines currently on the NIP.

However, where mass vaccination of a population is required, such as during the 2009–2010 H1N1 influenza pandemic, multi-dose vials have some advantages over single-dose vaccines. The production of vaccines in multi-dose vials is more cost effective and can also mean that the vaccine takes less time to manufacture. Multi-dose vials also take up less storage room in a vaccine fridge.[5]

The primary risk with use of multi-dose vials is a breach in infection control through user error, for example, an unsterile needle is inserted into the vial or a contaminated syringe is re-used. It is recognised that there are multiple reports of instances of transmission of bacteria or blood-borne viruses through inappropriate use of multi-dose vials; however, the majority of these have been in high-risk settings such as haemodialysis units or with use of anaesthetics and did not involve immunisations.

2.2.3 Route of administration

Most vaccines available in Australia are given intramuscularly. Only a few vaccines are given subcutaneously, orally or intradermally.

Rotavirus vaccines are *only* available for oral administration and must *never* be injected.

Special training is required for intradermal administration, which is important for several vaccines (see 4.15 *Q fever* and 4.20 *Tuberculosis*).

Table 2.2.1 summarises the route of administration for vaccines used in Australia.

Table 2.2.1: Route of administration for vaccines used in Australia

Intramuscular (IM) injection	Subcutaneous (SC) injection	IM or SC injection	Intradermal	Oral
Diphtheria-tetanus vaccine (dT)	Inactivated poliomyelitis vaccine (IPV)*	Influenza vaccine†	Influenza vaccine (Intanza only)	Rotavirus vaccine
Diphtheria-tetanus-acellular pertussis vaccine (DTPa and dTpa)	Quadrivalent meningococcal polysaccharide vaccine (4vMenPV)	Measles-mumps-rubella vaccine (MMR) (Priorix only)	Bacille Calmette-Guérin (BCG) vaccine‡	Cholera vaccine
DTPa- and dTpa-combination vaccines	Varicella vaccine (VV)	Measles-mumps-rubella-varicella vaccine (MMRV) (Priorix-tetra only)	Q fever skin testing‡	Typhoid vaccine
Hepatitis A vaccine and Hepatitis A combination vaccines	Japanese encephalitis vaccine (Imojev)	23-valent pneumococcal polysaccharide vaccine (23vPPV)†		
Hepatitis B vaccine and Hepatitis B combination vaccines	Q fever vaccine‡	Rabies vaccine (HDCV)		
Haemophilus influenzae type b (Hib) vaccine	Measles-mumps-rubella vaccine (MMR) (M-M-R II only)	Yellow fever vaccine		
Human papillomavirus (HPV) vaccine	Measles-mumps-rubella-varicella vaccine (MMRV) (ProQuad only)			
IPV-containing combination vaccines*	Zoster vaccine			
Japanese encephalitis vaccine (JEspect)				
10-valent pneumococcal conjugate vaccine (10vPCV)				
13-valent pneumococcal conjugate vaccine (13vPCV)				
Typhoid Vi polysaccharide vaccine				

Intramuscular (IM) injection	Subcutaneous (SC) injection	IM or SC injection	Intradermal	Oral
Meningococcal C conjugate vaccine (MenCCV) Quadrivalent meningococcal conjugate vaccine (4vMenCV) Rabies vaccine (PCECV)				

* IPV-containing combination vaccines are administered by IM injection; IPV (IPOL) is administered by SC injection.

† The IM route is preferred to the SC route because it causes fewer local adverse events.[6,7]

‡ Q fever skin testing and BCG vaccine should be administered only by specially trained immunisation service providers.

2.2.4 Preparation for vaccine administration

Skin cleaning

Provided the skin is visibly clean, there is no need to wipe it with an antiseptic (e.g. alcohol wipe).[3,8] If the immunisation service provider decides to clean the skin, or if the skin is visibly not clean, alcohol and other disinfecting agents *must* be allowed to dry before vaccine injection (to prevent inactivation of live vaccines and to reduce the likelihood of irritation at the injection site).[9]

Distraction techniques

The routine use of distraction, relaxation and other measures have been shown to reduce distress and pain following vaccination in young children.[10-13] Reducing children's distress may enhance parents' timely attendance for subsequent vaccinations.

Distraction measures that may decrease discomfort following vaccination in young children include:[10-13]

- swaddling and holding the infant securely (but not excessively)
- shaking a noisy toy (for infants and very young children)
- playing music
- encouraging an older child to pretend to blow away the pain using a windmill toy or bubbles
- breastfeeding the infant during administration of the vaccine.

Discomfort may also be decreased by administering sweet-tasting fluid orally immediately before the injection (with parental consent). In infants, 15–25% sucrose drops have been used.[14]

Topical anaesthetic agents, including vapocoolant sprays, are available but, to be effective, must be applied at the correct time before vaccine administration. Topical anaesthetics, such as EMLA, are not recommended for routine use, but could be considered in a child with excessive fear or dislike of needles; they require application 30 to 60 minutes before an injection.[15]

Vapocoolant sprays are applied 15 seconds before vaccination. These sprays have been shown to be more effective in adults than children as children can perceive coldness as painful and spray application may also focus the child more on the procedure. Topical lignocaine/prilocaine is not recommended for children <6 months of age due to the risk of methaemoglobinaemia.[10]

2.2.5 Vaccine injection techniques

Intramuscular injection technique[16,17]

- For intramuscular (IM) injection, use a 25 mm needle in most cases (see Table 2.2.2).
- Depending on the injection site, position the limb so as to relax the muscle into which the vaccine is to be injected.
- Pierce the skin at an angle of 90° to the skin, so the needle can be safely inserted to the hub.[18] Provided an injection angle of >70° is used, the needle should reach the muscle layer.[19]
- If using a 25 gauge needle for an IM vaccination, ensure the vaccine is injected slowly over a count of 5 seconds to avoid injection pain and muscle trauma (see Table 2.2.2).
- If you have drawn back on the syringe plunger before injecting a vaccine (which is not considered necessary),[10] and a flash of blood appears in the needle hub, withdraw the needle and select a new site for injection.[20]

Studies have demonstrated that, for most vaccines, local adverse events are minimised and immunogenicity is enhanced by ensuring vaccine is deposited into the muscle and not into the subcutaneous layer.[10,21-24] However, some vaccines (e.g. inactivated poliomyelitis, varicella and meningococcal polysaccharide vaccines) are only registered for SC administration (see Table 2.2.1).

In the instance where a vaccine that is registered for administration only via the IM route is inadvertently administered via the SC route, check the vaccine product information and the 'Vaccines' section in relevant disease-specific chapters in Part 4 for additional information. Some vaccines may still be immunogenic when given via the SC route, and as such, would not need to be repeated. One vaccine that should be considered invalid and that therefore needs to be repeated is Rabipur Inactivated Rabies Virus Vaccine (PCECV) (see 4.16 *Rabies and other lyssaviruses (including Australian bat lyssavirus)*). In general, hepatitis B vaccines should also be repeated if inadvertently given SC. However, in special circumstances, for example, in persons with bleeding disorders, some hepatitis B vaccines may be given via the SC route (see 3.3.5 *Vaccination of persons with bleeding disorders*).

A clinical trial demonstrated that for infant vaccination long (25 mm) needles (with the skin stretched flat and the needle inserted at 90°) were associated with significantly fewer local adverse events, while achieving comparable immunogenicity. Little difference in local adverse events or immune response was found between needles of the same length but with different gauges.[18]

Subcutaneous injection technique

For subcutaneous (SC) injection, administer the injection at a 45° angle to the skin. The standard needle for administering vaccines by SC injection is a 25 or 26 gauge needle, 16 mm in length.

The immune response to vaccines inadvertently given IM rather than SC is unlikely to be affected. Therefore it is usually not necessary to repeat doses in this instance.

Intradermal injection technique

For intradermal injection of BCG vaccine or Q fever skin test, a 26 or 27 gauge, 10 mm needle is recommended. The intradermal injection technique requires special training, and should be performed only by a trained provider (see 4.20 *Tuberculosis* and 4.15 *Q fever*).

One brand of influenza vaccine (Intanza) is administered via the intradermal route. This vaccine is presented with a specifically designed needle and syringe called the Micro-Injection System and will deliver the 0.1 mL dose of vaccine into the dermal layer of the skin without the need for special training. Manufacturer's instructions in the product packaging should be followed for correct administration.

Table 2.2.2: Recommended needle size, length and angle for administering vaccines[10,16,18,21,25]

Age or size of child/adult	Needle type	Angle of needle insertion
Infant, child or adult for IM vaccines	23 or 25 gauge,* 25 mm in length†	90° to skin plane
Preterm babies (<37 weeks gestation) up to 2 months of age; and/or very small infants	23 or 25 gauge,* 16 mm in length	90° to skin plane
Very large or obese patient	23 or 25 gauge, 38 mm in length	90° to skin plane
Subcutaneous injection in all persons	25 or 26 gauge, 16 mm in length	45° to skin plane

* If using a narrow 25 gauge needle for an IM vaccination, ensure vaccine is injected slowly over a count of 5 seconds to avoid injection pain and muscle trauma.

† The use of short needles for administering IM vaccines may lead to inadvertent SC injection and increase the risk of significant local adverse events, particularly with aluminium-adjuvanted vaccines (e.g. hepatitis B, DTPa, DTPa-combination or dT vaccines).

Interruption to a vaccination

If the process of administration of a vaccine given parenterally (IM or SC) is interrupted (e.g. by syringe–needle disconnection) and *most* of the dose has not been administered, the whole dose should be repeated as soon as practicable.

If *most* of an oral rotavirus vaccine dose has been spat out or vomited within minutes of administration, a single repeat dose can be administered during the same visit. If an infant regurgitates or vomits only a *small part* of a dose of oral rotavirus vaccine, it is not necessary to repeat the dose. Therefore, the regurgitated (and incomplete volume) dose is still considered as the valid dose (see 4.17 *Rotavirus*).

2.2.6 Recommended injection sites

The choice of injection sites depends primarily on the age of the person to be vaccinated. The two anatomical sites recommended as routine injection sites are the anterolateral thigh (Figures 2.2.5 and 2.2.6) and the deltoid muscle (Figure 2.2.8). Immunisation service providers should ensure that they are familiar with the landmarks used to identify any anatomical sites used for vaccination. Photographs and diagrams are provided in this section, but are not a substitute for training. Further detail on identifying the recommended injection sites is provided in 2.2.8 *Identifying the injection site*.

Infants <12 months of age

The vastus lateralis muscle in the anterolateral thigh is the recommended site for IM vaccination in infants <12 months of age, due to its larger muscle size (see Figures 2.2.5 and 2.2.6 in 2.2.8 *Identifying the injection site*).

The ventrogluteal area (see Figure 2.2.7 in 2.2.8 *Identifying the injection site*) is an alternative site for IM vaccination of infants. It is important that vaccine providers who choose to use this site are familiar with the landmarks used to identify it. The reactogenicity and immunogenicity of vaccines given in this site are comparable to those of vaccines given in the anterolateral thigh.[26-28]

The deltoid muscle is not recommended for IM vaccination of infants <12 months of age.

Children ≥12 months of age

The deltoid muscle is the recommended site for IM vaccination in children ≥12 months of age (see Figure 2.2.8 in 2.2.8 *Identifying the injection site*).

The ventrogluteal area is an alternative site for IM vaccination of children ≥12 months of age (see Figure 2.2.7 in 2.2.8 *Identifying the injection site*). However, vaccine providers should be familiar with the landmarks used to identify this site.

The vastus lateralis in the anterolateral thigh may also be used in children ≥12 months of age (see Figures 2.2.5 and 2.2.6 in 2.2.8 *Identifying the injection site*),

but, if this site is used, the less locally reactogenic vaccines (e.g. MMR) should be given in the thigh.

Children with congenital limb malformation or children in spica casts

Children with congenital limb malformation(s) should receive their vaccines in an unaffected limb where possible. The ventrogluteal area can also be considered (see Figure 2.2.7 in 2.2.8 *Identifying the injection site*).[29]

Administration of vaccines to children in spica casts can be timed to occur when the cast is being changed. Parents should be informed of the importance of looking for any signs of swelling that may compromise circulation and, if this occurs, to seek advice from their physiotherapist or doctor as soon as possible.[29] Some resources suggest the use of the deltoid muscle as an alternative route for children in spica casts. If using this site, it is important to be aware of the radial nerve, which is located superficially near the deltoid in children <12 months of age.

Precaution:

Vaccine injections should not be given in the dorsogluteal site or upper outer quadrant of the buttock because of the possibility of a suboptimal immune response.[30,31] Immunoglobulin can be administered intramuscularly into the upper outer quadrant of the buttock, but care must be taken to ensure that the other quadrants are not used.

Adolescents and adults

The deltoid muscle is the recommended site for IM vaccination in adolescents and adults (see Figure 2.2.8 in 2.2.8 *Identifying the injection site*).

The anterolateral thigh can also be used in older children and adults (see Figure 2.2.5 in 2.2.8 *Identifying the injection site*). However, it is important to administer the least reactogenic vaccine in this muscle to decrease the likelihood of local injection site reactions.

The ventrogluteal area is an alternative injection site (see Figure 2.2.7 in 2.2.8 *Identifying the injection site*). However, vaccine providers should be familiar with the landmarks used to identify this site.

Patients undergoing treatment for breast cancer or patients with lymphoedema

It has been routine practice for many years to avoid giving injections, including vaccination, into a person's arm(s) affected by lymphoedema.[32-34] This recommendation is based on the potential for arm swelling related to vaccination to lead to, or exacerbate, lymphoedema, although there is limited evidence to support this. Where possible, use an alternative site, such as the other arm or thigh.[32-34] For further information about vaccination of persons undergoing cancer treatment, see 3.3 *Groups with special vaccination requirements*.

2.2.7 Positioning for vaccination

It is important that infants and children do not move during injection of vaccines. However, excessive restraint can increase their fear and result in increased muscle tension. The following section describes a variety of positions that may be used for vaccinating different age groups.

Infants <12 months of age

Cuddle position for infants

Position the infant in a semi-recumbent cuddle position on the lap of the parent/carer (see Figure 2.2.1). The infant's inside arm adjacent to the parent/carer should be restrained underneath the parent/carer's arm or against the parent/carer's chest. The infant's outside arm must also be held securely. The parent/carer's hand should restrain the infant's outside leg and the knee should be flexed to encourage relaxation of the vastus lateralis for IM vaccinations. This position can also be used for young children.

Figure 2.2.1: Positioning a child <12 months of age in the cuddle position

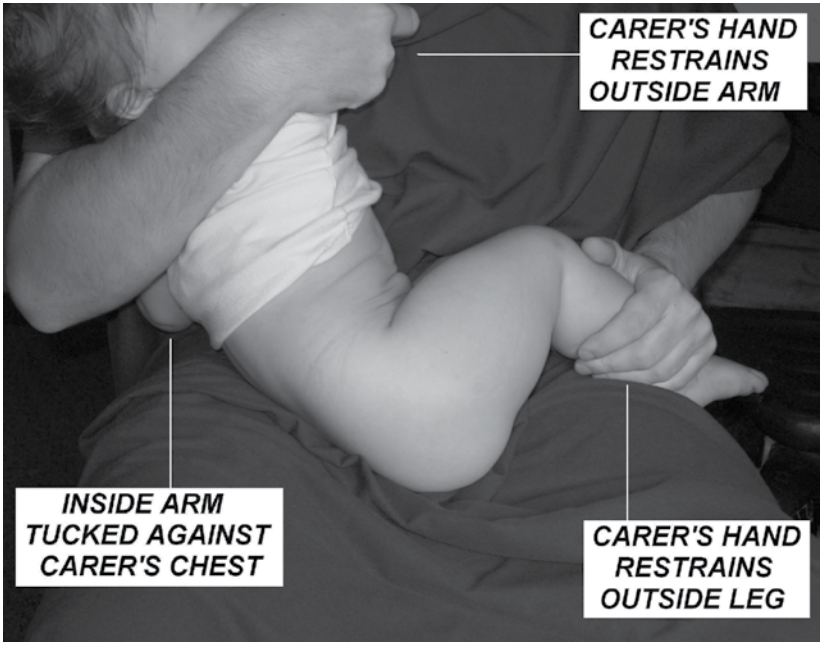


Photo courtesy Dr Joanne Molloy, Victoria

Positioning an infant on an examination table

An alternative is to lay an infant on his/her back on an examination table, with the infant's feet towards the immunisation service provider, and the parent/carer beside the provider to immobilise and distract the baby (see Figure 2.2.2).

Keep the infant's hip and knee flexed by cupping the patella in the non-injecting hand.

The thumb and index finger of the non-injecting hand may be used to stabilise the hub of the needle once the needle has been inserted.

Although the exact mechanism is unclear, recent studies have shown that placing a child in the supine position may result in more pain than if the child is held in an upright position.[15]

Figure 2.2.2: Positioning an infant on an examination table for vaccination

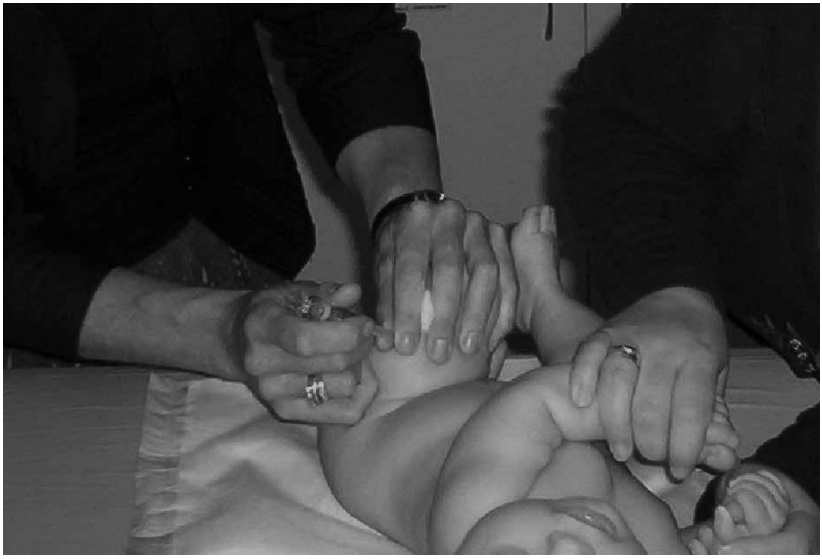


Photo courtesy Dr Joanne Molloy, Victoria

Prone position across the lap for ventrogluteal vaccination

For ventrogluteal injection, position the child face-down across the parent/carer's lap (see Figure 2.2.7 below). This allows the hips to be flexed and provides access to the ventrogluteal area.

Children ≥12 months of age

Cuddle position for an older child

Sit the child sideways on the lap of the parent/carer, with the arm to be injected held close to the child's body while the other arm is tucked under the armpit and behind the back of the parent/carer.

The child's exposed arm should be secured at the elbow by the parent/carer, and the child's legs should also be secured by the parent/carer (see Figure 2.2.3).

Figure 2.2.3: Positioning an older child in the cuddle position

Photo courtesy CHW Photography

Straddle position

An older child may be positioned facing the parent/carer with the legs straddled over the parent/carer's lap. The child's arms should be folded in front, with the parent/carer hugging the child's body to the parent/carer's chest. Alternatively the child may be positioned to 'hug' the parent/carer with the parent/carer's arms holding the child's arms in a reciprocal hug (see Figure 2.2.4). This position allows access to both deltoids and both anterolateral thighs.

Figure 2.2.4: Positioning a child in the straddle position

Photo courtesy CHW photography

Prone position across the lap for ventrogluteal vaccination

For ventrogluteal injection, position the child face-down across the parent/carer's lap (see Figure 2.2.7 below).

Older children, adolescents and adults

Solo sitting position for deltoid injections

Most vaccines can be administered into the deltoid area. Adults should sit in a straight-backed chair, feet resting flat on the floor with forearms and hands in a relaxed position on the upper thighs. Keep the arms flexed at the elbow to encourage the deltoid muscle to relax.

Encourage the shoulders to drop by asking the person to raise the shoulders up while taking a deep breath in and to drop them while breathing out fairly forcefully. Use distraction to keep muscles relaxed during the procedure, for example, have an interesting poster or similar for the person to concentrate on during the procedure and ask him/her to give you a detailed description of what can be seen.

The ventrogluteal and vastus lateralis are alternative sites if needed (see 2.2.6 *Recommended injection sites* and 2.2.8 *Identifying the injection site*).

2.2.8 Identifying the injection site

The choice of injection site depends on the age of the person to be vaccinated, and is discussed in 2.2.6 *Recommended injection sites*.

The anterolateral thigh (vastus lateralis)

- Make sure the infant's nappy is undone to ensure the injection site is completely exposed and the anatomical markers can be easily identified by sight and palpation.
- Position the leg so that the hip and knee are flexed and the vastus lateralis is relaxed (see Figure 2.2.6).
- Identify the following anatomical markers: the upper marker is the midpoint between the anterior superior iliac spine and the pubic tubercle, and the lower marker is the upper part of the patella.
- Draw an imaginary line between the two markers down the front of the thigh. The correct site for IM vaccination is lateral to the midpoint of this line, in the outer (anterolateral) aspect (see Figures 2.2.5 and 2.2.6).
- Do not inject into the anterior aspect of the thigh where neurovascular structures can be damaged.

Figure 2.2.5 Anatomical markers used to identify the vastus lateralis injection site (X) on the anterolateral thigh

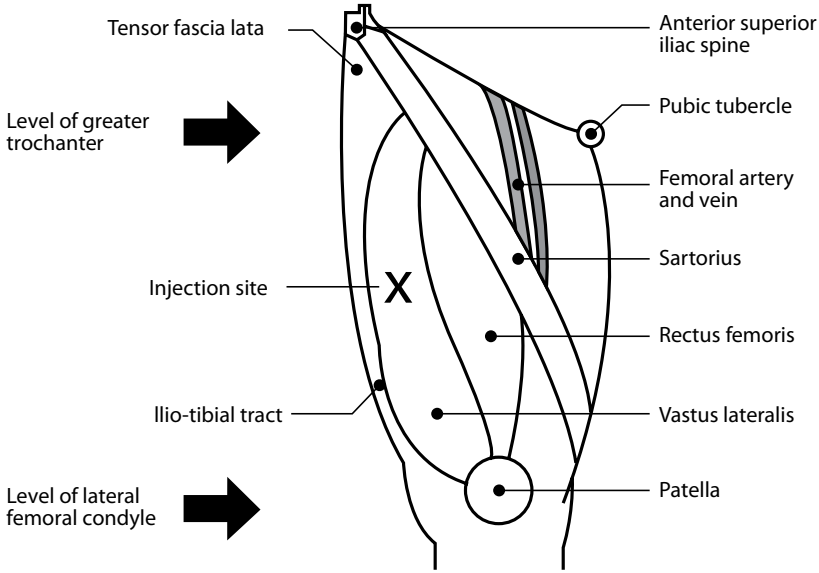


Figure 2.2.6: The vastus lateralis injection site (X) on the anterolateral thigh

Photo courtesy Lloyd Ellis, The Royal Children's Hospital, Victoria

The ventrogluteal area

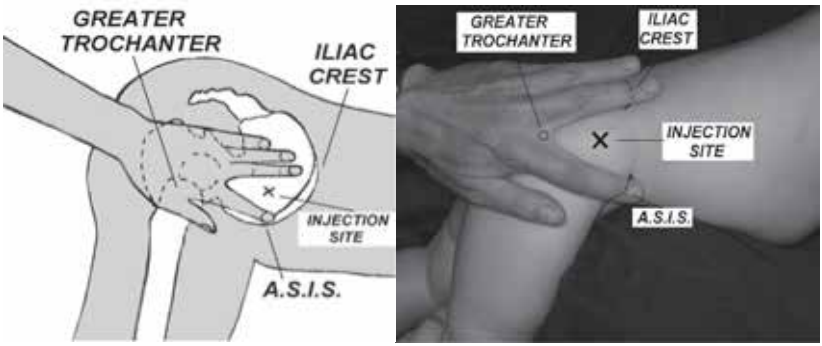
Note: This area should not be confused with the dorsogluteal area (buttock).

The ventrogluteal area provides an alternative site for administering vaccines to a child of any age, especially when multiple injections at the same visit are required. The ventrogluteal area is relatively free of major nerves and blood vessels, and the area provides the greatest thickness of gluteal muscle.[35,36] There is a relatively consistent thinness of subcutaneous tissue over the injection site.[36,37]

- Make sure the child's nappy is undone to ensure the injection site is completely exposed and the anatomical markers can be easily identified by sight and palpation. Anatomical markers are the anterior superior iliac spine (ASIS), the greater trochanter of the femur and the iliac crest (see Figure 2.2.7).
- Place the child in a prone position (face-down) on the parent/carer's lap or on the clinic table/bed, with the child's arms tucked against their chest. Allow the child's legs to dangle towards the floor (see Figure 2.2.7).
- Ensure the knee and hip are turned inwards to encourage muscle relaxation at the injection site.
- Use the injection site that is closest to you.

- Place the palm over the greater trochanter (the uppermost bony prominence of the thigh bone), with the thumb pointing towards the umbilicus. Point the index finger towards the anterior superior iliac spine, and spread the middle finger so it aims at the iliac crest, thus creating a 'V' outlining the ventrogluteal triangular area. The injection site is at the centre of this area as shown in the diagram in Figure 2.2.7.
  Note: In small children and infants, the placement of the hand in relation to these anatomical markers may vary, as shown in the photograph in Figure 2.2.7.

Figure 2.2.7: Anatomical markers used to identify the ventrogluteal injection site (X)



ASIS = anterior superior iliac spine

Photo courtesy of Dr Joanne Molloy, Victoria

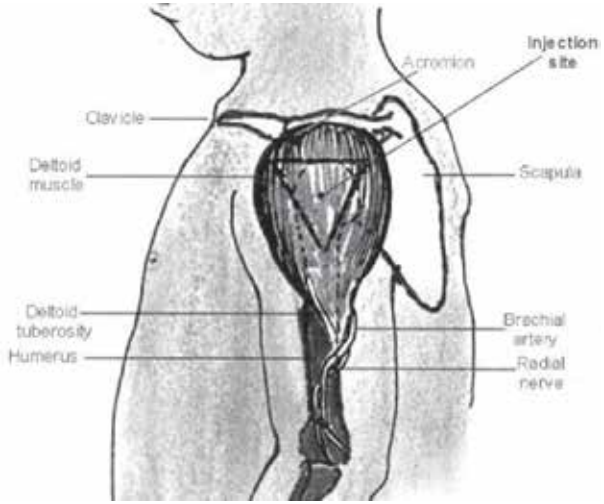
The deltoid area

To locate the deltoid site for injection:

- Expose the arm completely, from the top of the shoulder to the elbow; roll up the sleeve or remove the shirt if needed.
- Locate the shoulder tip (acromion) and the muscle insertion at the middle of the humerus (deltoid tuberosity).
- Draw an imaginary inverted triangle below the shoulder tip, using the identified anatomical markers (see Figure 2.2.8).

The deltoid site for injection is halfway between the acromion and the deltoid tuberosity, in the middle of the muscle (triangle).

Figure 2.2.8: Anatomical markers used to identify the deltoid injection site



Subcutaneous injection sites

Subcutaneous injections should be administered either over the deltoid muscle or over the anterolateral thigh. There are no studies that describe any specific differences in the technique used for an 'SC injection' compared with a 'deep SC injection'. Figure 2.2.9 demonstrates the recommended technique for *any* SC injection.

Figure 2.2.9: A subcutaneous injection into the deltoid area of the upper arm using a 25 gauge, 16 mm needle, inserted at a 45° angle

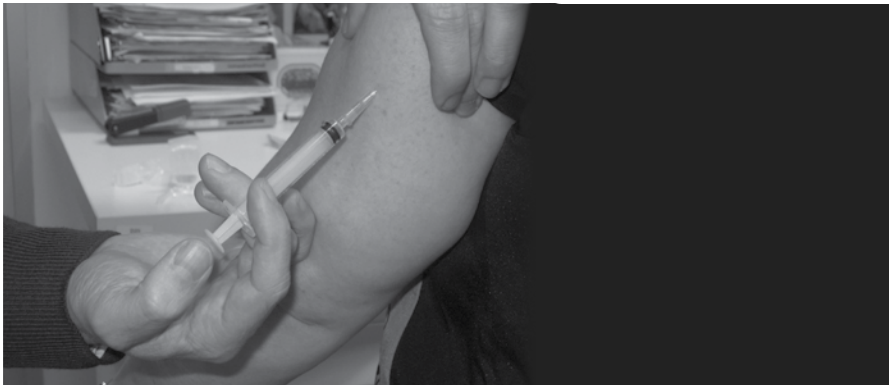


Photo courtesy Jane Jelfs NCIRS

2.2.9 Administering multiple vaccine injections at the same visit

When sequentially administering multiple vaccines to children, give the most painful vaccine last (e.g. pneumococcal conjugate vaccine). Evidence suggests that this may decrease the overall pain response.

The location of each separate injection given should be recorded, so that if a local adverse event occurs, the implicated vaccine(s) can be identified.

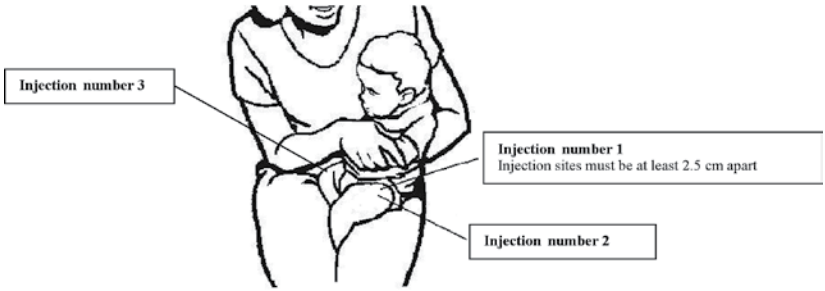
Infants <12 months of age

The suitable sites for this age group are the anterolateral thighs (preferred) and the ventrogluteal areas. For the routine schedule where only two vaccines are required, one can be given in each thigh.

When three or four injectable vaccines are to be given at the same visit, the options are:

- two injections in the same anterolateral thigh, separated by at least 2.5 cm (see Figure 2.2.10, injection numbers 1 and 2); further IM vaccines can be given in this way in the other thigh (injection number 3), or
- one injection into each anterolateral thigh and one injection into each ventrogluteal area (only one injection should be given into each ventrogluteal area).

Figure 2.2.10: Recommended technique for giving multiple vaccine injections into the anterolateral thigh in an infant <12 months of age



Children ≥12 months of age, adolescents and adults

A single injection can be given into each deltoid muscle.

When three or four IM vaccines are to be given to a child at the same visit, the options will depend on the muscle mass of the child's deltoid.

- If the deltoid mass is adequate, give a further injection into each deltoid muscle (separated by 2.5 cm from the initial injection site).

- If the deltoid muscle mass is small:
  - » give further injections into either anterolateral thigh (2.5 cm apart if two vaccines are given in the same thigh), or
  - » give one injection into each ventrogluteal area.

For younger children, the cuddle or straddle positions (Figures 2.2.3 and 2.2.4) are suitable for accessing multiple limbs during the one vaccination encounter.

Simultaneous injections by two immunisation providers

Currently there is insufficient evidence for or against having two immunisation providers administer vaccines at the same time rather than one vaccine after the other.[38,39] Two studies were unable to demonstrate a difference in pain response in the child between simultaneous administration and sequential administration.[38,39] If multiple immunisation providers are available, the technique has been explained to the parent and the parent gives consent, then the vaccines may be administered simultaneously, providing different sites can be safely accessed.

References

A full reference list is available on the electronic *Handbook* or website www.immunise.health.gov.au

2.3 POST-VACCINATION

2.3.1 Immediate after-care

Immediately after vaccine administration:

- dispose of clinical waste, including sharps and vaccine vials, at the point of use (refer to state/territory health authorities for management guidelines for the safe disposal of clinical waste or refer to the National Health and Medical Research Council's *Australian guidelines for the prevention and control of infection in healthcare*)[1]
- cover the injection site quickly with a dry cotton ball and tape as needed
- gently apply pressure for 1 or 2 minutes – do not rub the site as this will encourage the vaccine to leak back up the needle track, which can cause pain and may lead to local irritation
- to distract the vaccinated person and reduce distress, immediately change the position of the child/person after completing the vaccination, for example, ask the parent/carer to put the infant over his/her shoulder and move around with the infant[2]
- remove the cotton wool after a few minutes and leave the injection site exposed to the air
- record the relevant details of the vaccines given (see 2.3.3 *Documentation of vaccination*).

The vaccinated person and/or parent/carer should be advised to remain in the vicinity for a minimum of 15 minutes after the vaccination. The area should be close enough to the immunisation service provider so that the vaccinated person can be observed and medical treatment provided rapidly if needed.

Paracetamol is not routinely used before, or at the time of, vaccination, but may be recommended as required for fever or pain occurring following immunisation.

Before departure, inform the vaccinated person or parent/carer, preferably in writing, of any expected adverse events following immunisation, and of the date of the next scheduled vaccination(s).

Take the opportunity to check the vaccination status of other family members (as appropriate) and discuss any catch-up vaccination requirements and options available (this can also be done earlier in the visit).

2.3.2 Adverse events following immunisation

What are adverse events following immunisation?

An adverse event following immunisation (AEFI) is any untoward medical occurrence that follows immunisation and does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.[3] Such an event may be caused by the vaccine(s) or may occur by chance

(i.e. it would have occurred regardless of vaccination). Most vaccine adverse events are minor, such as low-grade fever, and pain or redness at the injection site; these should be anticipated.[4] The frequency of adverse events has been classified by regulatory agencies, and is often reported in clinical trials as follows: very common (>10% of persons vaccinated), common (1–10%), uncommon (0.1–<1%), rare (0.01%–<0.1%) and very rare (<0.01%).[5] Detailed information on types of expected common and rare adverse events is provided below.

An important factor in reducing the likelihood of an adverse event occurring is to screen each person to be vaccinated (using the pre-vaccination screening checklists in Tables 2.1.1 and 2.1.2) to ensure that the person does not have a condition that either increases the risk of an AEFI or is a contraindication to vaccination. Immunisation service providers should also check the relevant chapters of this *Handbook,* including the variations from product information, and any other relevant sources, such as state/territory guidelines. The use of correct injection procedures is also important (see 2.2 *Administration of vaccines*).

Expected common AEFI are described in the table *Comparison of the effects of diseases and the side effects of NIP vaccines* inside the back cover of this *Handbook*. Detailed information on the adverse events that are known to occur after vaccination is contained in the 'Adverse events' section of each disease-specific chapter in Part 4. Persons to be vaccinated and/or their parents/carers should be given advice (preferably written) as part of the consent procedure on what common or expected adverse events are likely and what they should do about them. The table inside the front cover of this *Handbook*, *Side effects following immunisation for vaccines used in the National Immunisation Program (NIP) schedule*, can be used for this purpose.

Parents/patients should be encouraged to contact their healthcare provider if they are concerned about an adverse event occurring after vaccination, particularly if it is an unexpected, uncommon and/or serious adverse suspected reaction to vaccination. Healthcare providers and parents/carers are encouraged to report any untoward medical occurrence that follows immunisation, particularly events that are serious and/or unexpected, and/or relate to a new vaccine or condition of interest. For more detailed information on reporting AEFI, see 'Reporting adverse events following immunisation' below and Table 2.3.3 *Contact information for notification of adverse events following immunisation*. In addition to reporting AEFI, immunisation providers should provide the patient/parents with information and a plan of management regarding the adverse event experienced, including the implications for subsequent vaccination. This is discussed more in the next three sections on management of immediate, common and rare adverse events, and also in 3.3.1 *Vaccination of persons who have had an adverse event following immunisation*.

Management of an immediate adverse event following immunisation

The vaccinated person should remain under observation for a short interval to ensure that they do not experience an immediate adverse event. It is recommended that vaccinated persons remain in the vicinity of the place of vaccination for at least 15 minutes. Severe anaphylactic reactions usually have a rapid onset; life-threatening adverse events are most likely to begin within 15 minutes of vaccination.

The most serious immediate AEFI is anaphylaxis. However, in adults and older children, the most common immediate adverse event is a vasovagal episode (fainting), either immediately or soon after vaccination. Because fainting after vaccination can lead to serious consequences, anyone who complains of giddiness or light-headedness before or after vaccination should be advised to lie down until free of symptoms.

Anaphylaxis and vasovagal episodes

Anaphylaxis following routine vaccination is very rare, but can be fatal.[6] All immunisation service providers must be able to recognise all the symptoms and signs of anaphylaxis and distinguish between anaphylaxis, convulsions and fainting. The features listed in Table 2.3.1 may be useful in differentiating between fainting (vasovagal episode) and anaphylaxis.

Anaphylaxis is a severe adverse event of rapid onset, characterised by sudden respiratory compromise and/or circulatory collapse.[7] Early signs include involvement of the skin (e.g. generalised erythema, urticaria and/or angioedema) and/or gastrointestinal tract (e.g. diarrhoea, vomiting). In severe cases, there is circulatory collapse with alteration in the level of consciousness, hypotension and weak or absent pulses, and/or marked respiratory compromise from upper airway oedema or bronchospasm.

Fainting (vasovagal episode) is relatively common after vaccination of adults and adolescents, but infants and children rarely faint. Sudden loss of consciousness in young children should be presumed to be anaphylaxis, particularly if a strong central pulse is absent. A strong central pulse (e.g. carotid) persists during a faint or convulsion.

If a diagnosis of anaphylaxis is suspected, treatment, including administration of adrenaline, should be instituted promptly[8] (see 'Management of anaphylaxis' below). Under-treatment of anaphylaxis is more harmful, and potentially life-threatening, than over-treatment of a mild or moderate allergic reaction.[9]

Table 2.3.1: Clinical features that may assist differentiation between a vasovagal episode and anaphylaxis

		Vasovagal episode	Anaphylaxis*
Onset		Immediate, usually within minutes of, or during, vaccine administration	Usually within 15 minutes, but can occur within hours, of vaccine administration
Symptoms/ Signs	Respiratory	Normal respiration; may be shallow, but not laboured	Cough, wheeze, hoarseness, stridor, or signs of respiratory distress (e.g. tachypnoea, cyanosis, rib recession) Upper airway swelling (lip, tongue, throat, uvula or larynx)
	Cardiovascular	Bradycardia, weak/absent peripheral pulse, strong carotid pulse Hypotension – usually transient and corrects in supine position Loss of consciousness – improves once supine or in head-down position	Tachycardia, weak/absent carotid pulse Hypotension – sustained and no improvement without specific treatment (*Note*: in infants and young children, limpness and pallor are signs of hypotension) Loss of consciousness – no improvement once supine or in head-down position
	Skin	Generalised pallor, cool, clammy skin	Pruritus (skin itchiness), generalised skin erythema (redness), urticaria (weals) or angioedema (localised or general swelling of the deeper layers of the skin or subcutaneous tissues)
	Gastrointestinal	Nausea/ vomiting	Abdominal cramps, diarrhoea, nausea and/or vomiting
	Neurological†	Feels faint, light-headed	Sense of severe anxiety and distress

* Modified from The Brighton Collaboration Case Definition Criteria for Anaphylaxis.[6]

† Neurological symptoms are not listed in the Brighton case definition criteria for anaphylaxis;[6] however, symptoms of anxiety and distress, including feelings of impending doom, are reported in persons experiencing anaphylaxis.[7,10]

Management of anaphylaxis

Rapid IM administration of adrenaline is the cornerstone of treatment of anaphylaxis. Adrenaline is life saving and must be used promptly.[8]

Anaphylaxis occurs without warning, usually within 15 minutes of giving a vaccine. A protocol for the management of anaphylaxis, adrenaline and 1 mL syringes must always be immediately at hand whenever vaccines are given.

- If the patient is unconscious, lie him/her on the left side and position to keep the airway clear.
- If the patient is conscious, lie him/her supine in 'head-down and feet-up' position (unless this results in breathing difficulties).
- If there are any respiratory and/or cardiovascular symptoms or signs of anaphylaxis, give adrenaline by IM injection into the anterolateral thigh (see 'Use of adrenaline' below for dosage). Adrenaline is not required for generalised non-anaphylactic reactions (such as skin rash or angioedema). If in doubt, IM adrenaline should be given. No serious or permanent harm is likely to occur from mistakenly administering adrenaline to an individual who is not experiencing anaphylaxis.[11]
- Call for assistance. Never leave the patient alone.
- If oxygen is available, administer by facemask at a high flow rate.
- If there is no improvement in the patient's condition within 5 minutes, repeat doses of adrenaline every 5 minutes until improvement occurs.
- Check breathing; if absent, commence basic life support or appropriate cardiopulmonary resuscitation (CPR), as per the Australian Resuscitation Council guideline[12] (available at www.resus.org.au/policy/guidelines).
- In all cases, transfer the person to hospital for further observation and treatment.
- Complete full documentation of the event, including the time and dose(s) of adrenaline given.

Antihistamines and/or hydrocortisone are not recommended for the emergency management of anaphylaxis.

Use of adrenaline

The use of 1:1000 adrenaline is recommended because it is universally available. Adrenaline 1:1000 (one in one thousand) contains 1 mg of adrenaline per mL of solution in a 1 mL glass vial. Adrenaline 1 in 10 000 is no longer recommended for the treatment of anaphylaxis. A 1 mL syringe should be used to improve the accuracy of measurement when drawing up small doses of adrenaline.

The recommended dose of 1:1000 adrenaline is 0.01 mL/kg body weight (equivalent to 0.01 mg/kg or 10 µg/kg) up to a maximum of 0.5 mL, given by deep IM injection *preferably in the anterolateral (upper outer) thigh.* The anterolateral thigh is the preferred site because there is a more predictable dispersal of

adrenaline from this site.[13] Administration of adrenaline in the anterolateral thigh is also in accordance with recommendations from various emergency medicine, anaesthetic and immunology professional bodies.[9]

Adrenaline 1:1000 *must not* be administered intravenously.

Table 2.3.2 lists the dose of 1:1000 adrenaline to be used if the exact weight of the person is not known.

The dose of 1:1000 (one in one thousand) adrenaline may be repeated every 5 minutes, as necessary, until there is clinical improvement.

Table 2.3.2: Doses of intramuscular 1:1000 (one in one thousand) adrenaline for anaphylaxis*[14]

Approximate age and weight	Adrenaline dose
<1 year (approx. 5–10 kg)	0.05–0.1 mL
1–2 years (approx. 10 kg)	0.1 mL
2–3 years (approx. 15 kg)	0.15 mL
4–6 years (approx. 20 kg)	0.2 mL
7–10 years (approx. 30 kg)	0.3 mL
10–12 years (approx. 40 kg)	0.4 mL
>12 years and adult (over 50 kg)	0.5 mL

* Modified from insert published in *Australian Prescriber*[14] (available at www.australianprescriber.com/magazine/34/4/article/1210.pdf). Endorsed by the Australasian Society of Clinical Immunology and Allergy, the Royal Australasian College of Physicians, the Royal Australian College of General Practitioners, the Australasian College for Emergency Medicine, the Royal Australian and New Zealand College of Radiologists, the Internal Medicine Society of Australia and New Zealand, and the Australian Dental Association.

Use of adrenaline autoinjectors for anaphylaxis treatment

Adrenaline autoinjectors, EpiPen or Anapen, are devices that administer a single, pre-measured dose of adrenaline. They are designed for use by any person, whether medically trained or not. Clear instructions on correct use are provided on the barrel and in the packaging of these devices. They are designed to be administered in the mid-outer thigh.

Autoinjectors are usually recommended or prescribed for an individual who is at risk of anaphylaxis due to an existing allergy or where skin testing indicates a high risk of an allergic reaction on exposure to an allergen. If a patient who carries an autoinjector device develops anaphylaxis post vaccination, it is appropriate to use their autoinjector to administer adrenaline.

Autoinjectors are generally not appropriate for inclusion in first aid kits for general use, due to several limitations:

- they are single-use only
- they are dose-specific
  - » EpiPen Jr or Anapen Jr containing 150 µg of adrenaline are recommended for children weighing between 10 kg and 20 kg
  - » EpiPen or Anapen containing 300 µg of adrenaline are recommended for children and adults weighing over 20 kg
- multiple pens would be required to allow for repeat dosing and varying ages/weights of patients, and shelf-life is limited to 1 to 2 years maximum.

Autoinjectors are not recommended for use in children weighing less than 10 kg.

Common adverse events following immunisation and their management

Commonly occurring AEFI are described in the table *Comparison of the effects of diseases and the side effects of NIP vaccines* inside the back cover of this *Handbook* and in the disease-specific chapters in Part 4.

The most commonly encountered adverse events are local reactions related to vaccine injection(s), such as pain, redness, itching, swelling or burning at the injection site. These are to be expected, are generally mild and usually last for 1 to 2 days. Injection site nodules are also relatively common. They are fibrous remnants of the body's interaction with the vaccine components (usually an adjuvant) in the muscle. They may remain for many weeks after vaccination and do not require any specific treatment.

Low-grade fever and tiredness (malaise), lasting a few days, are also common after many vaccines. These responses are usually mild and self-limiting, and generally do not require specific treatment.

Routine use of paracetamol at the time of, or immediately after, vaccination is not recommended. However, if an infant, child or adult has a fever of >38.5°C following vaccination or has pain at the injection site, paracetamol can be given. The dose of paracetamol for an infant or child up to 12 years of age is 15 mg/kg/dose, up to a maximum dose of 60 mg/kg per day in four divided doses. Adults and children aged ≥12 years can receive 500 to 1000 mg every 4 to 6 hours; dosage must not exceed 4 g in 24 hours. Paracetamol should not be given for more than 48 hours without seeking medical advice.[15]

If patients exhibit unexpected, serious or prolonged adverse symptoms or signs following immunisation, medical advice should be sought. The symptoms and signs from medical illness unrelated to vaccination can sometimes be attributed to a recent immunisation and should be investigated and managed accordingly.

Uncommon/rare adverse events following immunisation

Some vaccines have been shown to cause uncommon or rare serious adverse events, although the rate of vaccine adverse events is usually hundreds to thousands times less frequent than the disease complications. Information on the benefits compared with risks of immunisation is always taken into account when making recommendations for vaccine use. It is important to provide persons to be vaccinated or their parent/carer with advice regarding known, but rare, adverse events following immunisation, and to place the advice in the context of the benefits of vaccination (see 3.3.1 *Vaccination of persons who have had an adverse event following immunisation*).

If a patient has experienced a serious or uncommon/rare AEFI, it is important that they or their immunisation service provider seek advice from a specialist immunisation clinic or contact state/territory health authorities for more information regarding the need for further investigation and management (see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*). This will enable an assessment to determine the relationship to vaccination, consideration of the benefits and risks of further vaccination, and planning for receiving additional doses of that or other vaccines, as appropriate. Persons who have had a serious adverse event following immunisation (other than a contraindication, such as the confirmed identity of the vaccine component that triggered anaphylaxis) can usually subsequently be vaccinated under close medical supervision. For more detailed information see 3.3.1 *Vaccination of persons who have had an adverse event following immunisation.*

Examples of uncommon and rare adverse events are given below. It is important to remember that, although these events are uncommon or rare, they are still not necessarily causally related to vaccination, even if they occur following vaccination.

- Febrile convulsions are a relatively common response to fever of any cause in young children, particularly in those aged <3 years, with a peak incidence at 14–18 months of age. Overall, by the age of 5 years, approximately 3% of all children will have experienced a febrile convulsion, irrespective of vaccination. Febrile convulsions are rare following immunisation. They do, however, occur more commonly, but still at a low rate, after some vaccines. For example, MMR and MMRV vaccines are associated with an increased risk of febrile convulsions approximately 7 to 12 days after the 1st vaccine dose (see 4.9 *Measles* for more information). Co-administration of trivalent influenza vaccine and 13-valent pneumococcal conjugate vaccine may also be associated with an increased risk of febrile convulsions (see 4.7 *Influenza* and 4.13 *Pneumococcal disease*). In 2010, there was an increased incidence of high fevers and febrile convulsions (estimated at 4.4 per 1000 doses in Western Australia) following administration of one brand of seasonal influenza vaccine (Fluvax and Fluvax Junior, CSL Limited) in children aged <5 years in

Australia.[16] This vaccine is no longer registered for use in this age group. An excess risk of fever and febrile convulsions was not observed with the other influenza vaccines given to children.[16,17]

- Brachial neuritis (inflammation of a nerve in the arm, causing weakness or numbness) has been described following the administration of tetanus toxoid-containing vaccines, with an estimated excess risk of approximately 0.5–1 in 100 000 doses in adults.[5,18] Case reports of brachial neuritis following administration of other vaccines, including HPV vaccines,[19] are rare and a causal relationship has not been established.[20]
- Oral rotavirus vaccines are associated with a small increased risk of intussusception (IS), a rare form of bowel blockage caused by telescoping of the intestine into itself. This risk appears to be particularly in the 7 days following the 1st vaccine dose; however, a smaller increased risk in the week following the 2nd dose has also been reported.[21-23] It is not currently clear whether there is an overall increase in the risk of IS above that which would be expected in the 1st year of infancy without vaccine use. The increased risk represents approximately 6 additional cases of intussusception among every 100 000 infants vaccinated, or 14 additional cases per year in Australia.[23] Children who have had IS are recommended to not receive rotavirus vaccine (see 4.17 *Rotavirus*).
- Anaphylaxis following receipt of vaccines has been reported, but generally occurs very rarely.[24] For example, the estimated incidence rate of anaphylaxis following 4vHPV vaccine in Australia as at June 2010 was 2.6 anaphylaxis episodes per million doses of vaccine distributed.[25] This is within the same rate range as for other vaccines given to children and adolescents in international studies, such as hepatitis B vaccine, which is associated with anaphylaxis in approximately 1 in 1.1 million doses distributed.[26] (For more information on the management of immediate AEFI/anaphylaxis, see above.)
- Hypotonic-hyporesponsive episode (HHE) is the sudden onset of pallor or cyanosis, limpness (muscle hypotonia), and reduced responsiveness or unresponsiveness occurring after vaccination, where no other cause is evident such as a vasovagal episode or anaphylaxis. The episode usually occurs 1 to 48 hours after vaccination and resolves spontaneously. There are no known long-term side effects from HHE.[27,28] In Australia during 2009, 3.2 cases of HHE were reported per 100 000 doses of DTPa-containing vaccine given to children <1 year of age.[29]
- Guillain-Barré syndrome (GBS) is a rare autoimmune condition with acute onset of a rapidly progressive, ascending, symmetrical flaccid paralysis, with or without sensory loss. Diagnosis of GBS is complex and must be made by a physician. A small increased risk of GBS was associated historically with one influenza vaccine in the United States in 1976, but since then close surveillance has shown that GBS has occurred at a very low rate of up to 1 in 1 million doses of influenza vaccine, if at all.[30]

Events where evidence demonstrates no causal link with immunisation

Since vaccines are mainly given to healthy people, a range of conditions that occur after a vaccine dose may be attributed to vaccination. This is particularly so for illnesses that are complex and have an unknown or unclear cause. As many of these illnesses are rare and/or manifest months to years after vaccination, they are difficult to study in randomised controlled clinical trials, which are typically conducted before vaccines are registered for use. However, there is strong epidemiological evidence, usually derived from multiple well-conducted post-marketing studies, that indicates there is no causal association between immunisation and many diseases/conditions in which vaccines were suggested to have been involved.

Examples of events unrelated to vaccination include:

- sudden infant death syndrome (SIDS) and any vaccine[31-33]
- autism and MMR vaccine[34-39]
- multiple sclerosis and hepatitis B vaccine[40-43]
- inflammatory bowel disease and MMR vaccine[44]
- diabetes and Hib vaccine[45-47]
- asthma and any vaccine.[48]

Despite this evidence, patients/parents seeking further advice should discuss this with their immunisation provider or could be referred to a specialist immunisation clinic for further reassurance (see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*).

Reporting adverse events following immunisation

Surveillance for adverse events following immunisation is an integral part of the Australian National Immunisation Program, and underpins the safe use of all vaccines in Australia. Surveillance of AEFI aims to detect changes in the rates of known adverse events, any unrecognised or unexpected adverse events, or adverse events that result from program errors, such as incorrect vaccine schedule, delivery or storage. It is very important that all immunisation service providers report AEFI, particularly if serious or unexpected, as this will enable vaccine safety issues to be identified and managed appropriately as soon as possible. For example, reporting of AEFI by immunisation service providers in Australia in 2010 resulted in the detection of an unexpectedly high rate of fever and febrile convulsions in young children, associated with the use of one brand of seasonal influenza vaccine.[49,50] All reported AEFI are included in the Adverse Drug Reactions System (ADRS) database of the Therapeutic Goods Administration (TGA). For details on how to report AEFI, see the next section below.

Any serious or unexpected adverse event following immunisation should be promptly reported. Providers should use clinical judgment in deciding which adverse events to report and parents/carers should be encouraged to notify the immunisation service provider or health authorities of any untoward medical occurrence that follows immunisastion.

No time limit has been set to report AEFI; however, timely notification of adverse events, particularly rapid reporting of serious events, is important to identify any potential concerns. Notification does not necessarily imply a causal association with vaccination, as some events may occur coincidentally following vaccination. Any event that is suspected of being related to vaccination can be reported. All identifying information relating to the reporter and patient is kept strictly confidential. Any person, medical or non-medical, including providers who did not give the vaccine(s), can report an AEFI; however, it is very important that as much detail as possible is provided on all reports.

In addition to reporting of AEFI, immunisation service providers may need to provide additional clinical management and advice regarding future vaccination(s) for their patient and may require expert advice. Information about specialist immunisation clinics, or the contact details for paediatricians or medical specialists with experience in management of patients with AEFI, are usually available from state and territory health authorities (see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*) and from the Immunise Australia website (www.immunise.health.gov.au). For more information on managing common and rare AEFI, see above and also 3.3.1 *Vaccination of persons who have had an adverse event following immunisation*.

How to report adverse events following immunisation

AEFI are notifiable via different routes; immunisation service providers should be aware of the method of reporting for their location. In most jurisdictions (the Australian Capital Territory, New South Wales, the Northern Territory, Queensland, South Australia, Victoria and Western Australia), AEFI should be reported directly to the relevant state/territory health authority (see Table 2.3.3). AEFI notified to these state and territory health departments are then forwarded to the TGA, who manage the ADRS database, which includes all adverse reaction reports related to drugs and vaccines. Reporting can also be done directly to the TGA as described below.

Table 2.3.3: Contact information for notification of adverse events following immunisation

State/Territory	Report adverse events to	Contact information
Australian Capital Territory	ACT Health Department	02 6205 2300
New South Wales	NSW Public Health Units	1300 066 055 (for connection to Public Health Unit)
Northern Territory	NT Department of Health	08 8922 8044
Queensland	Queensland Health	Complete an AEFI initial report form, available at: www.health.qld.gov.au/immunisation or by phoning 07 3328 9888. Fax the completed form to the number provided on the form.
South Australia	SA Health	1300 232 272 www.sahealth.sa.gov.au
Tasmania	Direct to the TGA	1800 044 114 or complete the 'Blue card' reporting form (see below)
Victoria	SAEFVIC	03 9345 4143 or online at www.saefvic.org.au
Western Australia	State Health Department, WAVSS	08 9321 1312 or online at wavss.health.wa.gov.au

Alternatively, reporting directly to the TGA can be done by any person in any jurisdiction. Reports are submitted using the 'Blue card' adverse reaction reporting form. Paper copies of the 'Blue card' are available from:

Office of Product Review
Therapeutic Goods Administration
Reply Paid 100
Woden ACT 2606
Telephone: 1800 044 114

or online at www.tga.gov.au/safety/problem-medicines-forms-bluecard.htm.

Alternatively, the adverse reaction reporting form can be completed and submitted online via the TGA website at www.ebs.tga.gov.au/ebs/ADRS/ADRSRepo.nsf?OpenDatabase.

Consumers and immunisation service providers can also report AEFI (and adverse drug reactions) via the national Adverse Medicines Events telephone reporting line on 1300 134 237. This service is operated by the National Prescribing Service (NPS) (www.nps.org.au) and funded by the Australian Government through the Department of Health.

The TGA, in turn, forwards copies of individual reports of AEFI from vaccines on the NIP schedule back to state/territory health departments for their information.

Information on AEFI reports to the TGA from all sources are aggregated, and detailed information on AEFI reporting rates and trends in AEFI are published on a 6-monthly basis in the journal *Communicable Diseases Intelligence* (www.health.gov.au/internet/main/publishing.nsf/content/cda-pubs-cdi-cdiintro.htm).[24,51]

2.3.3 Documentation of vaccination

It is essential that immunisation service providers ensure there is appropriate documentation of all vaccinations given to persons of any age. There are a number of ways in which this should be done.

All vaccines administered to children should be documented in the child's clinical file and the individual child health record that is established for all newborn infants. This record should be kept by the parent/carer and presented every time the child is seen by a health professional.

Vaccines administered to adolescents and adults should be recorded in both the vaccinated person's clinical file and the personal health record, or individual record, of vaccination. The following details should be recorded:

- the person's full name and date of birth
- the details of the vaccine given, including the brand name, batch number and dose number
- the date and time of vaccination
- the site of administration
- the name of the person providing the vaccination
- the date the next vaccination is due.

Some state/territory health departments also have specific requirements for documentation of vaccines administered to healthcare workers/healthcare students undertaking work or clinical placement within state/territory health facilities. Refer to the relevant state/territory health department for further details (see Appendix 1).

Immunisation service providers should also report vaccination details to the appropriate immunisation register(s) – discussed in detail below.

2.3.4 Immunisation registers

Australian Childhood Immunisation Register

The Australian Childhood Immunisation Register (ACIR) is a national database for recording details of vaccinations given to children <7 years of age who live in Australia. The ACIR commenced on 1 January 1996 and is administered by the Department of Human Services under the legislative mandate of the Commonwealth *Health Insurance Act 1973* Part IVA. Section 46B of the Act specifies how the ACIR is to be implemented and managed. Section 46E sets out the provisions for giving both de-identified and identified information to recognised immunisation service providers and other specified agencies.

Children enrolled in Medicare are automatically included on the ACIR. Children not enrolled in Medicare will be included when an immunisation service provider sends details of a vaccination to the ACIR. No vaccination information is recorded on the ACIR once a child turns 7 years of age, but any information already held is retained. The information will relate only to vaccines received between birth and the child's 7th birthday.

The ACIR provides an important means of accountability and evaluation of the childhood vaccination program. The ACIR is the primary means of determining vaccination coverage at national, state/territory and local levels. It also provides a central vaccination history for each child, which is accessible to any Australian immunisation service provider wishing to assess vaccination status. Since 1998, data held on the ACIR have been used to determine a family's entitlement to the Child Care Benefit and, from July 2012, the Family Tax Benefit Part A supplement. It is, therefore, important that immunisation service providers submit vaccination data to the ACIR promptly.

Reporting to the Australian Childhood Immunisation Register

Immunisation service providers should send to the ACIR details of all NIP and private vaccinations given to children <7 years of age. Vaccination details may be submitted by sending data electronically via Medicare Online or the ACIR secure Internet site, or by using a paper form. Immunisation service providers in Queensland and the Northern Territory who currently send data to the ACIR via their state/territory health department should continue to do so. Immunisation service providers in all other states/territories should send data directly to the ACIR.

A child's vaccination record can also be updated with vaccination details where the vaccination was performed by another immunisation service provider, including vaccines given while the child was overseas, by completing and sending an Immunisation History form to the Department of Human Services. Forms are available on the health professionals section of the Medicare Australia website (www.medicareaustralia.gov.au/provider/pubs/forms/files/acir-immunisation-encounter-form-0911.pdf).

When relevant, immunisation service providers should complete either the 'Medical Contraindication' or other objection forms and forward these to the ACIR.

For further information about the ACIR and reporting vaccination information, see 'The ACIR on the Internet' below. In addition, assistance on any reporting issues can be obtained from the ACIR Enquiry Line, 1800 653 809 (free call).

The Australian Childhood Immunisation Register on the Internet

The Department of Human Services (DHS) website (www.humanservices.gov.au/customer/services/medicare/medicare-online-services) houses ACIR information and resources. The website has a general information area for individuals and families, a general information area for health professionals and a secure area for approved immunisation service providers only.

The secure ACIR Internet site (https://www1.medicareaustralia.gov.au/ssl/acircirssamn) allows approved immunisation service providers to obtain a range of statistical and identified reports. Depending on the access level granted to the provider, these reports enable approved providers to view a child's vaccination details, record vaccination information and access a range of other reports. All health professionals with access to Health Professional Online Services (HPOS) can access the ACIR Internet site through this platform. In addition, immunisation service providers can register for access to the secure ACIR Internet site only by completing the online request form, available from the Department of Human Services website. Further information or assistance may be obtained by calling the ACIR Internet Helpline on 1300 650 039.

Immunisation History Statement

Immunisation History Statements contain details of all vaccines administered to a child that are recorded on the ACIR and list the vaccines that are next due. These Statements are automatically generated when a child turns 18 months of age, 5 years of age, and on completion of the childhood vaccination schedule. These Statements will be mailed to the address most recently recorded by Medicare for that child.

Parents/carers can also get an Immunisation History Statement at any other time:

- online at www.humanservices.gov.au/customer/services/medicare/australian-childhood-immunisation-register
- from their local DHS Service Centres
- by calling 1800 653 809 (free call).

Immunisation History Statements can be used to assist in recalling vaccination history when required. For example:

- for school enrolment – a sentence will be displayed at the bottom of the Statement that says the child has received all the vaccinations required by 5 years of age
- to determine eligibility for the Child Care Benefit and the Family Tax Benefit Part A supplement – this requires that children are assessed as fully immunised; this replaced the Maternity Immunisation Allowance on 1 July 2012.

The ACIR Enquiry Line can be contacted on 1800 653 809 (free call) and any record held for a person who is now ≥7 years of age can be made available to an immunisation service provider or parent/carer.

Recording details of a deceased child

The ACIR should be notified of the death of a child to prevent an Immunisation History Statement being sent to bereaved parents/carers. Advice of a child's death can be provided to the ACIR by calling 1800 653 809 (free call), or by sending details on practice stationery. Details should include the child's name, address, date of birth, Medicare number and date of death.

Children who have moved to live overseas

A child who has moved overseas can be removed from the ACIR by sending details to the ACIR by fax, phone or secure site email. This prevents the child's name continuing to appear on ACIR reports of overdue children.

Children born overseas who have moved to live in Australia permanently

A child born overseas who has moved permanently to Australia will be automatically added to the ACIR upon enrolment with Medicare. Children residing temporarily in Australia are not included on the ACIR.

Ascertaining individual vaccination status

Parents/carers can telephone the ACIR on 1800 653 809 (free call) for information about their child's vaccination status, regardless of where the child's vaccination was given. Immunisation service providers can also request a child's vaccination status by telephone.

Vaccination coverage and other reports

ACIR reports assess progress towards national targets, help to identify areas with low vaccination levels, and assist in planning vaccination programs.

Practices can receive quarterly reports on vaccination coverage for children within their practice. Other reports, including those that identify a child's vaccinations and due/overdue details, are available through the secure area of the ACIR Internet site (https://www1.medicareaustralia.gov.au/ssl/acircirssamn) to approved immunisation service providers.

National Human Papillomavirus Vaccination Program Register

The National HPV Vaccination Program Register (NHVPR), also referred to as the 'HPV Register', was established following the passing of the *National Health Amendment Act (National HPV Vaccination Program Register) Bill* in 2007. Establishment and maintenance of the HPV Register facilitates the implementation of the National HPV Vaccination Program funded by the Australian Government. The HPV Register is run by the Victorian Cytology Service, together with the Department of Health. It plays an essential role in monitoring and evaluating the HPV Vaccination Program by recording information about HPV vaccine doses administered in Australia.

Reporting to the HPV Register

Details on HPV vaccinations given in the community are provided to the HPV Register by the immunisation service provider who administers the vaccine. Vaccination details may be submitted electronically, via data uploads or direct entry using the secure website, or in hard copy, using one of the approved notification forms. Immunisation service providers in Queensland and the Northern Territory report data to the HPV Register via their state/territory health authority. Immunisation service providers wishing to submit vaccination data electronically need to be approved and registered with the HPV Register in order to notify administered doses. General practitioners are required to register with the HPV Register in order to notify administered doses. Further information about registration and notification procedures is available from the HPV Register website (www.hpvregister.org.au) or by phoning 1800 478 734 (1800 HPV REG).

HPV vaccination coverage and other reports

For immunisation service providers, the HPV Register has developed overdue HPV vaccine dose reports for their patients, which are available online via the secure website. De-identified HPV vaccination coverage data and other reports have also been developed to inform policy making, and support program delivery and approved research. National coverage data are made publicly available via the Immunise Australia website (www.immunise.health.gov.au).

HPV Register statements

The HPV Register sends Completion Statements and History/Reminder Statements. Immunisation History Statements, containing details of the vaccinations recorded on the HPV Register, are sent to persons who are overdue for HPV vaccination within the school-based program. Completion Statements are sent to persons who have completed the 3-dose HPV vaccination course. Vaccinated persons and parents/guardians can request a statement at any time by phoning 1800 478 734 (1800 HPV REG). In the event that booster doses are required in future, all eligible persons will be notified by the HPV Register.

HPV vaccination status

Vaccinated persons and parents/guardians can phone the HPV Register on 1800 478 734 (1800 HPV REG) to obtain their or their child's HPV vaccination status. Immunisation service providers can also request a person's vaccination status by phone or can view these online if they are registered with the HPV Register. The HPV Register initially only recorded vaccinations for females, but from 2013 will also record vaccinations given to males.

HPV Register secure website

The HPV Register secure website allows registered and approved immunisation service providers access to the live national HPV Register database to view a patient's vaccination history as well as access to overdue dose reports. Further information on how to request access to the HPV Register secure website can be found on the health professionals page of the HPV Register website (www.hpvregister.org.au) or by phoning 1800 478 734 (1800 HPV REG).

Other immunisation registers

The Australian Q Fever Register (www.qfever.org), established by Meat and Livestock Australia (MLA), has records of receipt of Q fever vaccination for some individuals, which can be accessed by registered users (see also 4.15 *Q fever*).

State/territory government health departments maintain records of immunisations provided through school-based vaccination programs. Information on how to access records of vaccines received through school-based vaccination programs can be obtained from state/territory government health departments (see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*).

Some state/territory governments operate a jurisdictional immunisation register, though the scope of these varies.

Queensland

The Vaccine Information and Vaccine Administration System (VIVAS) is a database of vaccination events for all children up to 10 years of age, adolescents and (some) adults in Queensland who are vaccinated with nationally- or state-funded vaccines.

Immunisation service providers in Queensland are encouraged to report all vaccinations, either directly to VIVAS via the Queensland Health Vaccination Record form or using practice software to electronically transfer data (via the ACIR) to Queensland Health. Vaccination Record forms can be posted reply paid to VIVAS or faxed directly. Providers reporting to VIVAS should do so at least once a week to ensure the supply of data is not delayed and is available for the purposes of calculating parental and provider incentive payments using ACIR data.

Immunisation service providers enrolled on VIVAS have access to a range of services, such as reminder notices for overdue or unimmunised patients, individual vaccination records via local public health units, and Queensland's centralised Vaccine Distribution System (www.health.qld.gov.au/immunisation/health_professionals/vivas.asp).

The Northern Territory

The NT Immunisation Register records details of all vaccines administered to anyone in the Northern Territory (NT). Immunisation service providers in the NT are encouraged to report all administered vaccines to the NT Immunisation Register. This can be done by direct electronic transfer from some services or via printed lists from clinical software programs and/or by completing the NT childhood or adult vaccination recording form (www.health.nt.gov.au/Centre_for_Disease_Control/Immunisation/Recording_and_Reporting_Forms/index.aspx).

The NT Immunisation Register routinely provides relevant data on vaccination encounters to the ACIR and the HPV Register.

The NT Immunisation Register provides a number of services, such as recall lists for childhood immunisations in remote areas, individual vaccination records, and web-based access for NT immunisation service providers for immunisation histories for children <15 years of age (www.health.nt.gov.au/Centre_for_Disease_Control/Immunisation/NT_Immunisation_Database/index.aspx).

References

A full reference list is available on the electronic *Handbook* or website www.immunise.health.gov.au

PART 3 VACCINATION FOR SPECIAL RISK GROUPS

3.1 VACCINATION FOR ABORIGINAL AND TORRES STRAIT ISLANDER PEOPLE

After European colonisation, Aboriginal and Torres Strait Islander (Indigenous) peoples experienced successive epidemics of infectious diseases with very high morbidity and mortality; many of these diseases have now become vaccine preventable. The diseases with the most serious impact were smallpox, tuberculosis, influenza, measles and syphilis, with estimated mortality rates of over 30% for smallpox epidemics and 20% for measles epidemics.[1] These high rates of disease were mainly due to a lack of previous exposure,[2] followed by high-density living in newly established settlements. Over many decades, higher rates of infectious disease have been associated with lower standards of living and poorer access to water, housing and health care.[3] Social determinants of health, such as low educational outcomes, lack of control over life circumstances and lack of cultural safety, are also associated with poor health outcomes, including increased infectious disease risk.[4]

In recent decades, vaccination has been very successful in eliminating or substantially reducing the rates of many vaccine-preventable diseases (VPDs), such as diphtheria, polio, tetanus, hepatitis B, measles, mumps and rubella, in all Australians, and has made a substantial contribution to improvements in Indigenous child mortality.[5] For some VPDs, control is suboptimal in the general population despite high vaccination coverage (e.g. pertussis). For others, such as invasive pneumococcal disease (IPD), greater burdens of illness still occur in Indigenous persons than in non-Indigenous persons, largely due to the greater prevalence in Indigenous persons of serotypes for which vaccines do not protect, and high exposure levels associated with the environmental issues mentioned above.[5] Timeliness of immunisation can also be a factor.[5]

In recognition of the higher rates of disease in the Indigenous population, some vaccines are specifically recommended for use in Indigenous persons, or for administration to a broader age range than is recommended for non-Indigenous persons (see Table 3.1.1). This chapter discusses the vaccines for which there are currently different recommendations for Indigenous persons in at least some parts of Australia, or for which there have been recent changes in this respect. For children, these are bacille Calmette-Guérin (BCG), *Haemophilus influenzae* type b, hepatitis A, influenza and pneumococcal vaccines. For adults, these are hepatitis B, influenza and pneumococcal polysaccharide vaccines.

Table 3.1.1: Additional* vaccines recommended for Indigenous persons, due to their higher risk of disease

Vaccine	Recommendation for Indigenous persons
BCG	Neonates living in areas of high TB incidence† 1 dose
Hepatitis A	Children resident in the Northern Territory, Queensland, South Australia and Western Australia 2 doses in the 2nd year of life‡
Hepatitis B	Adults who have not previously been vaccinated against hepatitis B and are non-immune
Influenza	All persons aged ≥15 years Consider in all children aged ≥6 months, especially those aged <5 years Annual vaccination
Pneumococcal conjugate (13vPCV)	Children resident in the Northern Territory, Queensland, South Australia and Western Australia Booster dose in 2nd year of life in addition to primary course‡
Pneumococcal polysaccharide (23vPPV)	Persons aged 15–49 years with underlying conditions increasing the risk of IPD§ All persons aged ≥50 years§

* In addition to those vaccines recommended for all Australians or those in particular medical, occupational, behavioural or other risk groups.

† Northern Territory, Queensland, northern South Australia

‡ Exact ages may differ between jurisdictions.

§ See 4.13 *Pneumococcal disease* for recommendations on revaccination.

3.1.1 Children

BCG vaccine and tuberculosis

BCG vaccine is recommended for Indigenous neonates in regions of high tuberculosis (TB) incidence, where infants are at higher risk of acquiring this serious condition. BCG vaccine is provided for Indigenous neonates in the Northern Territory, Queensland and parts of northern South Australia, but no longer in Western Australia.[6] State/territory health authorities should be consulted to determine the recommendations for particular areas, including where BCG vaccination is being considered for neonates <2.5 kg in weight. (See also 4.20 *Tuberculosis*.)

Tuberculosis was most likely introduced to the Indigenous population in the early years of European settlement. It became the largest single cause of death for Indigenous persons in the last quarter of the 19th century and the first quarter of the 20th century, coinciding with large-scale movement from nomadic life to settlements.[1] In some communities tuberculosis was responsible for more than 20% of deaths.[1] Control measures in the second half of the 20th century were effective for both Indigenous and non-Indigenous populations, but disparities have persisted. In southern states the notification rate for tuberculosis in Indigenous persons is comparable to that of Australian-born non-Indigenous persons,[7] but there is considerable geographic variation. The Northern Territory has consistently had the highest rates of any jurisdiction, and, in 2007, TB incidence was 13-fold higher among Indigenous persons than non-Indigenous persons.[7] Very high rates among Indigenous persons have been documented in Far North Queensland[8] and northern South Australia,[9] but not in New South Wales in recent years.[10] BCG vaccine reduces pulmonary tuberculosis and provides substantial protection against disseminated forms of the disease in young children.[11] Nevertheless, as the incidence of pulmonary tuberculosis in adults and the risk of disseminated tuberculosis in infants decreases, the risk of severe complications of BCG vaccination, documented in indigenous persons of other countries, becomes a significant consideration.[12] BCG vaccine is usually administered to eligible infants by hospital staff (i.e. midwives or nurses who have been specially trained) soon after delivery. Injection technique is particularly important for BCG vaccination, which must be administered intradermally. Adverse events, such as regional lymphadenitis, are less common when vaccination is performed by trained staff.[13]

Haemophilus influenzae type b

Since October 2009, only one type of *Haemophilus influenzae* type b (Hib) vaccine (PRP-T) has been used in Australian infants (see 4.3 *Haemophilus influenzae type b*).

Before the introduction of an effective Hib vaccine, not only was the incidence of invasive Hib disease very high in Indigenous children, particularly in more remote areas, it also occurred at a younger age than in non-Indigenous children.

Thus, a vaccine to prevent Hib disease in Indigenous children needed to be immunogenic as early as possible in infancy. The previously used Hib-containing vaccines, known by the abbreviation PRP-OMP, were more immunogenic at 2 months of age than the other conjugate Hib (PRP-T) vaccines, and so were the preferred Hib vaccine type for Indigenous children in the first Hib vaccination programs beginning in 1993. Since then, there has been a dramatic decline in Hib disease in Indigenous children.[14,15] New combination vaccines that include a Hib (PRP-T) component, and have the advantage of reducing the number of injections, were introduced in some jurisdictions from November 2005. Initially PRP-T vaccines were not recommended for Indigenous children in jurisdictions with higher disease incidence, but either PRP-OMP or PRP-T vaccine could be given to other children. Following an international shortage of PRP-OMP vaccine, it was progressively replaced by PRP-T-containing vaccines for all children. Invasive Hib disease and nasopharyngeal colonisation with Hib are being closely monitored in high-incidence settings such as the Northern Territory and Western Australia following this change. To date, there has not been any change in Hib epidemiology found in association with the change to PRP-T-containing vaccines for Indigenous children.

Hepatitis A

Hepatitis A vaccination is recommended for Indigenous children in those jurisdictions with high disease incidence: the Northern Territory, Queensland, South Australia and Western Australia (see 4.4 *Hepatitis A*). Two doses should be given, commencing in the 2nd year of life. The recommended ages of administration vary between states and territories, so jurisdictional health authorities should be contacted for further details about local vaccination schedules.

Hepatitis A infection was common during the 1990s in Indigenous children across northern and central Australia.[16-18] Most children acquired the virus in the first 5 years of life, which is a typical finding in populations with disadvantaged living conditions. Although the symptoms of infection in early childhood are usually mild or absent, cases complicated by liver failure and death have been reported among Indigenous children in Far North Queensland[18] and the Kimberley,[16] and recorded hospitalisation rates are more than 50 times higher in Indigenous children than in non-Indigenous children.[5] A vaccination program for Indigenous children was introduced in north Queensland in 1999 and resulted in a 92% decrease in the number of reported cases, from 787 cases in all children during the period 1996–1999 to 66 cases in the period 2000–2003. This decrease in hepatitis A disease was observed in both Indigenous and non-Indigenous children, suggesting a substantial herd immunity effect.[19] From 2005, the hepatitis A vaccination program was extended to include all Indigenous children aged ≤2 years resident in the Northern Territory, Queensland, South Australia and Western Australia. Notifications have fallen by over 90%, from more than 50 per 100 000 in 2005 to less than 5 per 100 000 in 2009.

Hepatitis B

See 'Hepatitis B' under 'Adults' below.

Influenza

Annual influenza vaccination is recommended for any person ≥6 months of age (see 4.7 *Influenza*) for whom it is desired to reduce the likelihood of becoming ill with influenza. Young infants and children aged <5 years, particularly Indigenous children, are at increased risk for hospitalisation and increased morbidity and mortality following influenza.[5] Annual influenza vaccine is particularly recommended for Indigenous persons ≥15 years of age due to the substantially increased risk of hospitalisation and death from influenza and pneumonia in this age group (see 'Influenza' in 3.1.2 *Adults* below).[20]

Pneumococcal disease

The 13-valent pneumococcal conjugate vaccine (13vPCV) is recommended for all children in a 3-dose infant vaccination schedule, replacing the 7-valent pneumococcal conjugate vaccine (7vPCV) in all jurisdictions except the Northern Territory, where it replaced the 4-dose schedule of the 10-valent pneumococcal conjugate vaccine (10vPCV).

In addition to a primary course of 3 doses of 13vPCV, at 2, 4 and 6 months of age, a booster dose of 13vPCV is also recommended at 12–18 months of age for Indigenous children in areas of high incidence (i.e. the Northern Territory, Queensland, South Australia and Western Australia). This 13vPCV booster dose replaces the 23-valent pneumococcal polysaccharide booster or 4th dose of 10vPCV (which was used at this schedule point for a short time in the Northern Territory) (see 4.13 *Pneumococcal disease*).

Prior to the availability of conjugate pneumococcal vaccines, Central Australian Indigenous children had rates of IPD that were among the highest ever reported in the world.[21] Very high rates were also reported in Indigenous children in other parts of northern Australia.[22,23] High rates of pneumococcal pneumonia have also been documented in Central Australian Indigenous children,[24] and *Streptococcus pneumoniae* has been implicated in the high rates of otitis media in Indigenous children.[25] 7vPCV was made available for Indigenous children, and non-Indigenous children with medical risk factors, from 2001, 4 years prior to the universal program for all children in Australia. The initial program was highly successful, resulting in a rapid decline in invasive pneumococcal disease due to the serotypes contained in the 7vPCV among Indigenous and non-Indigenous children.[26-28] However, a wider range of serotypes is responsible for disease in Indigenous children, and therefore a smaller proportion of cases is vaccine preventable.[22,23] While an initial reduction in IPD was observed, IPD incidence still remains higher in Indigenous children than in non-Indigenous children.

3.1.2 Adults

Hepatitis B

Indigenous persons should have their risks and vaccination status for hepatitis B reviewed, be offered testing for previous hepatitis B infection, and be offered vaccination if non-immune. (See also 4.5 *Hepatitis B*.)

High rates of mortality and morbidity from hepatitis B among Indigenous persons have been recognised ever since the original identification of the 'Australia antigen' in 1965.[29] Prior to vaccination, estimates of the prevalence of markers of previous infection in Indigenous communities ranged from 20 to 100%. In the Northern Territory, the incidence of primary hepatocellular carcinoma was 10 times greater in Indigenous persons than in non-Indigenous persons, and comparable to high-incidence countries such as China.[30] Vaccination programs have had substantial impacts on infection and carriage rates in both Indigenous and non-Indigenous Australians.[5,31] However, there is evidence that new infections continue to occur at a higher rate in Indigenous persons,[5,32-34] probably due to a combination of pre-existing high carriage rates, susceptible persons in older age groups (who were not eligible for vaccination programs),[33,34] low coverage in early targeted programs,[33,34] and a poorer immunological response to vaccination.[35]

Influenza

Annual influenza vaccination is recommended for all Indigenous persons aged ≥15 years (see 4.7 *Influenza*).

Influenza and its complications, especially secondary pneumonia, have historically been major causes of morbidity and mortality in Indigenous persons, both during and outside pandemic periods. This is probably related to a high prevalence of medical risk factors such as diabetes, renal disease and excessive alcohol use, as well as poorer environmental living conditions that facilitate disease transmission.[3] Past pandemics have had disproportionately severe impacts on Indigenous persons,[1] as did the influenza A(H1N1)pdm09 pandemic in 2009. Reported rates of infection, hospitalisation and death due to pandemic A(H1N1)pdm09 were 6.6, 6.2 and 5.2 times higher, respectively, in Indigenous persons than in non-Indigenous persons.[36]

In recent times, respiratory disease has been responsible for around 8% of deaths in Indigenous persons, the vast majority being in adults.[3] Influenza disease incidence is greatest in young children and the elderly. Hospitalisation rates due to influenza and pneumonia are highest in young children and lowest in older children. Hospitalisation and death rates increase with age in all adults, but increase much earlier in Indigenous adults than in non-Indigenous adults. The vast majority of these hospitalisations and deaths are due to pneumonia, but it is not clear what proportion of these are associated with influenza.[5] Younger Indigenous adults (aged 25–49 years) have influenza and pneumonia

disease rates similar to older non-Indigenous adults (aged ≥50 years), but have much higher rates than non-Indigenous persons of the same age. In younger Indigenous adults rates are at least 8 times higher for hospitalisations and 20 times higher for deaths, compared to younger non-Indigenous adults.[5] In addition, hospitalisation rates in Indigenous children aged <5 years are more than twice the rates in non-Indigenous children of the same age, and a similar disparity exists for hospitalisation and death rates in Indigenous adults aged ≥50 years compared with non-Indigenous adults of the same age.[5] Some have suggested that previous estimates of substantial reductions in hospitalisation and mortality due to respiratory and cardiovascular disease that were attributed to influenza vaccination have over-estimated this impact.[37] However, the balance of evidence suggests influenza vaccines are effective in preventing influenza-associated disease, hospitalisation and death in healthy adults, the elderly and the medically at risk, including Indigenous persons, although this varies with the antigenic similarity between vaccine and circulating strains.[38]

Pneumococcal disease

Pneumococcal polysaccharide vaccine is recommended for all Indigenous adults aged ≥50 years, and those aged 15–49 years who have conditions associated with an increased risk of IPD. The broader age-based recommendation for Indigenous adults is due to the high rates of pneumococcal disease and higher prevalence of risk factors (certain medical conditions and tobacco smoking) in Indigenous adults, compared to non-Indigenous adults.[39] Revaccination is recommended 5 years after the 1st dose for those first vaccinated at ≥50 years of age, and a further revaccination is recommended in some circumstances (see 4.13 *Pneumococcal disease*). In the Northern Territory, 23-valent pneumococcal polysaccharide vaccine (23vPPV) is provided for all Indigenous persons aged ≥15 years. This can be counted as a 1st adult dose of 23vPPV (see 4.13 *Pneumococcal disease*). Jurisdictional health authorities should also be contacted to confirm local practices as they may vary, especially regarding revaccination.

Before the widespread use of pneumococcal conjugate vaccine in infants, IPD rates in Indigenous adults were up to 20 times higher than in non-Indigenous adults.[20] Studies in Far North Queensland and the Kimberley have demonstrated a favourable impact of 23vPPV on rates of invasive pneumococcal disease in Indigenous adults.[40,41] In some other regions there has been no decrease in disease, perhaps due to low vaccination coverage and/or non-vaccine serotype replacement.[26,42] At a national level, disparities remain in disease rates between Indigenous and non-Indigenous adults. As is the case for influenza and pneumonia, rates of invasive pneumococcal disease are highest in older Indigenous adults, with rates around 4 times higher in Indigenous than non-Indigenous adults aged ≥50 years.[5] Rates in younger adults are slightly lower, but the relative difference between Indigenous and non-Indigenous persons is much greater, around 12 times higher in Indigenous than in non-Indigenous adults aged 25–49 years.[5] Vaccination coverage has

been low in younger Indigenous adults, an issue that requires attention if the full benefits of vaccination are to be realised.[5]

Other diseases

Japanese encephalitis

The first ever outbreak of Japanese encephalitis (JE) in Australia occurred in the remote outer islands of the Torres Strait in 1995, with 3 cases, 2 of them fatal. There have been 5 cases to date acquired in Australia. Since then, JE virus has been detected frequently in sentinel animal surveillance in the outer islands. However, the sentinel pig surveillance system has been gradually disbanded since 2006, with surveillance of the last remaining herd on Cape York ceasing from the 2011–2012 wet season.

A JE vaccine (JE-Vax) was first offered to the residents of the Torres Strait Islands in late 1995 and the vaccine was integrated into the vaccination schedule for children resident in the Torres Strait Islands, commencing at 12 months of age.[43,44]

There has not been a case of JE in the Torres Strait since 1998 and the risk of JE has diminished considerably in the outer islands since the mid-1990s. Most communities have relocated pigs well away from homes, and major drainage works on most islands have markedly reduced potential breeding sites for vector mosquitoes.

In 2007, the supply of JE-Vax vaccine into Australia ceased as the manufacturer stopped production. Because of this shortage of vaccine, for a short period from September 2007 JE-Vax was restricted to use on the six outer Torres Strait Islands: Badu, Boigu, Dauan, Mabuiag, Moa and Sabai. Two new JE vaccines, Imojev and JEspect, are now available for use in those at risk in the Torres Strait (see **4.8** *Japanese encephalitis*).

Rubella

Although evidence suggests that endemic rubella is well controlled in Australia, Indigenous women living in rural and remote regions are more likely to be non-immune to rubella than non-Indigenous non-overseas-born Australians.[45] Every effort should be made to identify non-pregnant seronegative Indigenous women of child-bearing age and provide measles-mumps-rubella (MMR) vaccine, in order to prevent congenital rubella syndrome (see 4.18 *Rubella*). Vaccination with MMR vaccine also ensures adequate protection against measles (see 4.9 *Measles*).

3.1.3 Service delivery

General practitioners, Aboriginal Community Controlled Health Services, Community Health Services, the Royal Flying Doctor Service and state/territory corrective services all provide vaccination services to Indigenous persons and are important to the success of programs to vaccinate Indigenous persons. While vaccination coverage estimates vary over time and between communities, a relatively consistent finding has been higher coverage in Indigenous persons in remote areas than in urban areas.[46,47] More recently, however, this has not been the case for Indigenous children, where coverage has been high in both remote and urban areas;[48] coverage in remote areas is lower for adults than for children.[5] For vaccines recommended for both Indigenous and non-Indigenous persons, coverage is as high, or higher, in Indigenous persons as in non-Indigenous persons,[5] but vaccination is more frequently delayed.[49-52] For example, one study reported that at 7 months of age only 45.2% of Indigenous infants in the Northern Territory had completed the recommended schedule for that age point (DTPa-hepB-IPV-Hib/PCV/rotavirus), but by 18 months of age this figure had risen to 81.2%.[51] Coverage for vaccines recommended only for Indigenous persons is generally lower than for vaccines that are funded for all persons in a particular age group.[53]

These disparities point to the importance of identification of Indigenous status, particularly in mainstream health services, and particularly in urban areas. The use of patient information systems to record Indigenous status and schedule preventive health services has the potential to increase opportunistic vaccination and enable the provision of patient reminders, with resultant improvements in coverage and timeliness.[54] Culturally appropriate service delivery and communication strategies, as well as use of Indigenous-specific Medicare items, will also assist in improving access to health services for Indigenous Australians.[55-57]

References

A full reference list is available on the electronic *Handbook* or website www.immunise.health.gov.au

3.2 VACCINATION FOR INTERNATIONAL TRAVEL

3.2.1 Introduction

The number of Australians who travel overseas has increased over recent years. Data available through the Australian Bureau of Statistics suggest that there were about 6.7 million short-term departures in 2010, with more than half travelling to destinations other than New Zealand or countries in North America and Europe.[1] There are various risks to health associated with international travel, including exposures to infective agents, extremes of altitude and temperature, and other physical, psychological and environmental hazards. There could also be poor quality or limited access to clean water, shelter, hygiene and sanitation facilities, and health and medical care. The level of health risks will vary with individual factors, including the travellers' underlying health and physiological state, the itinerary and activities undertaken, and the duration of exposure to various hazards during travel.

Travellers with increased risks to their health include young children and infants; pregnant women; people with underlying medical conditions, especially immunocompromising conditions due to disease or medical treatment; travellers spending extended periods in multiple regions with poor resources or in remote regions; those participating in mass gatherings (major sporting, cultural, social or religious events involving large numbers of people); and migrant families travelling back to their country/region of origin to visit friends and relatives (VFR). Those undertaking VFR travel are more likely to have closer contact with local populations, stay in remote or rural areas, and consume higher-risk food and beverages. They are also less likely to adequately perceive health risks associated with travelling, specifically seek pre-travel health advice, or be adequately vaccinated or prophylaxed.[2,3]

3.2.2 Infections acquired by travellers

Exposure to infectious diseases, some of which are vaccine preventable, is one of the many health hazards of international travel. Although some of these diseases are present in Australia, the risk of acquiring them overseas may be higher because of higher disease incidence in other countries and/or increased risk of exposure resulting from activities undertaken during the travel period.

Common infections acquired by travellers include those that follow ingestion of contaminated food or beverages.[4,5] Most of these are diarrhoeal diseases due to enteric pathogens, but infections with extra-intestinal manifestations, such as hepatitis A and typhoid, are also acquired this way. Vaccines against hepatitis A, typhoid and cholera are available.

Insect-borne (particularly mosquito-borne) infections, such as malaria and dengue, are important causes of fever in Australian travellers returning from endemic areas, particularly Southeast Asia and Oceania.[5] Japanese encephalitis occurs throughout a large part of Asia and the Western Pacific region, including

Papua New Guinea. Yellow fever occurs only in parts of Africa and Central and South America, while tick-borne encephalitis occurs in parts of Europe and Asia. Vaccines are available for protection against Japanese encephalitis, yellow fever and tick-borne encephalitis.

Vaccine-preventable infections transmitted via aerosols and/or droplets include influenza, meningococcal disease, measles, mumps and varicella (chickenpox); influenza is typically the most frequent vaccine-preventable infection among travellers.[6] Incidences of measles and mumps are higher in many overseas countries, including some developed countries, than in Australia. Tuberculosis is a rare infection in travellers, and is more likely to be acquired by expatriates who live in endemic areas for long periods than by short-term visitors.

Blood-borne and sexually transmitted infections, such as hepatitis B, hepatitis C and human immunodeficiency virus (HIV), may pose a threat to some Australian travellers. In some areas, there is the possibility that these viruses and other blood-borne agents may be transmitted by healthcare workers using non-sterile medical equipment or other poor infection control practices. Hepatitis B vaccine is relevant to many travellers.

Travellers may be exposed to a variety of other exotic infectious agents, such as rabies (from bites or scratches from rabid dogs and other mammals in many countries), schistosomiasis (from exposure to water infested with the parasites, in Africa in particular), and leptospirosis (through activities like rafting or wading in contaminated streams). Of these, only rabies can be prevented by vaccination.

Some other vector-borne diseases and parasitic (including protozoal and helminthic) diseases are also important for international travellers, some of which are preventable through appropriate barrier precautions and chemoprophylaxis (e.g. malaria).

3.2.3 Practical aspects of recommending vaccinations for travellers

Although important, recommending appropriate vaccinations is not the only component of a pre-travel medical consultation, and vaccines relevant for travelling are not restricted to those for prevention of diseases that occur most commonly overseas ('travel vaccines'). Recommendation of a vaccine for travelling only on the basis of the destination country is undesirable. There is no single 'correct' list of vaccines for travelling to any single country.

In a pre-travel medical consultation, it is prudent to also acquire adequate information regarding:

- relevant personal information of the traveller, including age, pregnancy or planning of pregnancy, or even possible financial constraints
- underlying medical conditions of the traveller, particularly immunocompromising conditions, and current medications

- vaccination history (including adverse events following immunisation) and allergy history of the traveller
- detailed intended itinerary, including date of departure (and time period available for vaccinations), specific localities and routes, rural versus urban stay, duration of stay, likely access to healthcare and other services, and probability of deviation from planned itinerary
- purpose(s) of travel and intended activities, especially those susceptible to various environmental risks and hazards
- plans for travel insurance.

This information will not only facilitate recommendations of preventive vaccinations and/or chemoprophylaxis that are commensurate with exposure risks and tailored to the proposed trip, but also provision of other important preventive health advice (e.g. food and water precautions, avoidance of bites from mosquitoes or other arthropods) and advice regarding management of possible health conditions during travel.

Some overseas organisations, such as schools, colleges and universities, have policies requiring evidence of vaccination and/or immunity against some vaccine-preventable diseases, for example, measles and meningococcal disease. These requirements should be taken into account while planning and scheduling immunisation prior to departure.

The vaccination needs for a traveller may be conveniently considered in several categories.

Routinely recommended vaccines (not specifically related to travelling overseas)

All travellers should be up to date with current standard vaccination recommendations. Consideration should also be given to any other vaccines that may be relevant to the individual's health status or underlying medical conditions, occupation or lifestyle (e.g. pneumococcal polysaccharide vaccine for an elderly person or person otherwise recommended to have had pneumococcal vaccine, hepatitis B vaccine for a first aid officer). The probability of exposure to some of these diseases may be greater while travelling overseas, even to 'developed' countries (e.g. measles and mumps). For some itineraries, it may be appropriate for some booster doses to be received sooner (i.e. before travel) than at the routine recommended time (e.g. diphtheria-tetanus booster).

Selected vaccines based on travel itinerary, activities and likely risk of disease exposure

A risk assessment approach should be adopted in recommending some selective vaccines based on travel itineraries ('travel vaccines'). Potential risks of disease exposure and protective benefits from vaccinations should be weighed against potential adverse effects and both non-financial and financial costs arising from vaccinations. Priority should be given to vaccines for diseases that are common

and of significant impact (e.g. influenza and hepatitis A), and to those diseases that, although less common, have severe potential adverse outcomes (e.g. Japanese encephalitis and rabies). Booster doses should be considered where appropriate (see Table 3.2.1). Because of the imminence of departure, sometimes an 'accelerated schedule' may be considered appropriate (e.g. for hepatitis B or the combined hepatitis A/hepatitis B vaccine – see the relevant disease-specific chapters in Part 4). Note that, while immunity may be established sooner with the accelerated schedule, an additional dose is required about a year later for completion of the course to augment long-term protection. For children, the lower age limits for recommendation of selected vaccines should be noted (see Table 3.2.2).

Vaccines required by International Health Regulations or for entry into specific countries

Currently, yellow fever vaccination is the only vaccination that may be required by the International Health Regulations for travelling in certain situations, for the purpose of individual protection if one is likely to be exposed and/or for protection of vulnerable populations (in countries with relevant vectors) from importation of the disease. Some countries, including Australia, may require documented evidence of yellow fever vaccination as a condition of entry or exit. Although there are exceptions, this would mostly be relevant for travellers who originate from, or have travelled or made transit through, countries in Africa or South America (see 4.23 *Yellow fever* and 3.2.6 *Further information* below). *Current requirements should be referred to when advising travellers regarding yellow fever immunisation requirements*.

The Ministry of Health of Saudi Arabia annually issues specific requirements and recommendations for entry visas for travellers on pilgrimage to Mecca in Saudi Arabia (Hajj and Umra). For pilgrims travelling directly from Australia, only evidence of quadrivalent meningococcal vaccination is currently mandatory. However, current requirements should be referred to when advising prospective Hajj and Umra pilgrims (see 3.2.6 *Further information* below).

Vaccine administration and documentation

It is not unusual that multiple vaccines would be required before travelling. The standard recommendations and precautions for administration of multiple vaccines are applicable (see 2.2 *Administration of vaccines*).

Multiple clinic visits may be necessary when multiple vaccines and vaccines that involve multiple doses are involved (e.g. rabies pre-exposure prophylaxis or hepatitis B vaccine). Special attention should be paid to the appropriate scheduling of these visits, taking into account dose interval precautions (e.g. multiple live vaccines), requirement for pre-vaccination tests (e.g. tuberculin skin test), and potential interference by some antimalarials if relevant (e.g. rabies vaccine). Ideally, vaccination courses should be started early enough before

departure to allow for the period when most adverse events are expected to occur and to allow sufficient time for adequate immunity to develop.

It is important to document travel vaccines appropriately, not only in the clinic's record but also in a suitable record that can be carried by the traveller. It is recommended that the record also includes all the other 'routinely recommended' vaccines that the traveller has ever received. An International Certificate of Vaccination or Prophylaxis (ICVP), issued by an authorised medical practitioner in accordance with the International Health Regulations (2005), is required for yellow fever vaccination.

3.2.4 Vaccines

Detailed information regarding each of the vaccines discussed below is provided in each of the corresponding disease-specific chapters of this *Handbook*. This section provides some general guidance in considering whether a particular vaccine may be advisable for a traveller.

All prospective travellers should have been vaccinated according to the recommended vaccination schedule appropriate for the traveller's age and underlying health conditions. All children should be vaccinated according to the NIP schedule. In exceptional circumstances, the NIP vaccines may be administered at the minimum age rather than the recommended age (see 2.1.5 *Catch-up*, Table 2.1.5 *Minimum acceptable age for the 1st dose of scheduled vaccines in infants in special circumstances*). Children vaccinated using the minimum age rather than the recommended age may require extra vaccine doses to ensure adequate protection. The minimum interval requirements between doses must be observed (see 2.1.5 *Catch-up*, Table 2.1.7 *Minimum acceptable dose intervals for children <10 years of age*).

Routinely recommended vaccines (not specifically related to travelling overseas)

Diphtheria, tetanus and pertussis

Adult travellers should be adequately protected against tetanus before departure, particularly if their risk of sustaining tetanus-prone wounds is high or there could be delays in accessing health services where they can receive tetanus toxoid boosters safely if required. Protection against pertussis should also be offered at this opportunity (as dTpa) if no previous dose of dTpa has been given (see 4.12 *Pertussis*). Before departure, adults should be given a booster dose of dT, if more than 10 years have elapsed since the last dose, or dTpa if not given previously. For high-risk trips, consider giving a booster of either dTpa or dT if more than 5 years have elapsed (see 4.19 *Tetanus*).

Hepatitis B

Most Australian children born since 2000, and a high proportion of adolescents, will have been vaccinated against hepatitis B under the NIP or jurisdictional school-based vaccination programs. Long-term or frequent travellers to regions

of intermediate or high endemicity of hepatitis B, including Central and South America, Africa, Asia or Oceania, are recommended to be vaccinated against hepatitis B, due to the potential for inadvertent exposure to hepatitis B virus through blood-borne or sexual routes, including unplanned medical or dental procedures. A survey has shown that about half of Australian travellers who spent at least 3 nights in Southeast or East Asia had participated in at least one activity with a risk of acquiring hepatitis B.[7] (See also 4.5 *Hepatitis B*.)

Influenza and pneumococcal disease

Older travellers (usually those aged ≥65 years) and those with any relevant underlying medical or behavioural risk factors (see 4.7 *Influenza* and 4.13 *Pneumococcal disease*) should receive the seasonal influenza vaccine and/or should have received the 23-valent pneumococcal polysaccharide vaccine. All travellers should consider influenza vaccine, especially if travelling during the influenza season of the destination region(s). The influenza vaccine is particularly relevant if influenza epidemics are occurring at the traveller's destination(s), and for travellers in large tourist groups, especially those that include older persons, or travelling on cruises, where they are likely to be in confined circumstances for days to weeks (see 4.7 *Influenza*).

Measles, mumps, rubella and varicella

Most measles outbreaks in Australia now result from an infection imported by inadequately vaccinated young travellers. Incidences of measles and mumps are higher in some overseas countries, regions or communities, including developed countries, than in Australia. Australians born during or since 1966 who have not received 2 doses of measles-, mumps- and rubella-containing vaccines should be vaccinated with the MMR vaccine before travelling (noting pregnancy precautions) (see 4.9 *Measles*). Varicella vaccine should be offered to unvaccinated travellers who have not had clinical disease, or where serology demonstrates lack of immunity in those with an uncertain history of clinical disease (see 4.22 *Varicella*).

Poliomyelitis

All travellers should be age-appropriately immunised against polio (see 4.14 *Poliomyelitis*). If travelling to countries where wild poliovirus transmission still occurs (i.e. Afghanistan, Pakistan, Nigeria and others where polio may have been re-established or have been imported – check recent updates), inactivated poliomyelitis vaccine (IPV) should be offered to those who have not completed a 3-dose primary course of any polio vaccine, and a single booster dose should be given to those who have previously completed the primary course. For an up-to-date list of affected countries see www.polioeradication.org.

Selected vaccines based on travel itinerary, activities and likely risk of disease exposure

Cholera

Cholera vaccination is rarely indicated for most travellers,[8] as the risk of acquiring cholera for travellers in general is very low, provided that general precautions to avoid contaminated food and water are taken. The protective efficacy against *Vibrio cholerae* O1 is high (>80%) among children aged 2–5 years for the initial 4–6 months after 3 doses, but wanes to become insignificant afterwards. For those aged >5 years, protective efficacy is about 78% and 63% for the 1st and 2nd year, respectively, and wanes to become insignificant beyond 2 years after vaccination.[9] The vaccine does not protect against the *V. cholerae* O139 serogroup. It is only indicated for those travellers at considerable risk, such as those working in humanitarian disaster situations. However, since cholera and enterotoxigenic *Escherichia coli* (ETEC) share the same toxin, cholera vaccination does afford some partial short-term protection against ETEC-caused travellers' diarrhoea. The effect lasts only about 3 months, and the overall reduction of travellers' diarrhoea risk would be less than 15%;[10] however, there may be some travellers who would benefit from improved protection against travellers' diarrhoea, including those with achlorhydria and those at increased risk of severe or complicated diarrhoeal disease (see 4.1 *Cholera*).

Certification of cholera vaccination has been abandoned globally, and no countries have official entry requirements for cholera vaccination.

Hepatitis A

Hepatitis A vaccine should be recommended to all travellers ≥1 year of age travelling to moderately or highly endemic countries (including all developing countries), except those who are likely to have acquired natural immunity following previous infection (see 4.4 *Hepatitis A*). There is no longer any place for the routine use of normal human immunoglobulin to prevent hepatitis A in travellers (see 4.4 *Hepatitis A*).

Japanese encephalitis

The mosquito-borne Japanese encephalitis virus is endemic in many countries in Asia and the Western Pacific region, including Papua New Guinea. High risk of transmission occurs in rural irrigated paddy and pig-farming environments. Vaccination is recommended for travellers spending a month or more in rural areas of high risk in endemic regions and should be considered for shorter-term travellers, particularly if travel is during the wet season or anticipated to be repeated, and/or there is considerable outdoor activity and/or accommodation is inadequately screened against mosquitoes. Vaccination is also recommended for expatriates spending a year or more in Asia, even if much of the stay is in urban areas (see 4.8 *Japanese encephalitis*).

Meningococcal disease

All children ≥12 months of age receive meningococcal C conjugate vaccine (MenCCV) under the NIP.

Up-to-date epidemiological information should be sought to determine the need for meningococcal vaccination in travellers. The quadrivalent meningococcal vaccine (which includes serogroups A, C, W_{135} and Y antigens) is recommended for those who intend travelling to parts of the world where epidemics of meningococcal disease occur, in particular the 'meningitis belt' of sub-Saharan Africa.[11] The Saudi Arabian authorities require that all pilgrims travelling to Mecca (for the Hajj or Umra) have evidence of recent vaccination with the quadrivalent meningococcal vaccine[8] (see 3.2.6 *Further information* below). The quadrivalent meningococcal conjugate vaccine (4vMenCV) should be used in preference to the quadrivalent meningococcal polysaccharide vaccine (4vMenPV) (see 4.10 *Meningococcal disease*). There is currently no vaccine available against serogroup B meningococcal disease.

Rabies

Travellers to rabies-endemic regions should be advised of the risk of rabies infection, and to avoid close contact with either wild, stray or domestic animals, in particular dogs, cats, monkeys and bats. Travellers should also be aware of the importance of appropriate immediate wound care of all animal bites and scratches (see 4.16 *Rabies and other lyssaviruses (including Australian bat lyssavirus)*).

Recommendation for pre-travel (i.e. pre-exposure prophylaxis) rabies vaccination (or, where indicated, booster doses) is based on an assessment of the likelihood of contact and risk of exposure to potentially rabid animals, the access to appropriate healthcare and availability of post-exposure prophylaxis, including rabies immunoglobulin, should there be an at-risk exposure, and the timeliness of such access after exposure. The previous recommendation for pre-exposure prophylaxis based on duration of stay in rabies-endemic areas (i.e. for more than a month) is arbitrary, and most Australian travellers who have required post-exposure prophylaxis have undertaken shorter periods of travel. A lower threshold for recommending rabies pre-exposure prophylaxis should be adopted for children travelling to endemic areas (see 4.16 *Rabies and other lyssaviruses (including Australian bat lyssavirus)*). Vaccination against rabies before travel ensures that a safe and efficacious vaccine has been used and simplifies the management of a subsequent exposure because fewer doses of vaccine are needed. It also means that rabies immunoglobulin, which is often extremely expensive, difficult or even impossible to obtain in many developing countries, is not required, and reduces the urgency of post-exposure prophylaxis.

Tick-borne encephalitis

Tick-borne encephalitis (TBE) is caused by a tick-borne RNA flavivirus and may involve the central nervous system. The disease is prevalent in parts of temperate regions of central and northern Europe and across northern Asia. Travellers are at particular risk when hiking or camping in forested areas in endemic regions during the summer months. Safe and effective vaccines are available. Vaccination is recommended only for individuals with a high risk of exposure. Two inactivated TBE vaccine formulations (from Austria and Germany) are available in Europe (based on the European subtype), and two other formulations, based on the Far Eastern subtypes, are available in Russia. There is limited evidence that suggests the Austrian and German vaccines induce cross-protecting immunity against the Far Eastern and Siberian subtypes.[12] While the conventional schedule for completing the primary vaccination course takes 9 to 12 months, accelerated schedules are available (see 3.2.6 *Further information* below). While no TBE vaccine is registered in Australia, a small stock of vaccine may be available in Australia for use under the Special Access Scheme.

Tuberculosis

Vaccination with BCG vaccine is generally recommended for tuberculin-negative children <5 years of age who will be staying or living in countries with a high prevalence of tuberculosis for an extended period. There is less evidence of the benefit of vaccination in older children and adults, although consideration should be given to vaccination of tuberculin-negative children ≥5 years but <16 years of age who may be living or travelling for long periods in high-risk countries (defined as having an incidence >40 per 100 000 population) (see 4.20 *Tuberculosis*).

For travellers who would require the BCG vaccine, the following precautions need to be considered when scheduling their vaccination visits:

- The BCG vaccine should preferably be given at least 3 months prior to entry into endemic areas.
- Other live viral vaccines (e.g. MMR, varicella or yellow fever) should be administered concurrently or with a minimum 4-week interval from BCG vaccination.
- A 2-step tuberculin skin test (Mantoux test), performed by trained and accredited healthcare practitioners, is recommended prior to receiving the BCG vaccine for all individuals except infants aged <6 months.
- Reactivity to tuberculin may be depressed for as long as 4 weeks following viral infections or live viral vaccines, particularly measles infection and measles-containing vaccines.
- Tuberculin skin tests and BCG vaccine are available from state/territory tuberculosis services.

Typhoid

Typhoid vaccine may be recommended to travellers ≥2 years of age travelling to endemic regions, including the Indian subcontinent, most Southeast Asian countries and several South Pacific nations, including Papua New Guinea. This advice is also relevant for those travelling (back) to endemic regions to visit friends and relatives (VFR travel). Inactivated parenteral or live oral typhoid vaccine formulations are available (see 4.21 *Typhoid*).

Yellow fever

The World Health Organization no longer routinely reports on yellow fever 'infected areas'. The yellow fever vaccine is now recommended for all travellers aged ≥9 months to areas where there is evidence of persistent or periodic yellow fever virus transmission, or when required by the country for entry (see 4.23 *Yellow fever*).[3] Countries requiring yellow fever vaccination for entry have legislation to do so in accordance with the International Health Regulations. Country requirements are subject to change at any time. Updates can be found at www.who.int/ith. To minimise the risk of yellow fever introduction, some countries, including those without current disease transmission such as Australia, may require proof of vaccination from travellers who have travelled to countries with risk of transmission. See also the Australian Government Department of Health's yellow fever fact sheet (www.health.gov.au/yellowfever).

The risk of being infected with the yellow fever virus, country entry requirements, and individual factors like age, pregnancy and underlying medical conditions must be taken into account when considering yellow fever vaccination. Vaccination is generally not recommended when travelling to areas where there is low potential for yellow fever virus exposure (i.e. no human yellow fever cases ever reported and evidence to suggest only low levels of yellow fever virus transmission in the past). However, vaccination might be considered for a small subset of travellers to these areas who are at increased risk of exposure to mosquitoes or unable to avoid mosquito bites.[3] For people aged ≥60 years, the risk of adverse events associated with the vaccine should be weighed against the potential for disease exposure and benefit of yellow fever vaccination, as this age group has an increased risk of severe adverse events after primary yellow fever vaccination[13] (see 4.23 *Yellow fever*).

Table 3.2.1: Dose and routes of administration of commonly used vaccines in adult travellers (the lower age limit for the adult dosage varies with individual vaccines – please refer to the product information)

Vaccine (adults)	Brand name	Dose (adults)	Route	Dosing intervals	Duration of immunity and/or booster recommendations
Routinely recommended vaccines (not specifically related to travelling overseas)					
Diphtheria-tetanus (dT)	ADT Booster	0.5 mL	IM	A primary course is 3 doses of dT-containing vaccine, given a minimum of 4 weeks apart; followed by booster doses 10 and 20 years after.	Prior to travel, adults should receive a booster dose of dT (or dTpa if not given previously), if more than 10 years have elapsed since their last dose of dT-containing vaccine. For persons undertaking high-risk travel, consider giving a booster dose of either dTpa or dT (as appropriate) if more than 5 years have elapsed since their last dose of dT-containing vaccine.
Diphtheria-tetanus-pertussis (dTpa)	Boostrix or Adacel	0.5 mL	IM		
Diphtheria-tetanus-pertussis-inactivated poliomyelitis (dTpa-IPV)	Boostrix-IPV or Adacel Polio	0.5 mL	IM		
Hepatitis B	Engerix-B	1.0 mL	IM	0, 1, 6 months or 0, 1, 2, 12 months or 0, 7, 21 days and 12 months*	A completed series probably gives life-long immunity.
	H-B-Vax II	1.0 mL	IM	0, 1, 6 months	
Influenza (seasonal)	Various	0.5 mL	IM or intradermal, depending on the formulation	Single dose	As different strains circulate from year to year, annual vaccination with the current formulation is necessary.

Vaccine (adults)	Brand name	Dose (adults)	Route	Dosing intervals	Duration of immunity and/or booster recommendations
Routinely recommended vaccines (not specifically related to travelling overseas)					
Measles-mumps-rubella	Priorix	0.5 mL	SC/IM	Australians born during or since 1966 who do not have documented evidence of having received 2 doses of measles-, mumps- and rubella-containing vaccine should receive at least 1 dose of MMR vaccine before travel	A 2-dose schedule provides long-lasting immunity.
	M-M-R II	0.5 mL	SC		
Pneumococcal	Prevenar 13 or Pneumovax 23	0.5 mL	IM	Single dose, for older adults, and younger adults with predisposing medical conditions – see 4.13 *Pneumococcal disease*	Recommendations vary according to age, Indigenous status and predisposing conditions – see 4.13 *Pneumococcal disease*.
Poliomyelitis	IPOL	0.5 mL	SC	For unvaccinated adults, 3 doses with minimum interval of 1 to 2 months between doses	A booster dose 10-yearly is only necessary if travelling to a poliomyelitis endemic country.
	Combination vaccines (dTpa-IPV)	See Diphtheria-tetanus-pertussis-inactivated poliomyelitis (dTpa-IPV) above and 4.14 *Poliomyelitis*.			
Varicella (chickenpox)	Varilrix or Varivax Refrigerated	0.5 mL	SC	If there is a lack of reliable history of chickenpox or the person is non-immune, and has not been vaccinated in childhood 0, 4 weeks if aged ≥14 years	A 2-dose schedule provides long-lasting immunity.

Vaccine (adults)	Brand name	Dose (adults)	Route	Dosing intervals	Duration of immunity and/or booster recommendations
Selected vaccines based on travel itinerary, activities and likely risk of disease exposure					
Hepatitis A	Avaxim	0.5 mL	IM	0, 6–12 months	A completed series probably gives life-long immunity.
	Havrix 1440	1.0 mL	IM	0, 6–12 months	
	Vaqta Adult formulation	1.0 mL	IM	0, 6–18 months	
Hepatitis A/B combined	Twinrix (720/20)	1.0 mL	IM	0, 1, 6 months or 0, 7, 21 days and 12 months*	A completed series probably gives life-long immunity to both hepatitis A and B.
Hepatitis A/typhoid combined	Vivaxim† *Note*: Only for use in persons ≥16 years of age	1.0 mL (mixed vaccine)	IM	Single dose	A dose of monovalent hepatitis A vaccine given 6–36 months later probably gives life-long immunity. The duration of protection against typhoid is probably 3 years.
Japanese encephalitis	JEspect	0.5 mL	IM	0, 28 days	The need for, and timing of, a booster dose has not yet been determined.
	Imojev	0.5 mL	SC	Single dose	The need for, and timing of, a booster dose has not yet been determined.
Meningococcal $ACW_{135}Y$ (quadrivalent conjugate 4vMenCV)	Menveo or Menactra	0.5 mL	IM	Single dose	The need for, and timing of, a booster dose has not yet been determined. Where not otherwise indicated 4vMenCV should be given in preference to 4vMenPV.

Vaccine (adults)	Brand name	Dose (adults)	Route	Dosing intervals	Duration of immunity and/or booster recommendations
Selected vaccines based on travel itinerary, activities and likely risk of disease exposure					
Meningococcal $ACW_{135}Y$ (quadrivalent polysaccharide 4vMenPV)	Mencevax ACWY or Menomune	0.5 mL	SC	Single dose	Where not otherwise indicated, 4vMenCV should be given in preference to 4vMenPV. Give 3–5-yearly boosters if the person is at ongoing risk.
Rabies (pre-exposure prophylaxis)	Mérieux Inactivated Rabies Vaccine	1.0 mL	IM/SC	0, 7, 21–28 days	Boosters are not recommended for frequent travellers unless they are at ongoing, high occupational risk of exposure – then either measure rabies antibody titres (and boost if titres are reported as inadequate) or give a single booster dose 2-yearly.
	Rabipur Inactivated Rabies Virus Vaccine	1.0 mL	IM	0, 7, 21–28 days	
Typhoid	Vivotif Oral	A single oral capsule per dose	Oral	One capsule each on days 1, 3, 5 (3-dose course), and preferably also day 7‡ (4-dose course)	If the person is at ongoing risk, repeat the course after 3 years if a 3-dose course was given initially; repeat the course after 5 years if a 4-dose course was given initially.
	Typherix or Typhim Vi	0.5 mL	IM	Single dose	Give 3-yearly boosters if the person is at ongoing risk.
Yellow fever	Stamaril	0.5 mL	IM/SC	Single dose	Give 10-yearly boosters if the person is at ongoing risk.

* This 'rapid' schedule should be used only if there is very limited time before departure to endemic regions.

† Vivaxim is registered for use in persons aged ≥16 years.

‡ A 4th capsule of oral typhoid vaccine on day 7 is preferred (see 4.21 *Typhoid*).

3.2.5 Vaccinating the traveller with special risk factors

See 3.3 *Groups with special vaccination requirements* and the disease-specific chapters in Part 4 for recommendations for travellers who are either pregnant or immunocompromised.

Children should receive relevant travel vaccines, according to age-specific dosage and schedules as shown in Table 3.2.2; further information relating to administration is provided in the relevant disease-specific chapters in Part 4.

Particular effort should be made to encourage the families of recent migrants to Australia to seek health advice before travelling to their country of origin to visit relatives and friends.[14]

Table 3.2.2: Recommended lower age limits of travel vaccines for children*

Vaccine	Lower age limit	Dose/route	Dosing intervals
Hepatitis A			
Avaxim	2 years	0.5 mL IM	2 doses: 0 and 6–12 months
Havrix Junior	2 years	0.5 mL IM	2 doses: 0 and 6–12 months
Vaqta Paediatric/Adolescent formulation	1 year	0.5 mL IM	2 doses: 0 and 6–18 months
Hepatitis A/B combined			
Twinrix Junior (360/10)	1 year	0.5 mL IM	3 doses: 0, 1 and 6 months
Twinrix (720/20)	1 year	1.0 mL IM	2 doses: 0 and 6–12 months†
Japanese encephalitis			
JEspect	1 year (to <3years)‡	0.25 mL IM	2 doses: 0 and 28 days
	3 years‡	0.5 mL IM	2 doses: 0 and 28 days
Imojev	1 year	0.5 mL SC	Single dose
Meningococcal $ACW_{135}Y$ (quadrivalent conjugate 4vMenCV)			
Menveo	9 months	0.5 mL IM	Single dose
Menactra	9 months	0.5 mL IM	Single dose
Meningococcal $ACW_{135}Y$ (quadrivalent polysaccharide 4vMenPV)§			
Mencevax ACWY	2 years	0.5 mL SC	Single dose
Menomune	2 years	0.5 mL SC	Single dose

Vaccine	Lower age limit	Dose/route	Dosing intervals
Rabies			Pre-exposure:
Mérieux Inactivated Rabies Vaccine	No lower age limit	1.0 mL IM/SC	3 doses: 0, 7, 21–28 days
Rabipur Inactivated Rabies Virus Vaccine	No lower age limit	1.0 mL IM	3 doses: 0, 7, 21–28 days
Typhoid			
Vivotif Oral	6 years	Oral capsule	One capsule each on days 1, 3, 5 (3-dose course), and preferably also day 7¶ (4-dose course)
Typherix	2 years	0.5 mL IM	Single dose
Typhim Vi	2 years	0.5 mL IM	Single dose
Yellow fever			
Stamaril	9 months#	0.5 mL IM/SC	Single dose

* See also minimum ages in Table 2.1.5 *Minimum acceptable age for the 1st dose of scheduled vaccines in infants in special circumstances*.

† This schedule is not recommended if prompt protection against hepatitis B is required (see 4.5 *Hepatitis B*).

‡ JEspect is registered for use in persons aged ≥18 years, but can be administered to persons aged ≥12 months in circumstances where an alternative is not available or contraindicated (see 4.8 *Japanese encephalitis*).

§ 4vMenCV is preferred over 4vMenPV (see 4.10 *Meningococcal disease*).

¶ A 4th capsule of oral typhoid vaccine on day 7 is preferred (see 4.21 *Typhoid*).

Yellow fever vaccine is contraindicated in infants <9 months of age. (Vaccination may be considered in outbreak control situations for infants from 6 months of age.) (See 4.23 *Yellow fever*.)

3.2.6 Further information

International travellers' health risks are changing constantly. Up-to-date information and knowledge of the changing epidemiology and occurrence of outbreaks of a variety of infectious and emerging diseases is essential. Useful online information sources include:

- the World Health Organization (WHO) for disease outbreak news (www.who.int), and its *Travel and health* section (www.who.int/topics/travel/en) for more specific advice on travel and health, including travel vaccination recommendations
- *Travelers' health* section of the United States Centers for Disease Control and Prevention (CDC) website (wwwnc.cdc.gov/travel)

- *Travel health and quarantine* section of the Australian Government Department of Health website (www.health.gov.au/internet/main/publishing.nsf/Content/health-pubhlth-strateg-quaranti-index.htm)
- *Smartraveller* – the Australian Government's travel advisory and consular information service, which provides up-to-date advice regarding health, safety and other risks of specific destinations to Australian travellers (www.smartraveller.gov.au).

Comprehensive technical advice on international travel and health, including but not limited to vaccinations, is available in the latest editions of the WHO publication *International travel and health* (available at www.who.int/ith/en) and the US Centers for Disease Control and Prevention (CDC) publication *Health information for international travel* (the '*Yellow book*') (available at www.cdc.gov/travel).

The Ministry of Health of Saudi Arabia's requirements and recommendations for travellers on pilgrimage to Mecca (Hajj and Umra) are published annually in the *Weekly Epidemiological Record* of the WHO (www.who.int/wer).[8]

References

A full reference list is available on the electronic *Handbook* or website www.immunise.health.gov.au

3.3 GROUPS WITH SPECIAL VACCINATION REQUIREMENTS

This chapter considers the use of vaccines in persons who have special vaccination requirements, persons who may experience more frequent adverse events following immunisation and persons who may have a suboptimal response to vaccination. Recommendations for vaccination of persons at occupational or lifestyle-associated risk are also included. Although recommendations are discussed under each sub-heading in this chapter, it is also important to refer to the relevant disease-specific chapters in Part 4 for further information.

Administration of certain vaccines is a priority for some persons with medical conditions that increase the risk of infectious diseases, even in the absence of specific immune defects, for example, the use of influenza and pneumococcal vaccines in individuals with an increased risk of complications from these diseases. The presence of additional recommendations specific to groups discussed in this section underpins the importance of pre-screening those attending for immunisation and being certain to regularly review the vaccination needs of those seeking medical attention for any reason.

3.3.1 Vaccination of persons who have had an adverse event following immunisation

Adverse reactions after being given a vaccine (also known as 'vaccine side effects') do sometimes occur. It is usually not possible to predict which individuals may have a mild or a rare, serious reaction to a vaccine. However, by following guidelines regarding when vaccines should and should not be used, the risk of adverse effects can be minimised. The term 'adverse event following immunisation' (AEFI) refers to any untoward medical occurrence that follows immunisation, whether expected or unexpected, and whether triggered by the vaccine or only coincidentally occurring after receipt of a vaccine dose.[1] For more information on AEFI, see 2.3.2 *Adverse events following immunisation.*

Serious adverse events occur rarely after immunisation. Recognised rare and serious AEFI are described in 2.3.2 *Adverse events following immunisation*. Pre-vaccination screening should identify persons who have experienced an AEFI and also identify persons with conditions that are precautions and/or contraindications to vaccines (see Table 2.1.1 *Pre-vaccination screening checklist*). The relevant disease-specific chapter(s) in Part 4 of this *Handbook* should be consulted for each vaccine regarding contraindications and precautions that are relevant. In general, persons who have had a *non-serious* adverse event can be safely revaccinated by their usual immunisation service provider. Determining whether revaccination should be provided after a serious event has occurred following vaccination can be more challenging. At the individual patient level, an assessment should be made as to whether the vaccine(s) was causally related to the adverse event. This includes a thorough medical assessment, including determining the need for, or availability of, specific tests to predict

whether the AEFI is likely to recur with subsequent doses. Persons who have experienced a *serious* adverse event following immunisation (other than a contraindication, such as anaphylaxis confirmed as triggered by a vaccine or one of its components) can usually subsequently be vaccinated under close medical supervision. However, further advice should be sought where appropriate, by referral to a specialist clinic for the management of persons with special vaccination requirements (including persons who have had a previous AEFI).

Information about specialist immunisation clinics, or the contact details for paediatricians or medical specialists with experience in management of persons with AEFI, are usually available from state and territory health authorities (see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*) and from the Immunise Australia website (www.immunise.health.gov.au).

Allergies

Vaccines rarely produce allergy or anaphylaxis (a rapid and life-threatening form of allergic reaction). Overall, the risk of anaphylaxis after a single vaccine dose has been estimated as less than 1 case per 1 million; however, this risk varies depending on the vaccine type.[2] Antibiotics, gelatin and egg proteins are the components most often implicated in allergic reactions. Yeast has only rarely been associated with vaccine-related allergic reaction. Persons allergic to latex may be at risk from some vaccines. This is usually not from the vaccine formulation itself, but from the presence of latex in the equipment used to hold the vaccine, such as vaccine vial stoppers (bungs) and syringe plungers. However, very few vaccine bungs contain natural latex. Before administering the vaccine, consult the product information (PI) of each vaccine to check for the presence of latex or, where not listed on the PI, contact the vaccine manufacturer for specific details.

It is important that immunisation service providers assess each individual for a history of allergies and previous reactions to vaccines prior to giving any dose of vaccine. Depending on the allergy identified, there often may *not* be a contraindication to vaccination. For example, a history of allergy to antibiotics most commonly relates to β-lactam or related antibiotics and is not a contraindication to vaccines that contain neomycin, polymyxin B or gentamicin. Previous reactions to neomycin that only involved the skin are not considered a risk factor for a severe allergic reaction or anaphylaxis to vaccines manufactured with neomycin because there are only trace amounts of this antibiotic in the final product.[3] Similarly, the measles and mumps components of measles-mumps-rubella (MMR) vaccine contain only a negligible quantity of egg ovalbumin and *do not* contraindicate MMR vaccination of persons with egg allergy (even anaphylaxis) (see 'Vaccination of persons with a known egg allergy' below).[4-7]

It is important that persons who experience an allergic reaction associated with a vaccine dose are fully investigated appropriately to ascertain the possible causal

relationship to vaccination, and determine if, and under what circumstances, repeat doses of vaccine can be provided. Specialist advice should be sought where appropriate (see above).

Vaccination of persons with a known egg allergy

Influenza vaccines

A history of anaphylaxis or a severe allergic reaction to eggs has previously been considered an absolute contraindication to influenza vaccination. However, there have now been a number of studies indicating that the majority of persons with egg allergy, including anaphylaxis, can be safely vaccinated with influenza vaccines that contain less than 1 µg of ovalbumin per dose[8-10](see 4.7 *Influenza*).

The majority of vaccine-associated anaphylaxis cases reported as likely due to egg allergy occurred following administration of one of the older formulations of influenza vaccine.[9] Today, due to manufacturing changes, the quantity of egg ovalbumin present in the majority of influenza vaccines used in Australia is less than 1 µg of ovalbumin per dose.[8] Note that the amount of residual egg ovalbumin may vary from year to year due to manufacturing processes, vaccine batches and country of origin. The PI of the vaccine to be given should be checked for the vaccine's ovalbumin content prior to vaccine administration.[8,9,11,12]

Given that there is still a small risk of anaphylaxis, it is essential that persons with a history of a severe allergic reaction to eggs are vaccinated in facilities that have staff who are able to recognise and treat anaphylaxis.[8,9] Allergy testing (e.g. skin testing) with influenza vaccine prior to administration is not recommended, as there is poor correlation between test results and vaccine tolerance.[8,9] Detailed information on influenza vaccination of individuals with an allergy to eggs can be found in the Australasian Society of Clinical Immunology and Allergy (ASCIA) guidelines[8] (available at www.allergy.org.au/health-professionals/papers/influenza-vaccination-of-the-egg-allergic-individual).

Other vaccines

Vaccines used in Australia that contain traces of egg ovalbumin, in addition to most influenza vaccines, are:

- rabies vaccine, Rabipur (see 4.16 *Rabies and other lyssaviruses (including Australian bat lyssavirus)*)
- yellow fever vaccine, Stamaril (see 4.23 *Yellow fever*)
- Q fever vaccine, Q-Vax (see 4.15 *Q fever*).

Of these vaccines, yellow fever and Q fever vaccines contain a higher amount of ovalbumin than is present in the currently available influenza vaccines and are contraindicated in persons with known severe allergy to eggs. Persons with egg allergy requiring vaccination with either yellow fever or Q fever vaccines should seek specialist immunisation advice from state or territory health authorities

(see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*).

For rabies vaccination, pre- or post-exposure vaccination should be undertaken using the human diploid cell vaccine (HDCV; Mérieux Inactivated Rabies Vaccine), and *not* using the purified chick embryo cell vaccine (PCECV; Rabipur Inactivated Rabies Virus Vaccine) (see 4.16 *Rabies and other lyssaviruses (including Australian bat lyssavirus)*).

Although measles and mumps (but not rubella or varicella) vaccine viruses are grown in chick embryo tissue cultures, it is now recognised that measles- and mumps-containing vaccines contain negligible amounts of egg ovalbumin and can be safely administered to persons with a known egg allergy (see 4.9 *Measles*).[4-7]

3.3.2 Vaccination of women who are planning pregnancy, pregnant or breastfeeding, and preterm infants

Women planning pregnancy

The need for vaccination, particularly for hepatitis B, measles, mumps, rubella, varicella, diphtheria, tetanus and pertussis, should be assessed as part of any pre-conception health check. Where previous vaccination history or infection is uncertain, relevant serological testing can be undertaken to ascertain immunity to hepatitis B, measles, mumps and rubella. Routine serological testing for pertussis and varicella does not provide a reliable measure of vaccine-induced immunity, although varicella serology can indicate whether previous natural infection has occurred (see 4.22 *Varicella*). Influenza vaccine is recommended for any person who wishes to be protected against influenza and is recommended for women planning pregnancy. Those with risk factors for pneumococcal disease, including smokers and Aboriginal and Torres Strait Islander women, should be assessed for pneumococcal vaccination. Women who receive live attenuated viral vaccines should be advised against falling pregnant within 28 days of vaccination.

Refer to the relevant disease-specific chapters in Part 4 for more information about vaccination requirements for these diseases.

It is also important that women of child-bearing age who present for immunisation should be questioned regarding the possibility of pregnancy as part of the routine pre-vaccination screening, to avoid inadvertent administration of a vaccine(s) not recommended in pregnancy (see 2.1.4 *Pre-vaccination screening*).

Pregnant women

Table 3.3.1 summarises the recommendations for vaccine use in pregnancy. More detailed information is also provided under the 'Pregnancy and breastfeeding' sections of each disease-specific chapter in Part 4 of this *Handbook*.

Seasonal influenza vaccine is the only vaccine routinely recommended for pregnant women. dTpa vaccine can also be given in pregnancy, as an alternative to providing it immediately post-partum. Vaccination with dTpa during pregnancy will provide timely protection against pertussis in both the mother and her newborn child.

Many other inactivated vaccines are not routinely recommended during pregnancy on precautionary grounds; however, there is no convincing evidence that pregnancy should be an absolute contraindication to vaccination with these vaccines. There is some evidence that fever per se is teratogenic; however, in clinical studies most inactivated vaccines are not associated with increased rates of fever in adults (as compared with placebo).[13,14] Recommendations regarding vaccine use in pregnancy are made where the benefits of protection from vaccination outweigh the risks. Eliminating the risk of exposure to vaccine-preventable diseases during pregnancy (e.g. by changing travel plans, avoiding high-risk behaviours or occupational exposures) is both an alternative and complementary strategy to vaccination.

Live attenuated viral vaccines are contraindicated in pregnant women because of the hypothetical risk of harm should vaccine virus replication occur in the fetus. If a live attenuated viral vaccine is inadvertently given to a pregnant woman, or if a woman becomes pregnant within 28 days of vaccination, she should be counselled about the potential for adverse effects, albeit extremely unlikely, to the fetus (see also 4.18 *Rubella* and 4.22 *Varicella*). There is, however, no indication to consider termination of a pregnancy if a live attenuated vaccine has been inadvertently given. The live attenuated yellow fever vaccine is not recommended in pregnant women; however, where travel to a yellow fever risk country is unavoidable, the risks and benefits of yellow fever vaccination, and other strategies to mitigate the risk of acquiring yellow fever, should be discussed (see 4.23 *Yellow fever*).

Inadvertent receipt of a vaccine contraindicated in pregnancy can be reported to the Therapeutic Goods Administration (TGA). For mechanisms for reporting to the TGA, see 2.3.2 *Adverse events following immunisation*. Post-marketing studies of pregnancy outcomes following vaccine administration are important to understand the safety profile of vaccines in this setting. For this reason some vaccine manufacturers also operate pregnancy registries, specific for their products, that will accept reports of vaccines administered during pregnancy; for example, see information on the varicella vaccine registry in 4.22 *Varicella*.

Table 3.3.1: Recommendations for vaccination in pregnancy (see also disease-specific chapters in Part 4)

Vaccines routinely recommended in pregnancy		
Inactivated viral vaccines	**Recommendation**	**Comments**
Influenza vaccine	Recommended for all pregnant women at any stage of pregnancy, particularly those who will be in the second or third trimester during the influenza season.	There is evidence from clinical trial data and observational studies that there is no increased risk of congenital defects or adverse effects in the fetuses of women who are vaccinated against influenza in pregnancy. Influenza immunisation protects the mother, as pregnancy increases her risk of severe influenza, and also protects her newborn baby in the first few months after birth (see 4.7 *Influenza*).
Vaccines not *routinely* recommended in pregnancy		
Inactivated bacterial vaccines	**Recommendation**	**Comments**
Diphtheria-, tetanus-, and pertussis-containing vaccines (dTpa, dT)	dTpa can be given to pregnant women in the third trimester as an alternative to post-partum dTpa (if a dose of dTpa has not been given in the previous 5 years).	Vaccination in the third trimester is an acceptable alternative to post-partum vaccination, for pregnant women who have not been given a dTpa dose within the previous 5 years.[15] Receipt of dTpa in the third trimester of pregnancy may be preferred when the risk of the mother and/or infant acquiring pertussis is high, such as for pregnant women in close contact with infants. Vaccination during pregnancy has the advantage of achieving more timely and high pertussis antibody responses in the mother and infant after birth, as compared with vaccination given post-partum or prior to conception. Tetanus- and diphtheria-containing vaccines have been used extensively in pregnant women, with no increased risk of congenital abnormalities in fetuses of women who were vaccinated during pregnancy.[16-18] (See 4.12 *Pertussis* for more details.)[15]
Cholera (oral) vaccine	Not routinely recommended	There are limited data on the safety of oral cholera vaccine in pregnancy.[19]

Vaccines not *routinely* recommended in pregnancy		
Inactivated bacterial vaccines	**Recommendation**	**Comments**
Haemophilus influenzae type b (Hib) vaccine	Not routinely recommended Can be given to pregnant women at increased risk of Hib disease (e.g. with asplenia)	Limited available data suggest that it is unlikely that use of Hib vaccine in pregnant women has any deleterious effects on pregnancy outcomes.[20]
Meningococcal conjugate vaccines (MenCCV or 4vMenCV)	Not routinely recommended Can be given to pregnant women at increased risk of meningococcal disease (e.g. with asplenia) or as post-exposure prophylaxis in household contacts/cases of meningococcal serogroup A, C, W_{135} or Y	There are limited data on the safety of meningococcal conjugate vaccines in pregnancy.[21] Where clinically indicated, meningococcal conjugate vaccine can be given to pregnant women.[22]
Meningococcal polysaccharide vaccine (4vMenPV)	Not routinely recommended Can be given to pregnant women at increased risk of meningococcal disease who have not been vaccinated with 4vMenPV in the past 3 years (e.g. with asplenia), or as post-exposure prophylaxis in household contacts/cases of meningococcal serogroup A, W_{135} or Y	Limited available data suggest that it is unlikely that use of meningococcal polysaccharide vaccine in pregnant women has any deleterious effects on pregnancy outcomes.[23,24] Where clinically indicated, meningococcal polysaccharide vaccine can be given to pregnant women, although 4vMenCV is preferred.[22]
13-valent pneumococcal conjugate vaccine (13vPCV)	Not routinely recommended	No data are available. Vaccination during pregnancy has not been evaluated, although is unlikely to result in adverse effects.

Vaccines not *routinely* recommended in pregnancy		
Inactivated bacterial vaccines	**Recommendation**	**Comments**
23-valent pneumococcal polysaccharide vaccine (23vPPV)	Not routinely recommended Can be given to pregnant women at the highest increased risk of invasive pneumococcal disease (IPD) (e.g. with asplenia, immunocompromise, cerebrospinal fluid leak) who have not received 23vPPV in the past 5 years (and provided they have not received 2 previous doses)	23vPPV has been administered in pregnancy in the context of clinical trials[25] with no evidence of adverse effects; however, data are limited. Where clinically indicated, 23vPPV can be given to pregnant women. Women of child-bearing age with known risk factors for IPD (including smokers) should be vaccinated before pregnancy, according to recommendations (see 4.13 *Pneumococcal disease*).
Q fever vaccine	Not routinely recommended	Safe use in pregnancy has not been established.
Typhoid Vi polysaccharide vaccine	Not routinely recommended Can be given to pregnant women travelling to endemic countries where water quality and sanitation is poor	No data are available.[26] Vaccination during pregnancy has not been directly evaluated, although is unlikely to result in adverse effects.
Inactivated viral vaccines	**Recommendation**	**Comments**
Hepatitis A vaccine	Not routinely recommended Can be given to susceptible pregnant women travelling to areas of moderate to high endemicity or those who are at increased risk of exposure through lifestyle factors, or where severe outcomes may be expected (e.g. pre-existing liver disease)	Limited data are available. Hepatitis A vaccine should only be given to pregnant women who are non-immune and at increased risk for hepatitis A.[27]

Vaccines not *routinely* recommended in pregnancy		
Inactivated viral vaccines	**Recommendation**	**Comments**
Hepatitis B vaccine	Not routinely recommended Can be given to susceptible pregnant women for whom this vaccine would otherwise be recommended, for example, as post-exposure prophylaxis in a non-immune pregnant woman with a significant exposure to a HBsAg-positive source	Limited data are available. Hepatitis B vaccine should only be given to pregnant women who are non-immune and at increased risk for hepatitis B.[28]
Japanese encephalitis (JE) vaccine (JEspect)	Not routinely recommended Can be given to pregnant women at high risk of acquiring JE	Limited data are available. JE infection is associated with miscarriage, and women who are at high risk of JE should be assessed for the need for vaccination. Where the risk of JE disease is high, pregnant women should be vaccinated using the inactivated vaccine, JEspect (not Imojev, which is a live attenuated vaccine).[29]
Poliomyelitis vaccine (IPV)	Not routinely recommended Can be given to pregnant women at high risk of poliovirus exposure (e.g. travel to endemic countries)	Limited available data suggest that it is unlikely that use of inactivated poliomyelitis vaccine in pregnant women has any deleterious effects on pregnancy outcomes.[26] IPV should only be given to pregnant women when clearly indicated.
Rabies vaccine	Can be given to pregnant women for whom this vaccine would otherwise be recommended (e.g. post-exposure prophylaxis).	Limited available data suggest that it is unlikely that the use of rabies vaccine in pregnant women has any deleterious effects on pregnancy outcomes.[30-33] Pregnancy is never a contraindication to rabies vaccination in situations where there is a significant risk of exposure (related to occupation or travel), or where there has been a potential exposure to rabies virus, Australian bat lyssavirus or another bat lyssavirus.[34,35]

Vaccines not recommended in pregnancy		
Inactivated viral vaccines	**Recommendation**	**Comments**
Human papillomavirus (HPV) vaccine	Not recommended	Although HPV vaccination is not recommended during pregnancy, evidence from clinical trials and limited data from observational studies where HPV vaccine was inadvertently administered during pregnancy, indicate that there is no increased risk of adverse effects on the fetus.[36] In the event of pregnancy, completion of a 3-dose course of vaccination should be deferred until after delivery.
Live attenuated viral vaccines	**Recommendation**	**Comments**
Yellow fever vaccine	Not recommended	Pregnant women should be advised against going to the rural areas of yellow fever endemic areas. However, where travel to an at-risk country is unavoidable, such women should be vaccinated.[37,38] Yellow fever vaccine has been given to a large number of pregnant women with no adverse outcomes.[39]
Vaccines contraindicated in pregnancy		
Live attenuated bacterial vaccines	**Recommendation**	**Comments**
BCG vaccine	Contraindicated	There is only a hypothetical risk. BCG vaccine has not been shown to cause fetal damage.[40]
Oral typhoid vaccine	Contraindicated	There are limited data available (animal studies), suggesting no increased occurrence of fetal damage with oral live attenuated vaccine.[41] Inactivated typhoid Vi polysaccharide vaccine is preferred (see above).
Live attenuated viral vaccines	**Recommendation**	**Comments**
Japanese encephalitis (JE) vaccine (Imojev)	Contraindicated	There is only a hypothetical risk. There are currently no data available regarding the use of this vaccine in pregnant or breastfeeding women. Women of child-bearing age should avoid pregnancy for 28 days after vaccination.

Vaccines contraindicated in pregnancy		
Live attenuated viral vaccines	**Recommendation**	**Comments**
Measles-mumps-rubella (MMR) vaccine or Measles-mumps-rubella-varicella (MMRV) vaccine	Contraindicated	There is only a hypothetical risk. Despite concerns that live attenuated rubella vaccine virus might cause congenital abnormalities, rubella vaccine (either monovalent or as MMR) has been given to pregnant women (usually inadvertently) without harm to the fetus.[42,43] Even though rubella vaccine virus can infect the fetus, even for vaccine given in early pregnancy, there is no evidence that it causes congenital rubella syndrome in infants born to susceptible mothers.[44] Receipt of rubella vaccination during pregnancy is not an indication for termination.[43] Women of child-bearing age should avoid pregnancy for 28 days after vaccination. It is recommended practice to test all pregnant women for immunity to rubella, and to vaccinate susceptible women as soon as possible after delivery and check their serological status post vaccination.
Rotavirus vaccine	Contraindicated	Rotavirus vaccines are not registered or recommended for use in adolescents or adults.
Varicella vaccine	Contraindicated	There is only a hypothetical risk. Congenital varicella syndrome has not been identified in women who have been inadvertently vaccinated with varicella vaccine in early pregnancy.[45] Women of child-bearing age should avoid pregnancy for 28 days after vaccination.
Zoster vaccine	Contraindicated	There is only a hypothetical risk. Women of child-bearing age are unlikely to be eligible for vaccination, as zoster vaccine is registered for use in persons ≥50 years of age. If women of child-bearing age have inadvertently been vaccinated, they should avoid pregnancy for 28 days after vaccination.

Immunoglobulins for use as pre- or post-exposure prophylaxis		
Pooled or hyperimmune immunoglobulins	Not routinely recommended Can be used post exposure in susceptible pregnant women exposed to: measles, hepatitis A, hepatitis B, rabies, Australian bat lyssavirus, or varicella viruses, or tetanus	Limited data are available. There is no known risk to the fetus from passive immunisation of pregnant women with immunoglobulins. For more details, see Part 5 *Passive immunisation* and relevant disease-specific chapters in Part 4.

Contact between pregnant women and persons who have recently received live vaccines

Household contacts of pregnant women should be age-appropriately vaccinated. It is safe to administer measles-, mumps-, rubella- and varicella-containing vaccines, zoster vaccine and rotavirus vaccine to the contacts of pregnant women. There is no risk of transmission of measles, mumps or rubella vaccine viruses from vaccinated household contacts. There is an almost negligible risk of transmission of varicella-zoster vaccine virus (from persons vaccinated with varicella or zoster vaccines); however, vaccine recipients with a varicella-like rash should be advised to cover the rash if in contact with a pregnant woman. Although there is a very small possibility of transmission of the rotavirus vaccine viruses to pregnant contacts, the benefit of immunising infants to protect against rotavirus disease and, in turn, reduce the risk of rotavirus in household contacts, far outweighs any theoretical risk (see 4.17 *Rotavirus*).

Use of immunosuppressive therapy during pregnancy

Certain immunosuppressive medications given for management of a medical condition in a woman during pregnancy (e.g. biological disease modifying anti-rheumatic drugs [bDMARDs]) may cross the placenta and be detectable in the infant, particularly if given during the third trimester.[46-48] In this setting, administration of live attenuated vaccines in the first few months of the infant's life, particularly BCG vaccine, is not recommended.[49] (See also 4.20 *Tuberculosis*.) This is because of the risk that the infant's immune response to vaccination may be reduced and potentially associated with increased vaccine virus/bacteria replication and related adverse effects. Although no specific time intervals are indicated, withholding BCG vaccine until the infant is 6 months of age is prudent.[50] Although there is some theoretical concern that a risk also applies to the administration of rotavirus vaccines, there are currently no data to substantiate this.

Inactivated vaccines should be administered to these infants according to the recommended schedule. However, immune responses may be suboptimal. Additional inactivated vaccine doses may be required; expert advice should be sought regarding this.

Breastfeeding and vaccination

Vaccination is rarely contraindicated in breastfeeding women. The rubella vaccine virus may be secreted in human breast milk and there has been documented transmission to breastfed infants. However, where infection has occurred in an infant, the symptoms have been absent or mild.[51-53] Infants born to mothers who are hepatitis B surface antigen (HBsAg)-positive can also be breastfed, provided the infant is appropriately immunised at birth. Although studies have indicated the presence of hepatitis B virus (HBV) in the breast milk of mothers with HBV infection, breastfeeding poses no additional risk of virus transmission, compared with formula feeding, in vaccinated infants.[54] Administration of yellow fever vaccine to breastfeeding women should be

avoided, except in situations where the risk of acquiring yellow fever is high, and/or travel cannot be avoided or postponed.[55,56] While extremely rare, there have been several case reports of probable transmission of the yellow fever vaccine virus via breast milk.[55,56] For most vaccines, the immune response to vaccination of infants in relationship to breastfeeding has been studied and taken into account. In general, breastfeeding does not adversely affect immunisation, and breastfeeding is not a contraindication to the administration of any vaccines recommended in infants.

Preterm infants

Preterm (premature) infants are defined as those born at <37 weeks gestational age. Prematurity, particularly extreme prematurity (<28 weeks gestational age) can place children at increased risk of vaccine-preventable diseases.[57-59] However, despite their immunological immaturity, preterm infants generally respond satisfactorily to vaccines.[60-62] Provided they are medically stable and there are no contraindications to vaccination, preterm infants should be vaccinated according to the recommended schedule at the usual chronological age, without correction for prematurity.[63-65]

Immunisation has been associated with an increased risk of apnoea in preterm infants vaccinated in hospital, particularly those still requiring complex medical care and/or with an existing history of apnoea. Although in this setting, apnoea is generally self-limiting, measures to manage this anticipated AEFI should be taken.[66-68] Specifically, hospitalised preterm infants should be monitored for apnoea or bradycardia for up to 48 hours post vaccination.[68,69] If there is a history of apnoea post vaccination, consideration should be given to administering future immunisations under medical supervision.[70,71] Vaccination has not been associated with an increased risk of sudden infant death syndrome (SIDS).[72,73]

The following recommendations are specific for preterm infants. The child's birth weight, precise gestational age and the presence of a chronic medical condition(s) need to be considered.

Pneumococcal vaccines

All preterm infants born at <28 weeks gestation are recommended to be given 4 doses of 13-valent pneumococcal conjugate vaccine, at 2, 4, 6 and 12 months of age. A single booster dose of 23-valent pneumococcal polysaccharide vaccine at 4–5 years of age is also recommended (see 4.13 *Pneumococcal disease* and Table 2.1.11 *Catch-up schedule for 13vPCV (Prevenar 13) and 23vPPV (Pneumovax 23) in children with a medical condition(s) associated with an increased risk of IPD, presenting at age <2 years*). Children who were born at <28 weeks gestation but who do not have a chronic medical condition(s) that places them at ongoing increased risk of invasive pneumococcal disease (IPD) (see 4.13 *Pneumococcal disease*, List 4.13.1 *Conditions associated with an increased risk of IPD in children and adults, by severity of risk*), and who have received the additional pneumococcal vaccine doses to age 5 years recommended above, do not need further pneumococcal vaccine

doses after age 5 years. However, all children and adults who have chronic lung disease, or certain other chronic medical conditions, whether related to preterm birth or not, should also receive additional pneumococcal vaccine doses up to *and* beyond the age of 5 years (see 4.13 *Pneumococcal disease*).

Hepatitis B vaccine

Low-birth-weight preterm newborn infants do not respond as well to hepatitis B-containing vaccines as full-term infants.[69,74,75] Thus, for low-birth-weight infants (<2000 g) and/or infants born at <32 weeks gestation (irrespective of weight), who are born to mothers who are HBsAg-negative, it is recommended to give hepatitis B vaccine at birth, followed by 3 doses of a hepatitis B-containing vaccine, at 2, 4 and 6 months of age, with a booster dose at 12 months of age. The booster dose can be administered without measuring the antibody titre following the primary series. Alternatively, if an anti-HBs titre is measured, this should be done a minimum of 1 month after the 6-month dose, and if the anti-HBs titre is <10 mIU/mL, a booster dose should be given (see 4.5 *Hepatitis B*). Preterm infants born to HBsAg-positive mothers should be given hepatitis B vaccine and hepatitis B immunoglobulin (HBIG) after birth as specified in 4.5 *Hepatitis B.*

Influenza vaccine

Preterm infants have a high rate of underlying medical conditions – particularly respiratory, cardiac or neurological disease – that increase the risk of complications from influenza.[76] In accordance with the recommendations for use of influenza vaccine, it is particularly important to assess preterm infants for the presence of underlying conditions that make them eligible for influenza vaccination. Vaccination should be provided annually from ≥6 months of age. Two vaccine doses, at least 4 weeks apart, are required in the first year that influenza vaccine is received (see 4.7 *Influenza*).

Rotavirus vaccine

Preterm infants, including medically stable hospitalised infants, can receive the rotavirus vaccine at chronological age without correction for prematurity. Strict upper age limits for vaccine administration apply and depend on which rotavirus vaccine is administered (see 4.17 *Rotavirus*).

Hib vaccine

If a PRP-OMP Hib vaccine is used for primary immunisation of an extremely preterm low-birth-weight infant (<28 weeks gestation and/or <1500 g birth weight), a total of 3 (not 2) primary doses of vaccine should be given. Thus, the schedule should include 4 doses of a Hib-containing vaccine (either PRP-OMP or PRP-T-containing), given at 2, 4, 6 months and a booster dose at 12 months of age (see 4.3 *Haemophilus influenzae type b*).

3.3.3 Vaccination of immunocompromised persons

A person can be immunocompromised due to disease and/or medical treatment. Vaccination of immunocompromised persons presents numerous challenges. The immune protection attained from previous immunisation may be diminished; the response to vaccines administered in the setting of immunocompromise may be reduced, with additional booster vaccine doses required; the risk of vaccine-preventable diseases and/or their complications may be increased; and the risk of adverse events from live vaccines may be increased. Degrees of immunocompromise vary from insignificant to profound, and this, together with the risk of acquiring vaccine-preventable disease, should be taken into account when considering a vaccination schedule.

When considering vaccination of persons on immunosuppressive therapy, it is particularly important to consider a number of factors, including the biologic target of the medication being used (mechanism and duration of effect on the immune system) as well as the consequence of using combination therapies (e.g. prednisolone and methotrexate), which can contribute to the nature, extent and length of immunocompromise. It is also important to know the anticipated duration of immunocompromise, whether due to therapy or the underlying disease (see also 'Immunocompromise associated with corticosteroid administration' below). In some instances, additional booster doses of vaccines may be required to optimise protection in immunocompromised persons (e.g. pneumococcal vaccines at diagnosis of haematological malignancy). To determine the need for booster doses, it may be useful to measure post-vaccination antibody titres in selected groups in some circumstances, such as for adults or children who have received haematopoietic stem cell transplants (see 'Haematopoietic stem cell transplant recipients' below). Reliable serological testing is not readily available and/or validated to measure vaccine-induced immunity for all vaccines, and, in addition, results should be interpreted using standardised serological correlates. (See also 2.1.5 *Catch-up*, 'Use of serological testing to guide catch-up vaccination'.) Expert advice should be sought if required.

Many vaccine-preventable diseases are associated with an increased risk of morbidity and mortality in immunocompromised persons. Two important examples are influenza and invasive pneumococcal disease (IPD). Annual influenza vaccination should be given to all immunocompromised persons ≥6 months of age (see 4.7 *Influenza*). Immunocompromised persons may also require additional doses of pneumococcal vaccines; the timing, number of doses and type of vaccine(s) vary depending on age and the underlying risk for IPD (see 4.13 *Pneumococcal disease*). These, and other specific vaccine recommendations, are discussed in more detail below.

All immunocompromised persons, irrespective of age, who receive influenza vaccine for the first time are recommended to receive 2 vaccine doses, at least 4 weeks apart, and 1 dose annually thereafter (see 4.7 *Influenza*). Where it is

known that a new influenza vaccine strain is circulating in the community to which cross-protective immunity in the population is low (such as in the setting of an influenza pandemic), it may be appropriate that immunocompromised persons receive 2 doses of inactivated influenza vaccine, a minimum of 4 weeks apart, to achieve an optimal immune response. For example, in the 2009–2010 H1N1 global influenza pandemic it was shown that seroconversion to influenza vaccination in immunocompromised adolescents and adults was improved following receipt of 2 vaccine doses.[77] Further information and annual influenza vaccine recommendations are available on the Immunise Australia website (www.immunise.health.gov.au).

The recommendations in this section for the use of vaccines in immunocompromised persons have been divided where applicable into paediatric (0–18 years) and adult (≥19 years) recommendations. This distinction has been made on the basis of scientific evidence, where available, and to assist in vaccine delivery in paediatric and adult special risk settings.

Immunocompromise associated with corticosteroid administration

The dose and duration of therapy with corticosteroids determines the impact on the immune system. In adults, daily doses of oral corticosteroids in excess of 60 mg of prednisolone (or equivalent) for more than 1 week are associated with significant immunocompromise. In children, doses in excess of either 2 mg/kg per day for more than 1 week or 1 mg/kg per day for more than 4 weeks are associated with significant immunocompromise. Live attenuated vaccines are generally contraindicated in such persons (see also below). In addition, for both children and adults, even lower doses may be associated with some impairment of the immune response.[78] It is also important, once treatment with corticosteroids is ceased, to assess whether the person has other underlying immunocompromising disease or is receiving other immunosuppressive therapy that may influence decisions about whether vaccines, particularly live vaccines, can be given.

For adults treated with systemic corticosteroids in excess of 60 mg per day for more than 1 week, live attenuated viral vaccines (such as MMR, MMRV, zoster, varicella and yellow fever vaccines) should be postponed until at least 1 month after treatment has stopped.

Children receiving >2 mg/kg per day or ≥20 mg per day in total of prednisolone (or equivalent) for more than 1 week should not receive live attenuated vaccines until *after* corticosteroid therapy has been discontinued for at least 1 month.

Children on daily doses of ≤2 mg/kg per day of systemic corticosteroids for less than 1 week, and those on lower doses of 1 mg/kg per day or alternate-day regimens for periods of up to 4 weeks, may be given live attenuated viral vaccines. Some experts suggest withholding lower doses of steroids 2 to 3 weeks prior to vaccination with live viral vaccines if this is possible.[79,80]

Use of live viral or live bacterial vaccines in immunocompromised persons

There is a risk that the administration of live vaccines to immunocompromised persons may result in adverse events or vaccine-related disease due to unchecked infection (replication) of the vaccine virus or bacteria. This is particularly so for measles-, mumps-, rubella-[81,82] and VZV-containing (varicella and zoster) vaccines [83] and for bacille Calmette-Guérin (BCG) vaccine.[49,84] However, the risk of disease varies by vaccine and by individual. Caution is required for vaccination in the setting of immunocompromise, and in significantly immunocompromised persons most live vaccines are contraindicated.

The following is a list of current recommendations for use of live vaccines in immunocompromised persons.

- Tuberculosis vaccine (BCG) is *always* contraindicated.
- Live vaccines, such as MMR- and VZV-containing (varicella and zoster) vaccines, should *not* be given to persons with severe immunocompromise. Severely immunocompromised persons include those who have active leukaemia or lymphoma, generalised malignancy, aplastic anaemia, graft-versus-host disease or congenital immunodeficiency. Others in this category include persons who have received recent chemotherapy, persons who have had solid organ or bone marrow transplants (within 2 years of transplantation) or transplant recipients who are still taking immunosuppressive drugs, or others on highly immunosuppressive therapy, including high-dose corticosteroids (see above). Dependent on their age, persons infected with human immunodeficiency virus (HIV) with $CD4^+$ cell counts of <15%, history of an acquired immunodeficiency syndrome (AIDS)-defining illness, or clinical manifestations of symptomatic HIV are considered to have severe immunocompromise (see also Table 3.3.4).
- Rotavirus, MMR and varicella vaccines, but *not* the combined MMRV vaccine, may be given to children and adults with HIV infection who are asymptomatic or to those persons with an age-specific $CD4^+$ count of ≥15% (see 'HIV-infected persons' below).
- Zoster vaccine is *not* recommended for adults with AIDS or symptomatic HIV infection. However, adults with asymptomatic HIV infection may be considered for vaccination on a case-by-case basis after seeking appropriate specialist advice (see 4.24 *Zoster*).
- Immunocompetent persons who anticipate alteration of their immunity because of their existing illness can be given zoster vaccine on a case-by-case basis after seeking appropriate specialist advice (see 4.24 *Zoster*).
- Immunocompromised travellers should *not* receive oral typhoid vaccines. Use inactivated parenteral typhoid Vi polysaccharide vaccine instead (see 4.21 *Typhoid*).

- Yellow fever vaccine is generally *contraindicated* in immunocompromised travellers going to yellow fever endemic countries. The vaccine can, however, be considered on a case-by-case basis, including in persons with HIV (see 4.23 *Yellow fever*).

If there is uncertainty around the level of immunocompromise and when vaccine administration may be safe, this should be discussed with the treating physician and expert advice should be sought (see also 'Immunocompromise associated with corticosteroid administration' above).

Household contacts of immunocompromised persons

To best protect immunocompromised persons, whether adults or children, their household and other close contacts should be fully vaccinated according to current recommendations. Annual influenza vaccination is recommended for all household contacts (≥6 months of age) of immunocompromised persons. Assessment of the need for household contacts of immunocompromised persons to receive pertussis-containing and/or varicella vaccines is also very important (see 4.12 *Pertussis* and 4.22 *Varicella*).[85-87]

The use of live attenuated viral vaccines in contacts of immunocompromised persons (MMR, MMRV, varicella and rotavirus vaccines, where indicated) is safe, and strongly recommended to reduce the likelihood of contacts infecting the immunocompromised person. Persons ≥50 years of age who are household contacts of an immunocompromised person are also recommended to receive zoster vaccine. Although there is no risk of transmission of the MMR vaccine viruses, and an almost negligible risk of transmission of varicella-zoster vaccine virus (from varicella or zoster vaccine), there is a small risk of transmission of the rotavirus vaccine virus. Hand washing and careful disposal of soiled nappies is recommended to minimise transmission. Immunocompromised persons should avoid contact with persons with varicella and herpes zoster, where possible. (See also 4.9 *Measles*, 4.17 *Rotavirus*, 4.22 *Varicella* and 4.24 *Zoster*).

Oncology patients

Paediatric and adult patients undergoing cancer chemotherapy who have not completed a primary vaccination schedule before diagnosis

Live vaccines, including BCG, MMR, zoster and varicella vaccines, are contraindicated in cancer patients receiving immunosuppressive therapy and/or who have poorly controlled malignant disease. These vaccines are recommended to be administered to seronegative persons at least 3 months after completion of chemotherapy, provided the underlying malignancy is in remission.[88] Administration of live attenuated viral vaccines (MMR-containing or varicella-containing vaccines) should be deferred if blood products or immunoglobulins have been recently administered (see Table 3.3.6 *Recommended intervals between either immunoglobulins or blood products and MMR, MMRV or varicella vaccination*).

Influenza vaccination is recommended annually in all cancer patients aged ≥6 months. All immunocompromised persons, irrespective of age, who receive influenza vaccine for the first time are recommended to receive 2 vaccine doses, at least 4 weeks apart, and 1 dose annually thereafter.

Persons receiving chemotherapy may receive inactivated vaccines (e.g. 13vPCV, hepatitis B) according to a routine or catch-up vaccination schedule. The immune response may be suboptimal, but the vaccines are safe to administer.

Vaccines should not be administered during times of severe neutropenia (absolute neutrophil count $<0.5 \times 10^9/L$), to avoid precipitating an acute febrile episode.

Persons with underlying haematological malignancies (such as multiple myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, chronic lymphocytic leukaemia) are recommended to receive pneumococcal vaccination, due to the increased risk of invasive pneumococcal disease (IPD).[89] Newly diagnosed children or adults who have not previously received a dose of 13vPCV are recommended to receive at least one 13vPCV dose, depending on age, and should subsequently receive 23vPPV. These vaccines should be administered as early as possible after diagnosis, according to the person's age and previous vaccination history.[90-93] See 4.13 *Pneumococcal disease* for details.

Any deviations from these guidelines should be discussed with an oncologist.

Paediatric and adult patients with cancer who have completed cancer therapy and who completed a primary vaccination schedule before diagnosis

The majority of the following vaccines may be administered without checking antibody titres beforehand, and can be given at the same time.

The following schedule of booster vaccination is recommended if the person is well and in remission 6 months after chemotherapy:

- single dose of DTPa-containing vaccine if <10 years of age; use either dT or reduced antigen content dTpa if ≥10 years of age
- single dose of MMR, IPV, hepatitis B vaccines
- single dose of 13vPCV (if previous age-appropriate dose(s) not received; see 4.13 *Pneumococcal disease*)
- 23vPPV dose(s) (following 13vPCV, and as per 4.13 *Pneumococcal disease*)
- single dose of Hib vaccine (if either <5 years of age or if ≥5 years of age with asplenia, see Table 3.3.5)
- single dose of MenCCV (or 4vMenCV for persons with asplenia, see Table 3.3.5)
- 4vHPV vaccine: if >9 years of age, single dose if previously completed a primary course; 3-dose schedule if not previously received (schedule 0, 2 and 6 months) (see 4.6 *Human papillomavirus*)

- varicella vaccine: persons who are seronegative to varicella-zoster virus (VZV) should receive a 2-dose schedule of varicella vaccine, at least 6 months after chemotherapy has ceased (see 4.22 *Varicella*).

Measles and rubella antibody status should be checked 6 to 8 weeks after vaccination with MMR or MMRV vaccine. Persons who have not seroconverted should receive a further dose.

Administration of live attenuated viral vaccines (MMR-containing or varicella-containing vaccines) should be deferred if blood products or immunoglobulins have been recently administered (see Table 3.3.6 *Recommended intervals between either immunoglobulins or blood products and MMR, MMRV or varicella vaccination*).

Solid organ transplant recipients

For solid organ transplant (SOT) recipients, depending on the transplanted organ, and to prevent rejection, variable doses of immunosuppressive agents are required and may influence the effectiveness of vaccines. Where possible, children undergoing solid organ transplantation should be vaccinated well before transplantation. Inactivated vaccines can be administered safely after transplantation, but are usually administered from 6 months after transplantation to maximise the immune response.[94,95] Live vaccines are contraindicated in most post-transplantation protocols due to concerns of disseminated infection, although data in this population are limited.[95-97] Recommended vaccinations for child and adult SOT recipients are given in Table 3.3.2.

Table 3.3.2: Recommendations for vaccinations for solid organ transplant (SOT) recipients[96,98]

Vaccine	Vaccines recommended before transplantation		Vaccines recommended after transplantation, if not given beforehand		Comment
	Child (0–18 years)	Adult (≥19 years)	Child (0–18 years)	Adult (≥19 years)	
***Streptococcus pneumoniae* (pneumococcal disease)**					
13-valent pneumococcal conjugate vaccine (13vPCV)	Yes (aged ≥6 weeks)	Yes	Yes (aged ≥6 weeks)	Yes	Recommendations depend on age. See 4.13 *Pneumococcal disease* and Table 2.1.11 *Catch-up schedule for 13vPCV (Prevenar 13) and 23vPPV (Pneumovax 23) in children with a medical condition(s) associated with an increased risk of IPD, presenting at age <2 years.*
23-valent pneumococcal polysaccharide vaccine (23vPPV)	Yes (≥8 weeks after 13vPCV)	Yes (≥8 weeks after 13vPCV)	Yes (≥8 weeks after 13vPCV)	Yes (≥8 weeks after 13vPCV)	Recommendations depend on age. See 4.13 *Pneumococcal disease* and Table 2.1.11 *Catch-up schedule for 13vPCV (Prevenar 13) and 23vPPV (Pneumovax 23) in children with a medical condition(s) associated with an increased risk of IPD, presenting at age <2 years.*
***Haemophilus influenzae* type b**					
Hib vaccine	Yes	Not indicated	Yes	Not indicated	If possible, complete vaccination before transplantation.
Diphtheria, tetanus, pertussis					
DTPa-containing vaccine for children <10 years of age dTpa for those ≥10 years of age	Yes	Yes, provided dTpa has not been given in the last 10 years	Yes, if not previously vaccinated	Yes, provided dTpa has not been given in the last 10 years	The primary schedule should be completed before transplantation. For recipients <10 years of age, not previously vaccinated, give all 3 doses as DTPa-containing vaccine. For recipients ≥10 years of age, not previously vaccinated, give the 1st dose as dTpa, followed by 2 doses of dT. If dT is unavailable, complete vaccination course with dTpa. See also catch-up tables for children and adults in 2.1.5 *Catch-up*.

Vaccine	Vaccines recommended before transplantation		Vaccines recommended after transplantation, if not given beforehand		Comment
	Child (0–18 years)	Adult (≥19 years)	Child (0–18 years)	Adult (≥19 years)	
Influenza					
Influenza vaccine	Annual vaccination starting before transplantation for those ≥6 months of age. Two doses of influenza vaccine at least 4 weeks apart are recommended for all SOT recipients receiving influenza vaccine for the first time. Influenza vaccine should be given annually thereafter.				
Poliomyelitis					
IPV	Yes	Yes (see comments)	Yes	Yes (see comments)	Adults who have received a routine course of polio vaccination in childhood are recommended to receive a booster every 10 years if they plan to travel to a polio endemic area or have an occupational risk of polio exposure (e.g. laboratory workers).
Hepatitis B					
Hepatitis B vaccine	Yes	Yes, depending on serological status	Yes	Yes, depending on serological status	Recommended for all seronegative SOT candidates. Immunogenicity is likely to be improved when vaccination is administered before transplantation. Accelerated schedules can be used (see Table 4.5.2 *Accelerated hepatitis B vaccination schedules (for persons with imminent risk of exposure)*).
Hepatitis A					
Hepatitis A vaccine*	Yes, if seronegative (see comments)	Yes, if seronegative (see comments)	Yes, if seronegative (see comments)	Yes, if seronegative (see comments)	Recommended for all liver SOT recipients, or transplant candidates or recipients with chronic liver disease, or those chronically infected with either hepatitis B or hepatitis C.

Vaccine	Vaccines recommended before transplantation		Vaccines recommended after transplantation, if not given beforehand		Comment
	Child (0–18 years)	Adult (≥19 years)	Child (0–18 years)	Adult (≥19 years)	
***Neisseria meningitidis* (meningococcal disease)**					
Meningococcal C conjugate vaccine (MenCCV)	Yes	Not indicated	Yes	Not indicated	If the 1st MenCCV dose is given before 12 months of age, a 2nd dose should be given at least 8 weeks later. Give 4vMenCV, if clinically indicated (see below), once child is ≥12 months of age, and at least 8 weeks has elapsed since receipt of last MenCCV dose.
Quadrivalent meningococcal conjugate vaccine (4vMenCV)*	Yes, if ≥9 months of age with defined risk factors (see comments)	Yes, if defined risk factors (see comments)	Yes, if ≥9 months of age with defined risk factors (see comments)	Yes, if defined risk factors (see comments)	4vMenCV as a 2-dose schedule is recommended as a primary course of vaccination for those (≥9 months of age) with complement component deficiencies (e.g. C5-C9, properdin, Factor D, Factor H), functional hyposplenism or anatomical asplenia (see Table 3.3.5 *Recommendations for vaccination in persons with functional or anatomical asplenia*). Boosters of 4vMenCV should be given every 5 years.
Human papillomavirus					
HPV vaccine	Yes	Yes	Yes, if no history of prior immunisation	Yes, if no history of prior immunisation	3-dose schedule of 4vHPV is recommended for those aged >9 years. The routine schedule is 1st dose on day 0 (day of vaccination), 2 months, and 6 months (after 1st dose). Recommended in both females and males. For more detail, see 4.6 *Human papillomavirus*.
Measles, mumps and rubella					
MMR vaccine	Yes	Yes, unless 2 previous documented doses	Contraindicated	Contraindicated	The primary schedule should be completed before transplantation provided the transplant candidate is taking no immunosuppressive therapy and has no underlying cellular immunodeficiency.

Vaccine	Vaccines recommended before transplantation		Vaccines recommended after transplantation, if not given beforehand		Comment
	Child (0–18 years)	Adult (≥19 years)	Child (0–18 years)	Adult (≥19 years)	
Varicella					
Varicella vaccine	Yes, if non-immune (see comments)	Yes, if non-immune (see comments)	Contraindicated	Contraindicated	Confirm immunity with reliable history of varicella disease and confident clinical diagnosis or serological testing. The primary vaccination schedule should be completed before transplantation, provided the transplant candidate is taking no immunosuppressive therapy and has no underlying cellular immunodeficiency.

* Any transplant recipient who anticipates travelling may require additional vaccination, such as for hepatitis A and meningococcal disease (see also 3.2 *Vaccination for international travel*).

Haematopoietic stem cell transplant recipients[99,100]

Haematopoietic stem cells are sourced from peripheral blood, bone marrow or umbilical cord blood. Protective immunity to vaccine-preventable diseases is partially or completely lost following either allogeneic or autologous stem cell transplantation. Immunocompromise following allogeneic transplantation is caused by a combination of the preparative chemotherapy given before transplantation, graft-versus-host disease (GVHD), and immunosuppressive therapy following transplantation. Persisting immunocompromise is common, particularly in persons with chronic GVHD. Immunity is also impaired in autologous HSCT recipients due to high-dose chemotherapy and radiotherapy, but GVHD is not a concern as donor stem cells are derived from the transplant recipient. In most cases, autologous HSCT recipients will recover their immunity more quickly than allogeneic transplant recipients.

Separate vaccination schedules for autologous or allogeneic HSCT recipients have not been supported in published guidelines because of limited data. For practical purposes, the same schedule is recommended for these two groups, regardless of donor source (peripheral blood, bone marrow or umbilical cord), preparative chemotherapy (ablative or reduced intensity), or transplant type (allogeneic or autologous).[101,102]

HSCT recipients with ongoing GVHD or remaining on immunosuppressive therapy should *not* be given live vaccines. Chronic GVHD (cGVHD) is associated with functional hyposplenism and therefore increases susceptibility to infections with encapsulated organisms, especially *Streptococcus pneumoniae*. For persons with cGVHD who remain on active immunosuppression, antibiotic prophylaxis is recommended.[99]

The immune response to vaccinations is usually poor during the first 6 months after HSCT. Donor immunisation with hepatitis B, tetanus, Hib and pneumococcal conjugate vaccines before stem cell harvesting has been shown to elicit improved early antibody responses in HSCT recipients vaccinated in the post-transplantation period.[103-106] However, practical and ethical considerations currently limit the use of donor immunisation.

Routine serological testing for several infectious agents and antibody levels conferring protective immunity are poorly defined. For those vaccines that are recommended for all HSCT recipients (tetanus, diphtheria, poliomyelitis, influenza, pneumococcal, Hib), pre-vaccination testing is not recommended as the response to a primary course of these vaccines is generally adequate. The serological response to pneumococcal vaccine is less predictable. Pneumococcal serology is only available in a few specialised laboratories and is not routinely recommended. Serology before and approximately 4 to 6 weeks after vaccination with the final dose of a hepatitis B vaccine course, and after MMR vaccine, is recommended as antibody levels will determine the need for revaccination.[102] Post-vaccination varicella serology using commercial assays is very insensitive for vaccine-induced immunity (as compared with natural infection) and is not recommended (see 4.22 *Varicella*).

A recommended schedule of vaccination is outlined in Table 3.3.3.

Table 3.3.3: Recommendations for revaccination following haematopoietic stem cell transplant (HSCT) in children and adults, irrespective of previous immunisation history[99,100,107-111]

Vaccine	Months after HSCT				Comments
	6	8	12	24	
***Streptococcus pneumoniae* (pneumococcal disease)**					
13-valent pneumococcal conjugate vaccine (13vPCV)	Yes	Yes	Yes	Not needed	See 4.13 *Pneumococcal disease*
23-valent pneumococcal polysaccharide vaccine (23vPPV)	No	No	No	Yes (after 13vPCV)	See 4.13 *Pneumococcal disease*
***Haemophilus influenzae* type b**					
Hib	Yes	Yes	Yes	Not needed	
Diphtheria, tetanus, pertussis					
DTPa-containing vaccine for children <10 years of age dTpa for those ≥10 years of age	Yes	Yes	Yes	Not needed	For recipients <10 years of age, give all 3 doses as DTPa-containing vaccine. For recipients ≥10 years of age, give the 1st dose as dTpa, followed by 2 doses of dT. If dT is unavailable, complete vaccination course with dTpa.
Poliomyelitis					
IPV	Yes	Yes	Yes	Not needed	A 3-dose course of inactivated poliomyelitis vaccine is recommended. This can be given as DTPa-IPV or dTpa-IPV; see 'Diphtheria, tetanus, pertussis' above.
Hepatitis B					
Hepatitis B vaccine	Yes	Yes	Yes	Not needed	A high-dose formulation (H-B-Vax II dialysis formulation) is preferred. Alternatively, give single strength Hep B vaccine in each arm at each dosing interval *OR* administer a standard vaccination course, then check HBsAb titres 4–8 weeks following the last vaccine dose. If titres are <10 mIU/mL, repeat the vaccination course.
Influenza					
Two doses of influenza vaccine at least 4 weeks apart are recommended for all HSCT recipients receiving influenza vaccine for the first time, with the 1st dose given as early as 6 months after transplant (see also in the introduction of 3.3.3 *Vaccination of immunocompromised persons* above), then a single dose annually thereafter.					

Vaccine	Months after HSCT				Comments
	6	8	12	24	
***Neisseria meningitidis* (meningococcal disease)**					
Meningococcal C conjugate vaccine (MenCCV) (for those <12 months of age)	Yes	No	Yes	Not needed	If HSCT occurred prior to age 12 months, give up to 2 doses of MenCCV, followed by 2 doses of 4vMenCV from 12 months of age (see 4.10 *Meningococcal disease*).
Quadrivalent meningococcal conjugate vaccine (4vMenCV)* (for those ≥12 months of age)	Yes	Yes	Not needed	Not needed	Two doses of 4vMenCV are recommended for persons ≥12 months of age (see 4.10 *Meningococcal disease*).
Human papillomavirus					
HPV vaccine			A 3-dose course of 4vHPV is recommended at intervals of 0, 2 and 6 months. Specific immunogenicity data in this group are not available; better immune responses may be expected at >12 months post transplantation when a greater level of immune reconstitution has been achieved.		Individual recommendations for HPV vaccination in those >9 years of age should be determined by an individual risk assessment (see 4.6 *Human papillomavirus*).
Measles, mumps and rubella					
MMR vaccine	No	No	No	Yes, 1 or 2 doses separated by a minimum interval of 4 weeks (see comments)	Give only if the person is off immunosuppressive therapy, with no cGVHD and with reconstituted cell-mediated immunity. Check serology 4 weeks after 1st vaccine dose. If there is no seroconversion, repeat the dose.
Varicella					
Varicella vaccine	No	No	No	Yes, 2 doses separated by a minimum interval of 4 weeks (see comments)	Give to a seronegative recipient only if the person is off immunosuppressive therapy, with no cGVHD and with reconstituted cell-mediated immunity.

* Any transplant recipient who anticipates travelling may require additional vaccination, such as for meningococcal and hepatitis A disease (see also 3.2 *Vaccination for international travel*).

HIV-infected persons[112]

Vaccination schedules for HIV-infected persons should be determined by the person's age, degree of immunocompromise ($CD4^+$ count) and the risk of infection (see Table 3.3.4 below). Children with perinatally acquired HIV differ substantially from adults, as immunisation and first exposure to vaccine antigens occurs after HIV infection, whereas in adults, most vaccines are inducing a secondary 'boosted' immune response. HIV-infected persons of any age whose disease is well controlled on combination antiretroviral therapy (undetected or low viral load with good preservation of $CD4^+$ lymphocyte count) are likely to respond satisfactorily to vaccines.

Table 3.3.4: Categories of immunocompromise in HIV-infected persons, based on age-specific $CD4^+$ counts and percentage of total lymphocytes[113]

	Age					
	<12 months		1–5 years		≥6 years	
Category	$CD4^+$ per µL	%	$CD4^+$ per µL	%	$CD4^+$ per µL	%
No evidence of immunocompromise	≥1500	≥25	≥1000	≥25	≥500	≥25
Moderate immunocompromise	750–1499	15–24	500–999	15–24	200–499	15–24
Severe immunocompromise	<750	<15	<500	<15	<200	<15

HIV-infected persons should be vaccinated as described below.

Live attenuated vaccines

- Rotavirus vaccines appear to be safe and immunogenic in HIV-infected but clinically stable children,[114,115] although data on their use are limited. Vaccination can be given according to the routine schedule unless there is severe immunocompromise. (See also 4.17 *Rotavirus*.)
- MMR vaccine should be routinely administered to HIV-infected children in a 2-dose schedule at 12 months and 18 months of age unless the child has a $CD4^+$ count of <750 per µL.[116-118] The serologic response is likely to be greatly improved after the 2nd dose of MMR vaccine in HIV-infected children,[119,120] so consideration should be given to administering the 2nd dose soon after the 1st dose (minimum interval between doses of 4 weeks) to increase the likelihood of a serologic response to all three components. This is particularly important if the child is travelling overseas or during episodes of local measles virus transmission. Likewise, asymptomatic HIV-infected adults with a $CD4^+$ count ≥200 per µL who are seronegative to any of the vaccine components should receive 1 or 2 doses of MMR vaccine,

depending on the number of vaccines received previously and evidence for seroconversion. Administration of MMR vaccine does not have a significant effect on the CD4+ count or viral load of HIV-infected adults.[121] Measles may cause severe disease in HIV-infected children, particularly those with a CD4+ count of <750 per µL, in whom protection from vaccination may be reduced; therefore, normal human immunoglobulin (NHIG) should be given as post-exposure prophylaxis, regardless of vaccination status (see 4.9 *Measles*, and Part 5 *Passive immunisation*).[122] The combination MMRV vaccine is not recommended for use in HIV-infected persons, due to a lack of data on its use. (See also varicella text below.)

- Varicella vaccine may be given to HIV-infected adults or children ≥12 months of age who are asymptomatic, although data on efficacy and safety in HIV-infected persons is limited.[123-125] Use of the monovalent varicella vaccine (VV), given in 2 doses, at least 3 months apart, in children ≥12 months of age with age-specific CD4+ count of ≥15% is recommended.[126,127] The same 2-dose VV strategy can be considered for HIV-infected adults who are varicella-seronegative and who have a CD4+ count of ≥200 per µL.[126] The combination MMRV vaccine is not recommended for use in HIV-infected persons. (See also 4.22 *Varicella*.)
- Zoster vaccine is not recommended for adults with AIDS or symptomatic HIV infection. However, persons with asymptomatic HIV infection may be considered for vaccination. Serological confirmation of previous VZV infection must be obtained prior to vaccination. Zoster vaccine is only registered for use in adults ≥50 years of age. (See also 4.24 *Zoster*.)
- Yellow fever vaccine can be administered to HIV-infected persons with CD4+ counts >200 per µL, who are at a recognised risk of exposure; however, this should be discussed with the person's treating clinician.[128] (See also 4.23 *Yellow fever* and 3.2 *Vaccination for international travel*.)
- BCG vaccine should not be given to HIV-infected children or adults because of the risk of disseminated BCG infection.[129,130] (See also 4.20 *Tuberculosis*.)
- Oral live attenuated typhoid vaccines should be avoided in HIV-infected persons. Parenteral Vi polysaccharide typhoid vaccine should be used instead (see 4.21 *Typhoid*).

Inactivated (non-live) vaccines

- Diphtheria-tetanus-pertussis (DTPa/dTpa), Hib and IPV vaccines can be given according to routine recommendations[112,131] (see relevant disease-specific chapters in Part 4).
- The 4vHPV vaccine can be given to children (≥9 years of age) and adults with HIV. It was safe and immunogenic in a small study of HIV1-infected men.[132] HIV-infected persons should receive the routine course of 3 doses of 4vHPV vaccine at times 0, 2 and 6 months. Vaccination is recommended for persons in the age ranges for which the vaccine is registered (females aged 9–45 years

and males 9–26 years); use of HPV vaccine in males up to the age of 45 years is unlikely to be associated with immunogenicity or adverse events that differ from those observed in females. However, the benefit of HPV vaccination is optimal when delivered to children or young adolescents prior to sexual debut (see 4.6 *Human papillomavirus*).

- Pneumococcal disease, both respiratory and invasive (IPD), is a frequent cause of morbidity in HIV-infected children and adults (see List 4.13.1 in 4.13 *Pneumococcal disease*).[133] Children should be vaccinated initially with pneumococcal conjugate vaccine (13vPCV); the number of doses depends on age at diagnosis and vaccination history (see Table 2.1.11 *Catch-up schedule for 13vPCV (Prevenar 13) and 23vPPV (Pneumovax 23) in children with a medical condition(s) associated with an increased risk of IPD, presenting at age <2 years*). For children aged >5 years and adults, a single dose of 13vPCV is recommended, followed by 23vPPV; repeat doses of 23vPPV are also indicated. See 4.13 *Pneumococcal disease* for details.
- Annual influenza vaccination is recommended in all HIV-infected adults and children (≥6 months of age). In HIV-infected persons who are immunocompromised and children <10 years of age, 2 doses, administered a minimum of 4 weeks apart, are recommended the first time influenza vaccine is given. HIV viral load may increase after influenza vaccination, but $CD4^+$ counts are unaffected and the benefits exceed the risk.[134-137] (See also 4.7 *Influenza*.)
- Hepatitis B is safe to use in HIV-infected persons, but the immunological response may be diminished. Serological testing for evidence of previous hepatitis B infection should be undertaken prior to commencing vaccination. Limited studies in HIV1-positive adults have demonstrated an improved and accelerated serological response to a vaccination schedule that consists of 4 double doses, comprising two injections of the standard adult dose (using Engerix-B) on each occasion, at times 0, 1, 2 and 6 months.[138,139] HIV-positive children should receive 3 doses of hepatitis B vaccine using an adult formulation (i.e. double the standard recommended dose for children).[126,127] Antibody level should be measured at the completion of the vaccination schedule; if the anti-HBs titre is <10 mIU/mL, further doses are required (see 4.5 *Hepatitis B*).
- Hepatitis A vaccines are immunogenic in most HIV-infected children,[140] but are only recommended for use in non-immune HIV-infected persons if they have independent risk factors for acquisition of hepatitis A (see 4.4 *Hepatitis A*).
- Parenteral Vi polysaccharide typhoid, inactivated Japanese encephalitis and rabies vaccines are safe and can be used in HIV-infected persons, if indicated. (See relevant disease-specific chapters in Part 4.)

Persons with functional or anatomical asplenia

Persons with an absent or dysfunctional spleen are at a life-long increased risk of fulminant bacterial infection, most notably invasive pneumococcal disease (IPD).[89,141] Pneumococcal, meningococcal, Hib and influenza vaccination are particularly recommended for all persons with asplenia, whether functional or anatomical (such as splenectomy). Other vaccinations should be up to date. Vaccines should be provided according to the person's age and previous immunisation history, and immunisation status should be reviewed regularly.[142] Specific vaccine recommendations for persons with asplenia are discussed below and shown in Table 3.3.5.

In persons undergoing an elective splenectomy, vaccination should be completed, where possible, 2 weeks before the scheduled operation date. In an unplanned splenectomy, vaccination should commence approximately 1 week after the splenectomy has occurred.[143]

Children with splenic dysfunction should also be given antibiotic prophylaxis to prevent bacterial infection, until at least 5 years of age.[144,145] All asplenic persons and/or their parents/carers should also be educated about the importance of early investigation and treatment of febrile illnesses, including the use of emergency antibiotics. Asplenic persons are recommended to wear a medical alert. Vaccination cannot provide protection against all bacterial infections, or even all pneumococcal serotypes that cause IPD, hence it is particularly important that persons with asplenia are informed of the life-long increased risk of severe bacterial infection, even if they have been appropriately vaccinated.

Pneumococcal vaccination

Additional doses of pneumococcal vaccine are recommended for persons with asplenia, depending on their age and previous immunisation history, as shown in Table 3.3.5. Detailed information is provided in 4.13 *Pneumococcal disease* and in Table 2.1.11 *Catch-up schedule for 13vPCV (Prevenar 13) and 23vPPV (Pneumovax 23) in children with a medical condition(s) associated with an increased risk of IPD, presenting at age <2 years* in 2.1.5 *Catch-up.*

A single dose of 13vPCV is recommended for asplenic older children and adults who have not previously received any previous 13vPCV dose.[146] This should precede 23vPPV doses when possible. However, if 1 or more doses of 23vPPV have previously been given, 13vPCV should be given at the next available opportunity, and at least 1 year after the last 23vPPV dose. Subsequent doses of 23vPPV are recommended, with a maximum of 3 doses in adulthood (age ≥18 years). Age-specific recommendations are discussed in 4.13 *Pneumococcal disease*.

Meningococcal vaccination

In infants aged <12 months, MenCCV is recommended: those <6 months of age at diagnosis require 2 doses, given at least 8 weeks apart, and those 6–11 months of age at diagnosis are recommended to receive 1 dose.

4vMenCV is recommended from 12 months of age, instead of the routine NIP-scheduled MenCCV vaccination; a 2nd dose of 4vMenCV should be given at least 8 weeks later. (See also 4.10 *Meningococcal disease*.) For adults and children who are >12 months of age at diagnosis, 2 doses of 4vMenCV are recommended, a minimum of 8 weeks apart. Subsequent booster doses of 4vMenCV are recommended at 5-yearly intervals thereafter.

Hib vaccination

A single dose of Hib vaccine is recommended for asplenic persons who were not vaccinated in infancy or who are incompletely vaccinated (see 4.3 *Haemophilus influenzae type b* and Table 2.1.8 *Catch-up schedule for Hib vaccination for children <5 years of age* in 2.1.5 *Catch-up*). Subsequent booster doses of Hib vaccine are not required. Persons who have received all scheduled doses of Hib vaccine do not require a booster dose before or after splenectomy.[147]

Influenza vaccination

Annual influenza vaccine is recommended in all persons from ≥6 months of age (see 4.7 *Influenza*), particularly those who are immunocompromised. Influenza infection can be complicated by secondary bacterial infections, such as IPD. The influenza vaccine dose is dependent on previous influenza vaccination history and age. (See also Table 4.7.1 *Recommended doses of influenza vaccine* in 4.7 *Influenza*).

Table 3.3.5: Recommendations for vaccination in persons with functional or anatomical asplenia

Age	Recommendations
Pneumococcal vaccines	
6 weeks to <2 years	Give a 3-dose primary course of 13vPCV, with an additional dose of 13vPCV at age ≥12 months. See Table 4.13.1 and Table 2.1.11 for catch-up schedules.
2 to 5 years	If the primary course of PCV is incomplete or if the recommended 13vPCV dose at age ≥12 months was not received, give 1 or 2 doses of 13vPCV as per Table 4.13.2. Give a single dose of 23vPPV at age 4–5 years.*
>5 to <18 years	If a 13vPCVdose has not previously been given, give a single dose of 13vPCV, preferably prior to 23vPPV.* If a dose of 23vPPV was received at age 4–5 years, give another dose of 23vPPV 5 years later (at age 9–10 years). If asplenia is newly diagnosed, give 2 doses of 23vPPV, 5 years apart (after 13vPCV; see above).
≥18 years	If a 13vPCV dose has not previously been given, give a single dose of 13vPCV, preferably prior to 23vPPV.* There is a maximum limit of 3 doses of 23vPPV during adulthood† (age ≥18 years). Give the 1st adult dose at diagnosis (after 13vPCV: see above), or at least 5 years after the last 23vPPV dose, whichever is later.
Meningococcal vaccines	
6 weeks to <6 months	Give 2 doses of MenCCV, 8 weeks apart; then 2 doses of 4vMenCV, commencing at age ≥12 months (see below).
6 to 11 months	Give a single dose of MenCCV, then 2 doses of 4vMenCV, commencing at age ≥12 months (see below).
≥12 months	Give 2 doses of 4vMenCV,‡ 8 weeks apart. Give a 4vMenCV dose every 5 years thereafter.

Age	Recommendations
***Haemophilus influenzae* type b (Hib) vaccine**	
6 weeks–<5 years	Give the recommended course of Hib-containing vaccine, or catch-up vaccination, according to Table 2.1.8 *Catch-up schedule for Hib vaccination for children <5 years of age*. Additional/repeat doses are not required.
≥5 years	If a Hib vaccine dose has not previously been given, or if the primary course of Hib vaccine is incomplete, give a single dose of Hib-containing vaccine. If Hib vaccination is complete (as per children <5 years above), additional/repeat doses are not required.
Influenza vaccine§	
≥6 months–<3 years	Give 2 doses (0.25 mL each), 1 month apart, in the first year of vaccination. Give 1 dose (0.25 mL) in subsequent years.
3–9 years	Give 2 doses (0.5 mL each), 1 month apart, in the first year of vaccination. Give 1 dose (0.5 mL) in subsequent years.
>9 years	Give 1 dose.¶

* Whenever possible, 13vPCV dose(s) should precede the recommended 23vPPV dose(s). If 13vPCV follows 23vPPV, a minimum interval of 12 months between 13vPCV and the last previous 23vPPV dose is recommended. The recommended minimum interval between a 13vPCV dose and a subsequent 23vPPV dose is 2 months. Also note that the recommended minimum interval between any two 23vPPV doses is 5 years.

† If asplenia is diagnosed at age ≥65 years (age ≥50 years for Indigenous adults), only a single revaccination dose of 23vPPV is recommended.

‡ The minimum interval between 4vMenCV and any previous MenCCV dose is 8 weeks.

§ Influenza vaccination is required annually. Two doses of influenza vaccine are not required in the first year influenza vaccine is given, unless the asplenic person also has another immunocompromising condition such as post SOT or HSCT.

¶ In children >9 years and adults the dose of influenza vaccine is 0.5mL, if using intramuscular vaccine. If aged >18 years, intradermal vaccination (Intanza: 0.1 mL dose), may also be used (see 4.7 *Influenza*).

Persons with autoimmune diseases and other chronic conditions

Persons with autoimmune conditions, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and multiple sclerosis (MS), are at higher risk of infections, including vaccine-preventable diseases, with the associated potential morbidity and mortality from infection. They are also at risk of infection due to treatment with immunosuppressive agents such as bDMARDs and targeted biological therapies.[148] Some diseases can be reactivated during therapy, so screening for infections such as hepatitis B and tuberculosis should be undertaken prior to vaccination.[149,150]

Overall, theoretical concerns that vaccines exacerbate or cause autoimmune diseases such as rheumatoid arthritis, type 1 diabetes and multiple sclerosis have not been substantiated, with sporadic case reports not verified by larger epidemiological studies.[151-154] However, persons with a history of Guillain-Barré syndrome (GBS) have an increased likelihood in general of developing GBS again, and the chance of them coincidentally developing the syndrome following influenza vaccination may be higher than in persons with no history of GBS. A small increased risk of GBS was associated historically with one influenza vaccine in the United States in 1976, but, since then, close surveillance has shown that GBS has occurred at a very low rate of up to 1 in 1 million doses of influenza vaccine, if at all.[155]

In persons with autoimmune diseases and other chronic conditions, there is potential for reduced immunogenicity of vaccines, due to both immunosuppressive therapies and the underlying disease.[156-158] The duration of immunocompromise may be prolonged and caution must be taken when considering live vaccines. Inactivated vaccines are recommended, to optimise protection despite the potential for reduced immunogenicity in some people. Clinical and laboratory measures of disease activity, and the choice, duration and dose of immunosuppressive therapies, do not always predict who will respond poorly to vaccination.[157,159,160] In some instances, due to ongoing risk of disease, additional vaccine doses may be required, such as pneumococcal vaccine. Inactivated vaccines such as HPV and dTpa can be administered to immunocompromised persons. Annual influenza vaccine is also important in this population and should be administered annually (2 doses in the first year, 1 annually thereafter).

Hypopituitarism is not a contraindication to vaccination if the person is only receiving physiological corticosteroid replacement, as this is not considered immunosuppressive. If the person has been unwell and is on high-dose corticosteroids for more than 1 week, the use of live attenuated vaccines should be delayed for a minimum of 1 month.

Persons with metabolic diseases should be vaccinated using the routine schedule, as vaccinations are generally considered safe in these persons.[161] Influenza and pneumococcal vaccines are recommended for those with metabolic disease. Any individual concerns should be discussed with the treating metabolic physician.

3.3.4 Vaccination of recent recipients of normal human immunoglobulin and other blood products

The immune response to live parenteral viral vaccines (with the exception of yellow fever and zoster vaccine) may be inhibited by normal human immunoglobulin (NHIG). The interval recommended is dependent on the type and half-life of the immunoglobulin administered (see Table 3.3.6 *Recommended intervals between either immunoglobulins or blood products and MMR, MMRV or varicella vaccination*).

Rotavirus vaccine may be administered at any time before or after, or concurrently with, any blood product, including antibody-containing products, following the routinely recommended schedule for rotavirus vaccine among infants who are eligible for vaccination (see 4.17 *Rotavirus*). Minimal data are available on the impact of blood products on the immune response to the vaccine in these infants. Completing the full rotavirus vaccine series will optimise protection.[162]

Zoster vaccine can be given at any time before or after administration of immunoglobulin, or any antibody-containing blood product, because those for whom it is registered (persons ≥50 years of age) are assumed to have had a previous VZV infection and, therefore, already have serum antibody levels comparable to those found in blood products (see 4.24 *Zoster*).

In persons with agammaglobulinaemia who are receiving monthly NHIG, the use of live vaccines is not recommended as the immune response may be inhibited. In addition, these people will have sufficient circulating antibody (e.g. measles, varicella) from the NHIG to protect them in the case of exposure. Inactivated vaccines are recommended as per the routine schedule; the response may be suboptimal, but these vaccines are safe to administer.

Persons, who have received a blood transfusion, including mass blood transfusions, do not require any past vaccinations to be repeated. However, following the receipt of any blood product, including plasma or platelets, an interval of 3 to 11 months should elapse, dependent on the blood product transfused, before vaccination with an MMR, MMRV or varicella vaccine (see Table 3.3.6 *Recommended intervals between either immunoglobulins or blood products and MMR, MMRV or varicella vaccination*). An interval is suggested because there may be low levels of antibodies present in the blood product that may impair the immune response to the live vaccine.

Table 3.3.6: Recommended intervals between either immunoglobulins or blood products and measles-mumps-rubella (MMR), measles-mumps-rubella-varicella (MMRV) or varicella vaccination*[163]

Immunoglobulin/blood product	Route	Dose		Interval (months)
		IU or mL	Estimated mg IgG/kg	
Blood transfusion:				
Washed RBCs	IV	10 mL/kg	Negligible	0
RBCs, adenine-saline added	IV	10 mL/kg	10	3
Packed RBCs	IV	10 mL/kg	20–60	5
Whole blood	IV	10 mL/kg	80–100	6
Cytomegalovirus immunoglobulin	IV	3 mL/kg	150	6
HBIG as hepatitis B prophylaxis	IM	100 IU 400 IU	10	3
NHIG (intravenous) for ITP treatment	IV		400	8
NHIG (intravenous) for ITP treatment	IV		1000	10
NHIG (intravenous) for ITP or Kawasaki disease treatment	IV		1600–2000	11
NHIG as hepatitis A prophylaxis	IM	0.5 mL (<25 kg) 1.0 mL (25–50 kg) 2.0 mL (>50 kg)		3
NHIG as measles prophylaxis:		(max. dose 15 mL)		
Standard	IM	0.2 mL/kg		5
Immunocompromised	IM	0.5 mL/kg		6
Plasma or platelet products	IV	10 mL/kg	160	7
HRIG as rabies prophylaxis	IM	20 IU/kg	22	4
Replacement (or therapy) of immune deficiencies (as NHIG [intravenous], various doses)	IV		300–400	9
Rh (D) IG (anti-D)	IM			0
TIG (IM use) for tetanus prophylaxis	IM	250 IU (given within 24 hours of injury) 500 IU (>24 hours after injury)	10 20	3
ZIG as varicella prophylaxis	IM	200 IU (0–10 kg) 400 IU (11–30 kg) 600 IU (>30 kg)		5

* Zoster vaccine can be given at any time before or after administration of immunoglobulin or any antibody-containing blood product.

3.3.5 Vaccination of persons with bleeding disorders

Persons who are receiving anticoagulant therapy may develop haematomas in IM injection sites. The length of anticoagulant therapy should be clarified and immunisation delayed if therapy is going to be of short-term duration. Unless warfarin or low molecular weight heparin (LMWH) doses are known to be stable, persons receiving anticoagulants should have appropriate levels checked before vaccine administration, if possible. Intramuscular injections should be deferred if the INR is >3.0 (warfarin) or the anti-Xa (LMWH) level 4 hours post dose is >0.5 Units/mL.

If a person has haemophilia and is receiving clotting factor replacement or similar therapy, IM vaccine administration should be conducted as soon as possible after the medication is received.[163] The site should not be rubbed post administration, but firm pressure applied for approximately 5–10 minutes. Vaccine recipients and/or carers should be informed about the possibility of haematoma formation. Ice and immobilisation may be used in the case of a small haematoma. The subcutaneous route could be considered as an alternative in a person with haemophilia or on anticoagulant therapy; however, the intramuscular route is preferred if that is the usual recommended mode of vaccine administration – seek expert advice. If a vaccine is administered subcutaneously, there may be diminished immune response (e.g. requirement to check anti-HBs antibodies) and additional vaccine doses may be required.[164,165]

3.3.6 Vaccination before or after anaesthesia/surgery

Recent or imminent surgery is not a contraindication to vaccinations, and recent vaccination is not a contraindication to surgery (see 2.1.4 *Pre-vaccination screening*). There are no randomised controlled trials providing evidence of adverse outcomes with anaesthesia and surgery in recently vaccinated children. It is possible that the systemic effects from recent vaccination, such as fever and malaise, may cause confusion in the post-operative period. As the evidence is limited, it is possible to administer vaccines as per the routine schedule, or electively during a procedure for a person in a special risk group, if the appropriate vaccine delivery safety mechanisms are in place.[166]

If elective surgery and anaesthesia are to be postponed, some guidelines recommend postponing for 1 week after inactive vaccination and for 3 weeks after live attenuated viral vaccination in children. Routine vaccination may be deferred for 1 week after surgery.[167]

A person who receives any blood products during surgery will need to be informed of the need to delay some vaccinations (see Table 3.3.6 *Recommended intervals between either immunoglobulins or blood products and MMR, MMRV or varicella vaccination*).

3.3.7 Vaccination of persons at occupational risk

Certain occupations, particularly those associated with healthcare, are associated with an increased risk of some vaccine-preventable diseases.[168,169] Furthermore, some infected workers, particularly healthcare workers and those working in early childhood education and care, may transmit infections such as influenza, rubella, measles, mumps, varicella and pertussis to susceptible contacts, with the potential for serious health outcomes. Many infectious diseases, measles in particular, are highly infectious several days before symptoms become apparent. Healthcare workers employed within the public health system should check local state or territory healthcare worker immunisation requirements and the necessary documentation required (see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*).

Where workers are at significant occupational risk of acquiring a vaccine-preventable disease, the employer should implement a comprehensive occupational vaccination program, which includes a vaccination policy, current staff vaccination records, provision of information about the relevant vaccine-preventable diseases, and the management of vaccine refusal (e.g. reducing the risk of a healthcare worker transmitting disease to vulnerable persons). Employers should take all reasonable steps to encourage non-immune workers to be vaccinated.

Current recommended vaccinations for persons at risk of occupationally acquired vaccine-preventable diseases are listed in Table 3.3.7. In addition to the vaccines specific to a person's occupation and work-related activities recommended here, all adults should be up to date with routinely recommended vaccines, such as dT-containing and MMR vaccines. (See also Table 2.1.12 in 2.1.5 *Catch-up*.)

Standard precautions should be adopted where there is risk of occupational exposure to blood and body fluids. Preventive measures include the appropriate handling and disposal of sharps, the donning of gloves when handling body fluids, and the use of goggles/face shields when splashes are likely.

If a non-immune person is exposed to a vaccine-preventable disease, post-exposure prophylaxis should be administered where indicated (see relevant disease-specific chapters in Part 4, and Part 5 *Passive immunisation*).

Table 3.3.7: Recommended vaccinations for persons at increased risk of certain occupationally acquired vaccine-preventable diseases*†

Occupation	Vaccine
Healthcare workers (HCW)	
All HCW Includes all workers and students directly involved in patient care or the handling of human tissue, blood or body fluids	Hepatitis B Influenza MMR (if non-immune)‡ Pertussis (dTpa) Varicella (if non-immune)
HCW who work in remote Indigenous communities or with Indigenous children in NT, Qld, SA and WA, and other specified healthcare workers in some jurisdictions	Vaccines listed for 'All HCW', plus hepatitis A
HCW who may be at high risk of exposure to drug-resistant cases of tuberculosis (dependent on state or territory guidelines)	Vaccines listed for 'All HCW', plus consider BCG
Persons who work with children	
All persons working with children, including: • staff and students working in early childhood education and care • correctional staff working where infants/children cohabitate with mothers • school teachers (including student teachers) • outside school hours carers • child counselling services workers • youth services workers	Influenza MMR (if non-immune)‡ Pertussis (dTpa) Varicella (if non-immune)
Staff working in early childhood education and care	Vaccines listed for 'Persons who work with children', plus hepatitis A
Carers	
Carers of persons with developmental disabilities§	Hepatitis A Hepatitis B Influenza
Staff of nursing homes and long-term care facilities for persons of any age§	Influenza MMR (if non-immune)‡ Varicella (if non-immune)

Occupation	Vaccine
Providers of home care to persons at risk of high influenza morbidity	Influenza
Emergency and essential service workers	
Police and emergency workers	Hepatitis B Influenza Tetanus (dT or dTpa)
Armed forces personnel	Hepatitis B Influenza MMR (if non-immune)‡ Tetanus (dT or dTpa) Other vaccines relevant to deployment
Staff of correctional facilities	Hepatitis B Influenza MMR (if non-immune)‡ Tetanus (dT or dTpa)
Staff of detention and immigration centres	Hepatitis B Influenza MMR (if non-immune)‡ Tetanus (dT or dTpa)
Laboratory personnel	
Laboratory personnel handling veterinary specimens or working with Q fever organism (*Coxiella burnetii*)	Q fever
Laboratory personnel handling either bat tissues or lyssaviruses (including rabies virus and Australian bat lyssavirus)	Rabies
Laboratory personnel routinely working with these organisms:	
Bacillus anthracis	Anthrax¶
Vaccinia poxviruses	Smallpox¶
Poliomyelitis virus	Poliomyelitis (IPV)
Salmonella enterica subspecies *enterica* serovar Typhi (*S.* Typhi)	Typhoid
Yellow fever virus	Yellow fever
Neisseria meningitidis	Quadrivalent meningococcal conjugate vaccine (4vMenCV)
Japanese encephalitis virus	Japanese encephalitis

Occupation	Vaccine
Persons who work with specific communities	
Workers who live with, or make frequent visits to, remote Indigenous communities in NT, Qld, SA and WA	Hepatitis A
Workers assigned to the outer Torres Strait Islands for a total of 30 days or more during the wet season	Japanese encephalitis
Persons who work with animals	
Veterinarians, veterinary students, veterinary nurses[#]	Influenza Q fever Rabies
Agricultural college staff and students (aged >15 years) exposed to high-risk animals[#]	Q fever
Abattoir workers and contract workers in abattoirs (excluding pig abattoirs) Livestock transporters Sheep shearers and cattle, sheep and dairy farmers Those culling or processing kangaroos or camels Tanning and hide workers Goat farmers Livestock saleyard workers Those handling animal products of conception	Q fever
Wildlife and zoo workers who have contact with at-risk animals, including kangaroos and bandicoots	Q fever
Persons who come into regular contact with bats (both 'flying foxes' and microbats), bat handlers, bat scientists, wildlife officers, zoo curators	Rabies
Poultry workers and others handling poultry, including those who may be involved in culling during an outbreak of avian influenza, and swine industry workers	Influenza
Other persons exposed to human tissue, blood, body fluids or sewage	
Embalmers	Hepatitis B
Workers who perform skin penetration procedures (e.g. tattooists, body-piercers)	Hepatitis B
Funeral workers and other workers who have regular contact with human tissue, blood or body fluids and/or used needles or syringes	Hepatitis B
Plumbers or other workers in regular contact with untreated sewage	Hepatitis A Tetanus (dT or dTpa)

* Work activities, rather than job title, should be considered on an individual basis to ensure an appropriate level of protection is afforded to each worker. In addition to providing protection

against certain vaccine-preventable diseases that persons in these occupations may be at increased risk of acquiring, vaccination may also reduce the risk of transmission of diseases to others with whom these persons are in contact.

† In addition to the vaccines specific to a person's occupation and work-related activities recommended here, all adults should be up to date with routinely recommended vaccines, such as dT-containing and MMR vaccines (see also Table 2.1.12 in 2.1.5 *Catch-up*).

‡ All adults born during or since 1966 should have evidence of either receiving 2 doses of MMR vaccine or having immunity to measles, mumps and rubella. Adults born before 1966 are considered to be immune due to extensive measles, mumps and rubella circulating widely in the community during this period of time (see 4.9 *Measles*).

§ Carers of infants <6 months of age should be vaccinated against pertussis using dTpa (see 4.12 *Pertussis*).

¶ Persons with a repeated risk of exposure to, or working with large quantities or concentrations of, *Bacillus anthracis* or Vaccinia cultures. For information regarding anthrax or smallpox vaccination, contact the Office of Health Protection in the Australian Government Department of Health, Canberra.

Vaccines required in these occupations may depend on the animals with which the person comes in contact.

3.3.8 Vaccination of migrants to Australia

Vaccination status is not routinely assessed in children and adults entering Australia as refugees or migrants.[170] Refugees or migrants may be incompletely vaccinated according to the Australian schedule or have incomplete records of vaccination.[171] Most states and territories provide migrant/refugee immunisation through hospital outpatient departments. Some clinics have also linked families with local general practitioners who are of a similar ethnic and cultural background to ensure ongoing follow-up and referral where required. In addition, some local councils also provide a similar service.

Immunisation records, where available for refugees, are likely to have been given to the nominated head of the household at the refugee camp health centre. The Australian Government Department of Immigration and Citizenship (DIAC) may in some circumstances be able to provide further information regarding vaccine(s) administered to refugees before entering Australia, usually by accessing an electronic health manifest. The World Health Organization website (www.who.int/countries/en) lists immunisation schedules for most countries and may provide some information regarding vaccine schedules.

If there is a valid record of vaccination from overseas, the history of previous doses should be taken into account when planning a catch-up vaccination schedule. However, some doses may be invalid, as the interval between doses may be too short. This is often the case with oral poliomyelitis vaccines and tetanus vaccines.

If a migrant/refugee has no valid documentation of vaccination, the standard 'catch-up' schedule should be commenced. Serological testing to determine the need for specific vaccinations is *not* recommended in the absence of documented vaccination.

If a child is ≥12 months of age, the 1st doses of DTPa, hepatitis B, IPV, MMR, MenCCV, 13vPCV and Hib vaccines can be given at the same visit. For details, see 2.1.5 *Catch-up*.

Migrant/refugee adults also need to be targeted for vaccination, especially against rubella, using MMR vaccine. This is particularly important for women of child-bearing age. Some refugees aged between 9 months and 54 years may have been offered MMR as part of a pre-departure screening, but may require a subsequent dose on arrival in Australia.[170] It is important to take into account any live attenuated viral vaccines that may have been administered as part of a pre-departure screening, such as measles-containing vaccines or yellow fever vaccine (especially in those persons arriving from central and northern African nations). It is important to allow a minimum 4-week interval before administering any other live attenuated viral vaccines.

All vaccines administered to children <7 years of age should be reported to the Australian Childhood Immunisation Register (ACIR), including vaccinations documented pre-arrival and those for children not enrolled with Medicare. ACIR History Statements can be issued after documented overseas vaccination(s) have been recorded on the ACIR. In addition, vaccinations provided to adolescents via school-based programs are recorded by state/territory health authorities and HPV vaccines should be recorded on the National HPV Vaccination Program Register (NHVPR, or the 'HPV register') (see 2.3.4 *Immunisation registers*). It is particularly important to ensure that families are provided with a written record of all vaccines administered, and that all sources of vaccination records are checked prior to vaccination, as multiple immunisation providers may have been consulted after arrival.[170,171]

3.3.9 Vaccination of inmates of correctional facilities

Inmates of correctional facilities are at risk of acquiring influenza, hepatitis A and hepatitis B, and should be vaccinated against these infections (see 4.4 *Hepatitis A*, 4.5 *Hepatitis B* and 4.7 *Influenza*).[172-174] In addition, inmates of correctional facilities should be up to date with routinely recommended vaccines for adults, such as dT-containing and MMR vaccines. (See also Table 2.1.12 in 2.1.5 *Catch-up*.)

3.3.10 Vaccination of men who have sex with men

Men who have sex with men are at risk of acquiring hepatitis A and hepatitis B, and should be vaccinated against these infections (see 4.4 *Hepatitis A* and 4.5 *Hepatitis B*). Human papillomavirus vaccine may also be indicated (see 4.6 *Human papillomavirus*). In addition, men who have sex with men should be up to date with routinely recommended vaccines for adults, such as dT-containing and MMR vaccines. (See also Table 2.1.12 in 2.1.5 *Catch-up*.)

3.3.11 Vaccination of persons who inject drugs

Persons who inject drugs are at risk of acquiring hepatitis A and hepatitis B, and should be vaccinated against these infections (see 4.4 *Hepatitis A* and 4.5 *Hepatitis B*). In addition, persons who inject drugs should be up to date with routinely recommended vaccines for adults, such as dT-containing and MMR vaccines. (See also Table 2.1.12 in 2.1.5 *Catch-up*.)

3.3.12 Vaccination of sex industry workers

Sex industry workers are at risk of acquiring hepatitis A and hepatitis B, and should be vaccinated against these infections (see 4.4 *Hepatitis A* and 4.5 *Hepatitis B*). Human papillomavirus vaccine may also be indicated (see 4.6 *Human papillomavirus*). In addition, sex industry workers should be up to date with routinely recommended vaccines for adults, such as dT-containing and MMR vaccines. (See also Table 2.1.12 in 2.1.5 *Catch-up*.)

References

A full reference list is available on the electronic *Handbook* or website www.immunise.health.gov.au

PART 4 VACCINE-PREVENTABLE DISEASES

4.1 CHOLERA

4.1.1 Bacteriology

Vibrio cholerae is a motile, curved Gram-negative bacillus. Differences in the O antigens have led to the description of more than 150 serogroups, only two of which have been found to cause cholera. Cholera is caused by enterotoxin-producing *V. cholerae* of serogroups O1 and O139 (sometimes referred to as the 'Bengal' strain). Serogroup O1 includes two biotypes (classical and El Tor), each of which includes organisms of Inaba, Ogawa and Hikojima serotypes. The ability of *V. cholerae* to persist in water is determined by the temperature, pH, salinity and availability of nutrients; it can survive under unfavourable conditions in a viable dormant state.[1] Transmission predominantly occurs when people ingest faecally contaminated food or water.

4.1.2 Clinical features

Cholera is an acute bacterial infection that is generally characterised by the sudden onset of painless, profuse, watery diarrhoea. In rare situations more than half the severe cases will die. Mild cases also occur, as does subclinical infection.[1]

The cholera toxin does not produce intestinal inflammation. The cholera toxin induces secretion of increased amounts of electrolytes into the intestinal lumen, resulting in mild to severe dehydration and, in some cases, metabolic acidosis.

4.1.3 Epidemiology

The disease is usually transmitted via food and water contaminated with human excreta. Seafood such as shellfish obtained from contaminated waters have also been responsible for outbreaks.[1] Cholera is a substantial health burden in developing countries and is considered to be endemic in Africa, Asia, South America and Central America.[2] Cholera epidemics are common in circumstances where food and water supplies can become contaminated, such as after natural disasters and civil unrest.[2] Cases of cholera in Australia (about 2 to 6 cases a year) almost always occur in individuals who have been infected in endemic areas overseas.[3] However, the overall risk of cholera to travellers with access to a safe water source and hygienic food preparation is considered to be low, even when visiting countries where cholera is endemic. The risk of infection has been estimated at 0.2 cases per 100 000 travellers from western countries, and the risk of severe disease is considerably lower,[4] although under-detection and under-reporting of cholera among travellers is likely.[2,4,5]

In 1977, a locally acquired case led to the discovery of *V. cholerae* in some rivers of the Queensland coast.[6] Because of this, health workers should be aware that sporadic cases of cholera may, on rare occasions, follow contact with estuarine

waters. All cases of cholera reported since the commencement of the National Notifiable Diseases Surveillance System in 1991 have been acquired outside Australia, except for 1 case of laboratory-acquired cholera in 1996 and 3 cases in 2006.[3,7] The 3 cases in 2006, reported in Sydney, were linked and associated with consumption of raw imported whitebait.[7] These patients had no history of recent travel to known cholera-endemic areas.[7]

4.1.4 Vaccines

- ***Dukoral*** – CSL Limited and Crucell Sweden AB (inactivated whole-cell *V. cholerae* O1, in combination with a recombinant cholera toxin B subunit [rCTB]). Each 3.0 mL liquid vaccine dose vial contains heat and formalin-inactivated Inaba, Ogawa, classic and El Tor strains of *V. cholerae* O1, 31.25 x 10^9 vibrios of each, combined with 1.0 mg rCTB. The buffer consists of a sachet of effervescent granules of anhydrous sodium carbonate, sodium bicarbonate, anhydrous citric acid, sodium citrate, saccharin sodium and raspberry flavour. This formulation does not contain aspartame.

Trials of the oral cholera vaccine that contained inactivated whole-cell *V. cholerae* O1 combined with rCTB have been performed mainly in Bangladesh and Peru.[8-14] The large randomised controlled trial in Bangladesh included over 120 000 children (aged 2–15 years) and women (aged >15 years), with up to 5 years follow-up. About 13 000 children and 8 000 women received 3 doses of the study vaccine. When cholera cases in all age groups were aggregated, the protective efficacy of this vaccine (in a 3-dose regimen with inactivated *Escherichia coli* as control) was 85%, 6 months after the 3rd dose. The protective efficacy decreased to 62% after 1 year, and to 57% after 2 years.[8,10] On long-term follow-up (up to 5 years) no significant protective efficacy was observed beyond 2 years.[8,14] The efficacy of the vaccine was lower and waned more rapidly in children aged 2–5 years.[14] In this age group, while the efficacy was 100% during the first 4–6 months after vaccination, it became non-significant in the latter half of the 1st year of follow-up (during a cholera epidemic), resulting in an overall efficacy of 38% after 1 year; efficacy after 2 years was comparable. In contrast, for those aged >5 years, the efficacy estimates were 76%, 78% and 63%, respectively, at these three time points.[8,9,14] The protective efficacy of the vaccine, over a 3-year follow-up period, was not significantly different among those who received a total of 2 doses versus those who received 3 doses (including all ages).[8,9]

A randomised controlled trial in Peru among military recruits aged 16–45 years found a vaccine efficacy of 86% against symptomatic cholera after 2 vaccine doses.[13] Another Peruvian household study showed an overall efficacy of 61%

among 2–65-year olds,[12] after a booster dose given 10 months after a 2-dose primary series.[12] A field effectiveness case-control study in Mozambique, during a mass oral cholera vaccination program in an endemic population aged ≥2 years, found that 1 or more doses of the inactivated oral cholera vaccine was 78% protective (1–6 months after the 1st dose). The per-protocol effectiveness of 2 doses was 84% (0.5–4.5 months after the 2nd dose).[15]

There is structural similarity and immunologic cross-reactivity between the cholera toxin and the heat-labile toxin of *E. coli*, which is often associated with 'travellers' diarrhoea'. Therefore, it had been suggested that the rCTB-containing vaccine may also provide protection against heat-labile toxin producing enterotoxigenic *E. coli* (LT-ETEC). A study in short-term Finnish tourists[16] showed that the inactivated oral cholera vaccine also provided a 60% reduction in diarrhoea caused by LT-ETEC. A study in Bangladesh, an endemic area, showed 67% protection against LT-ETEC for 3 months only.[17] It can be expected that the inactivated vaccine will reduce the proportion of travellers' diarrhoea that is caused by LT-ETEC. Approximately 30 to 40% of travellers to developing countries contract travellers' diarrhoea, with an average of 20% of cases caused by LT-ETEC; hence, the 60% efficacy of the oral inactivated vaccine against LT-ETEC could be expected to prevent up to 15% of travellers' diarrhoea.[18-20] However, in Australia this vaccine is only registered for the prevention of cholera.

To date, there is no vaccine marketed in Australia to protect against infection with *V. cholerae* O139. An oral killed whole-cell bivalent cholera vaccine (against both serogroups O1 and O139) has been evaluated in Vietnam.[21,22] More recently, in India, an interim analysis of a cluster-randomised controlled trial reported a protective efficacy of 67% against *V. cholerae* O1 after 2 years. Specific efficacy against *V. cholerae* 0139 could not be assessed in this study, as cholera episodes caused by this serogroup were not detected.[23]

4.1.5 Transport, storage and handling

Transport according to *National vaccine storage guidelines: Strive for 5*.[24] Store at +2°C to +8°C. Do not freeze. Protect from light.

Because the person to be vaccinated will be responsible for looking after the vaccine following purchase, details of how it should be transported (from pharmacy to home) and stored in the refrigerator (at home) must be carefully explained.

4.1.6 Dosage and administration

Dukoral is an oral vaccine.

Food and drink should be avoided for 1 hour before and 1 hour after administration of the inactivated cholera vaccine, as the vaccine is acid labile.

Children aged 2–6 years

Three doses are required, given a minimum of 1 week and up to 6 weeks apart. If an interval of more than 6 weeks occurs between any of the doses, re-start the vaccination course.

Dukoral is administered orally. After dissolving the buffer granules in 150 mL of water, half the solution is then poured away and the entire contents of the vaccine vial are mixed with the remaining 75 mL for administration.

Adults and children aged >6 years

Two doses are required, given a minimum of 1 week and up to 6 weeks apart. If the 2nd dose is not administered within 6 weeks, re-start the vaccination course.

Dukoral is administered orally. After dissolving the buffer granules in 150 mL of water, the contents of the vaccine vial are then added to the solution for administration.

Co-administration with other vaccines

The inactivated oral cholera vaccine can be given with, or at any time before or after, other travel vaccines, such as yellow fever or parenteral Vi polysaccharide typhoid vaccines.

However, there should be an interval of at least 8 hours between the administration of the inactivated oral cholera vaccine and oral live attenuated typhoid vaccine (see 4.1.10 *Precautions* below).

4.1.7 Recommendations

Vaccination against cholera is not an official requirement for entry into any foreign country.

Routine cholera vaccination is not recommended as the risk to travellers is very low, despite the endemicity of cholera in some countries often visited by Australians. Careful and sensible selection of food and water is of far greater importance to the traveller than cholera vaccination.

Cholera vaccination should be considered for travellers at increased risk of acquiring diarrhoeal disease, such as those with achlorhydria, and for travellers at increased risk of severe or complicated diarrhoeal disease, such as those with poorly controlled or otherwise complicated diabetes, inflammatory bowel disease, HIV/AIDS or other conditions resulting in immunocompromise, or significant cardiovascular disease.

Cholera vaccination should also be considered for travellers with considerable risk of exposure to, or acquiring, cholera, such as humanitarian disaster workers deployed to regions with endemic or epidemic cholera.

Dukoral is not registered for use in children aged <2 years and is not recommended for use in this age group.

Booster doses

Booster doses are recommended for those who are at ongoing risk of exposure to cholera.

Children aged 2–6 years who are at ongoing risk should receive a single booster dose 6 months after completion of the primary course. If the interval between primary immunisation and the booster dose is more than 6 months, primary immunisation must be repeated.

Adults and children aged >6 years who are at ongoing risk should receive a single booster dose up to 2 years after completion of the primary course. If the interval between primary immunisation and the booster dose is more than 2 years, primary immunisation must be repeated.

4.1.8 Pregnancy and breastfeeding

Cholera vaccine is not routinely recommended for pregnant or breastfeeding women.

There is limited information on the use of inactivated oral cholera vaccines during pregnancy and breastfeeding.[25]

Refer to 3.3 *Groups with special vaccination requirements*, Table 3.3.1 *Recommendations for vaccination in pregnancy* for more information.

4.1.9 Contraindications

The only absolute contraindications to cholera vaccine are:

- anaphylaxis following a previous dose of the vaccine
- anaphylaxis following any vaccine component.

4.1.10 Precautions

Postpone administration of cholera vaccine during either an acute febrile illness or acute gastrointestinal illness with persistent diarrhoea or vomiting, until recovered.

Although the vaccine is not contraindicated in people who are immunocompromised, including those with HIV infection, data on effectiveness in this population are limited.

There should be an interval of at least 8 hours between the administration of the inactivated oral cholera vaccine and oral live attenuated typhoid vaccine, as the buffer in the cholera vaccine may affect the transit of the capsules of oral typhoid vaccine through the gastrointestinal tract.

4.1.11 Adverse events

The inactivated oral cholera vaccine has a good safety profile, with similar rates of adverse events reported among vaccine and placebo clinical trial participants.[12,16,25] Mild abdominal pain, discomfort and diarrhoea were reported in post-marketing surveillance at a frequency of 0.1–1%.[26]

4.1.12 Public health management of cholera

Cholera is a notifiable and quarantinable disease in all states and territories in Australia.

Further instructions about the public health management of cholera, including management of cases of cholera and their contacts, should be obtained from state/territory public health authorities (see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*).

4.1.13 Variations from product information

The production information for Dukoral states that a booster dose is recommended for adults 2 years after the completion of the primary vaccine course if there is an ongoing risk of cholera. The ATAGI recommends that a booster dose is also recommended 2 years after the completion of the vaccine course for children >6 years of age if there is an ongoing risk of cholera.

References

A full reference list is available on the electronic *Handbook* or website www.immunise.health.gov.au

4.2 DIPHTHERIA

4.2.1 Bacteriology

Diphtheria is an acute illness caused by toxigenic strains of *Corynebacterium diphtheriae*, a Gram-positive, non-sporing, non-capsulate bacillus. The exotoxin produced by *C. diphtheriae* acts locally on the mucous membranes of the respiratory tract or, less commonly, on damaged skin, to produce an adherent pseudomembrane. Systemically, the toxin acts on cells of the myocardium, nervous system and adrenals.

4.2.2 Clinical features

The incubation period is 2 to 5 days. The disease is communicable for up to 4 weeks, but carriers may shed organisms for longer. Spread is by aerosol transmission or by direct contact with skin lesions or articles soiled by infected persons. The disease can involve almost any mucous membrane. Pharyngeal diphtheria, by far the commonest form of disease in the unimmunised, is characterised by an inflammatory exudate that forms a greyish or green membrane in the upper respiratory tract, which can cause acute severe respiratory obstruction. Life-threatening complications from diphtheria toxin include myocarditis and neuritis (usually affecting motor nerves). The case-fatality rate in the last three decades has been reported as up to 16%.[1] Diphtheria antitoxin, which neutralises unbound toxin, was first used in the 1890s. Together with antibiotics, antitoxin is the mainstay of treatment for diphtheria, but this may not always be successful. The first death from diphtheria in Australia for over 20 years occurred in 2011 in an unvaccinated person.[2] Effective protection against diphtheria is only achieved by active immunisation with diphtheria toxoid-containing vaccines.[1,3]

4.2.3 Epidemiology

In the early 1900s, diphtheria caused more deaths in Australia than any other infectious disease, but increasing use of diphtheria vaccines since World War II has led to its virtual disappearance.[4] The current epidemiology of diphtheria in Australia is similar to that in other developed countries. Almost all recent cases in the United Kingdom and the United States have been associated with imported infections.[5] In Australia, there have been two imported infections identified, one case in 2001 and one imported infection in 2011, resulting in two additional cases, including one death.[2,6] The 2011 fatal case of pharyngeal diphtheria occurred in an unvaccinated person infected by a friend who acquired diphtheria in a less developed country.[2]

4.2.4 Vaccines

Diphtheria toxoid is available in Australia only in combination with tetanus and other antigens.

The acronym DTPa, using capital letters, signifies child formulations of diphtheria, tetanus and acellular pertussis-containing vaccines. The acronym dTpa is used for formulations that contain substantially lesser amounts of diphtheria toxoid and pertussis antigens than child (DTPa-containing) formulations; dTpa vaccines are usually used in adolescents and adults.

Diphtheria vaccination stimulates the production of antitoxin, which protects against the toxin produced by the organism. The immunogen is prepared by treating a cell-free preparation of toxin with formaldehyde, thereby converting it into the innocuous diphtheria toxoid. Diphtheria toxoid is usually adsorbed onto an adjuvant, either aluminium phosphate or aluminium hydroxide, to increase its immunogenicity. Antigens from *Bordetella pertussis*, in combination vaccines, also act as an effective adjuvant.

The circulating levels of antitoxin required for protection from diphtheria are well described. Antitoxin levels of <0.01 IU/mL are poorly protective, 0.01 to 0.1 IU/mL are usually protective, and titres of >0.1 IU/mL are associated with more certain and prolonged protection.[7] Complete immunisation induces protective levels of antitoxin lasting throughout childhood, but, by middle age, at least 50% of persons not vaccinated since childhood have levels <0.1 IU/mL.[8-10] This has been confirmed in Australia by a national serosurvey.[11] Single low doses of toxoid in previously immunised adults induce protective levels within 6 weeks.[12]

Formulations for children aged <10 years

- ***Infanrix hexa*** – GlaxoSmithKline (DTPa-hepB-IPV-Hib; diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus-*Haemophilus influenzae* type b). The vaccine consists of *both* a 0.5 mL pre-filled syringe containing ≥30 IU diphtheria toxoid, ≥40 IU tetanus toxoid, 25 µg pertussis toxoid (PT), 25 µg filamentous haemagglutinin (FHA), 8 µg pertactin (PRN), 10 µg recombinant HBsAg, 40 D-antigen units inactivated poliovirus type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett), adsorbed onto aluminium hydroxide/phosphate; traces of formaldehyde, polysorbate 80, polysorbate 20, polymyxin and neomycin; *and* a vial containing a lyophilised pellet of 10 µg purified Hib capsular polysaccharide (PRP) conjugated to 20–40 µg tetanus toxoid. May contain yeast proteins.

- ***Infanrix IPV*** – GlaxoSmithKline (DTPa-IPV; diphtheria-tetanus-acellular pertussis-inactivated poliovirus). Each 0.5 mL pre-filled syringe contains ≥30 IU diphtheria toxoid, ≥40 IU tetanus toxoid, 25 µg PT, 25 µg FHA, 8 µg PRN, 40 D-antigen units inactivated poliovirus type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett), adsorbed onto aluminium hydroxide; traces of formaldehyde, polysorbate 80, polymyxin and neomycin.
- ***Pediacel*** – Sanofi Pasteur Pty Ltd (DTPa-IPV-Hib; diphtheria-tetanus-acellular pertussis-inactivated poliovirus-*Haemophilus influenzae* type b). Each 0.5 mL monodose vial contains ≥30 IU diphtheria toxoid, ≥40 IU tetanus toxoid, 20 µg PT, 20 µg FHA, 3 µg PRN, 5 µg pertussis fimbriae (FIM) 2+3, 40 D-antigen units inactivated poliovirus type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett), 10 µg Hib capsular polysaccharide conjugated to 20 µg tetanus protein; 1.5 mg aluminium phosphate; ≤50 ng bovine serum albumin; phenoxyethanol as preservative; traces of formaldehyde, glutaraldehyde, polysorbate 80, polymyxin, neomycin and streptomycin.
- ***Quadracel*** – Sanofi Pasteur Pty Ltd (DTPa-IPV; diphtheria-tetanus-acellular pertussis-inactivated poliovirus). Each 0.5 mL monodose vial contains ≥30 IU diphtheria toxoid, ≥40 IU tetanus toxoid, 20 µg PT, 20 µg FHA, 3 µg PRN, 5 µg FIM 2+3, 40 D-antigen units inactivated poliovirus type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett); 1.5 mg aluminium phosphate; ≤50 ng bovine serum albumin; phenoxyethanol as preservative; traces of formaldehyde, glutaraldehyde, polysorbate 80, polymyxin and neomycin.
- ***Tripacel*** – Sanofi Pasteur Pty Ltd (DTPa; diphtheria-tetanus-acellular pertussis). Each 0.5 mL monodose vial contains ≥30 IU diphtheria toxoid, ≥40 IU tetanus toxoid, 10 µg PT, 5 µg FHA, 3 µg PRN, 5 µg FIM 2+3; 1.5 mg aluminium phosphate; 3.4 mg phenoxyethanol.

Reduced antigen formulations for adults, adolescents and children aged ≥10 years

- ***ADT Booster*** – CSL Limited/Statens Serum Institut (dT; diphtheria-tetanus). Each 0.5 mL monodose vial or pre-filled syringe contains ≥2 IU diphtheria toxoid and ≥20 IU tetanus toxoid, adsorbed onto 0.5 mg aluminium as aluminium hydroxide.

- ***Adacel*** – Sanofi Pasteur Pty Ltd (dTpa; diphtheria-tetanus-acellular pertussis). Each 0.5 mL monodose vial contains ≥2 IU diphtheria toxoid, ≥20 IU tetanus toxoid, 2.5 µg PT, 5 µg FHA, 3 µg PRN, 5 µg FIM 2+3; 0.33 mg aluminium as aluminium phosphate; phenoxyethanol as preservative; traces of formaldehyde and glutaraldehyde.
- ***Adacel Polio*** – Sanofi Pasteur Pty Ltd (dTpa-IPV; diphtheria-tetanus-acellular pertussis-inactivated poliovirus). Each 0.5 mL monodose vial or pre-filled syringe contains ≥2 IU diphtheria toxoid, ≥20 IU tetanus toxoid, 2.5 µg PT, 5 µg FHA, 3 µg PRN, 5 µg FIM 2+3, 40 D-antigen units inactivated poliovirus type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett); 0.33 mg aluminium as aluminium phosphate; phenoxyethanol as preservative; traces of formaldehyde, glutaraldehyde, polysorbate 80, polymyxin, neomycin and streptomycin.
- ***Boostrix*** – GlaxoSmithKline (dTpa; diphtheria-tetanus-acellular pertussis). Each 0.5 mL monodose vial or pre-filled syringe contains ≥2 IU diphtheria toxoid, ≥20 IU tetanus toxoid, 8 µg PT, 8 µg FHA, 2.5 µg PRN, adsorbed onto 0.5 mg aluminium as aluminium hydroxide/phosphate; traces of formaldehyde, polysorbate 80 and glycine.
- ***Boostrix-IPV*** – GlaxoSmithKline (dTpa-IPV; diphtheria-tetanus-acellular pertussis-inactivated poliovirus). Each 0.5 mL pre-filled syringe contains ≥2 IU diphtheria toxoid, ≥20 IU tetanus toxoid, 8 µg PT, 8 µg FHA, 2.5 µg PRN, 40 D-antigen units inactivated poliovirus type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett), adsorbed onto 0.5 mg aluminium as aluminium hydroxide/phosphate; traces of formaldehyde, polysorbate 80, polymyxin and neomycin.

4.2.5 Transport, storage and handling

Transport according to *National vaccine storage guidelines: Strive for 5*.[13] Store at +2°C to +8°C. Do not freeze. Protect from light.

Infanrix hexa *must be reconstituted* by adding the entire contents of the syringe to the vial and shaking until the pellet is completely dissolved. Reconstituted vaccine should be used as soon as practicable. If storage is necessary, hold at room temperature for not more than 8 hours.

4.2.6 Dosage and administration

The dose of all diphtheria-containing vaccines is 0.5 mL, to be given by IM injection.

Do not mix DTPa- or dTpa-containing vaccines or dT vaccine with any other vaccine in the same syringe, unless specifically registered for use in this way.

4.2.7 Recommendations

Infants and children

Diphtheria toxoid is given in combination with tetanus toxoid and acellular pertussis as DTPa vaccine. The recommended 3-dose primary schedule is at 2, 4 and 6 months of age. The 1st dose can be given as early as 6 weeks of age, due to the high morbidity and occasional mortality associated with pertussis in very young infants. If the 1st dose is given at 6 weeks of age, the next scheduled doses should still be given at 4 months and 6 months of age (see 4.12 *Pertussis*).

A booster dose of diphtheria-containing vaccine, usually provided as DTPa-IPV, is recommended at 4 years of age, but can be given as early as 3.5 years. For this booster dose, all brands of DTPa-containing vaccines are considered interchangeable.

Where required, DTPa-containing vaccines can be given for catch-up for either the primary doses or booster dose in children aged <10 years (see 2.1.5 *Catch-up*).

Older children and adolescents

A 2nd booster dose is recommended for adolescents between 10 and 17 years of age, using the reduced antigen content dTpa. The optimal age for administering this dose is 11–13 years, due to waning immunity (particularly the pertussis antibody responses) following the 1st booster dose recommended at 4 years of age. (See also 4.12 *Pertussis*.) This 2nd booster dose of diphtheria-containing vaccine is essential for maintaining immunity to diphtheria (and tetanus and pertussis) into adulthood.

It is recommended to use the reduced antigen content dTpa for booster doses. However, when necessary, dT can also be used for the booster dose or, if necessary, for the primary dT course, in persons aged ≥10 years (see 4.2.12 *Variations from product information* below).

For details on the management of children and adolescents who require catch-up vaccination for diphtheria, see 2.1.5 *Catch-up*.

Adults

Booster vaccination

All adults who reach the age of 50 years without having received a booster dose of dT in the previous 10 years should receive a further diphtheria booster dose. This should be given as dTpa, to also provide protection against pertussis (see 4.12 *Pertussis*). This stimulates further production of circulating diphtheria

antibodies at an age when waning of diphtheria and tetanus immunity is commencing in the Australian population.[11] Diphtheria can be a significant risk for travellers to some countries (particularly Southeast Asia, New Guinea, the states of the former Soviet Union, Baltic countries or eastern European countries). Travellers to countries where health services are difficult to access should be adequately protected against diphtheria before departure. They should receive a booster dose of dT (or dTpa if not given previously) if more than 10 years have elapsed since the last dose of dT-containing vaccine.

For persons undertaking high-risk travel, consider giving a booster dose of either dTpa or dT (as appropriate) if more than 5 years have elapsed since the last dose of a dT-containing vaccine.

Primary vaccination

Persons who have not received any diphtheria vaccines are also likely to have missed tetanus vaccination. Therefore, 3 doses of dT should be given at minimum intervals of 4 weeks, followed by booster doses at 10 and 20 years after the primary course. One of these 3 doses (preferably the 1st) should be given as dTpa, to also provide additional protection against pertussis. In the event that dT vaccine is *not* available, dTpa can be used for all primary doses. However, this is not recommended routinely because there are no data on the safety, immunogenicity or efficacy of dTpa in multiple doses for primary vaccination.

For additional information on adults with no history of a primary course of dT vaccine requiring catch-up, see 2.1.5 *Catch-up*.

4.2.8 Pregnancy and breastfeeding

Although dT or dTpa vaccines are not routinely recommended for pregnant women, they can be given under certain circumstances, such as for management of a tetanus-prone wound (see 4.19 *Tetanus*) or to prevent pertussis in pregnant women and their newborns (see 4.12 *Pertussis*).[14]

dT or dTpa vaccines can be given to breastfeeding women.

Refer to 3.3 *Groups with special vaccination requirements*, Table 3.3.1 *Recommendations for vaccination in pregnancy* for more information.

4.2.9 Contraindications

The only absolute contraindications to diphtheria-containing vaccines are:

- anaphylaxis following a previous dose of any diphtheria-containing vaccine
- anaphylaxis following any vaccine component.

4.2.10 Adverse events

Mild discomfort or pain at the injection site persisting for up to a few days is common. Uncommon general adverse events following dT vaccine include headache, lethargy, malaise, myalgia and fever. Anaphylaxis, urticaria and peripheral neuropathy occur very rarely. Brachial neuritis (inflammation of a

nerve in the arm, causing weakness or numbness) has been described following the administration of tetanus toxoid-containing vaccines, with an estimated excess risk of approximately 0.5–1 in 100 000 doses in adults.[15,16] For specific adverse events following combination vaccines containing both diphtheria and pertussis antigens, see 4.12 *Pertussis*.

4.2.11 Public health management of diphtheria

Diphtheria is a notifiable disease in all states and territories in Australia.

Further instructions about the public health management of diphtheria, including management of cases of diphtheria and their contacts, should be obtained from state/territory public health authorities (see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*).

Confirmed or suspected diphtheria is of considerable public health importance and should be notified immediately to state/territory public health authorities. In general, contacts of a proven or presumptive diphtheria case will require vaccination (either primary or booster, depending on vaccination status), and appropriate prophylactic antibiotics[17] (see 4.12 *Pertussis*).

Advice should be sought with respect to diphtheria antitoxin access and dosage, and special arrangements made if hypersensitivity is suspected; this can be coordinated through the relevant state/territory health authority (see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control* and Part 5 *Passive immunisation*).

4.2.12 Variations from product information

The product information for Infanrix hexa states that this vaccine is indicated for primary immunisation of infants from the age of 6 weeks. The ATAGI recommends that this vaccine may also be used for catch-up of the primary schedule in children <10 years of age.

The product information for Infanrix IPV states that this vaccine is indicated for use in a 3-dose primary schedule for immunisation of infants from the age of 6 weeks and as a single booster dose for children ≤6 years of age who have previously been vaccinated against diphtheria, tetanus, pertussis and poliomyelitis. In addition, the ATAGI recommends that this product may also be used for catch-up of the primary schedule or as a booster in children <10 years of age.

The product information for Quadracel states that this vaccine is indicated for use in a 3-dose primary schedule from the age of 2 months to 12 months and may also be used as a booster dose for children from 15 months to 6 years of age who have previously been vaccinated against diphtheria, tetanus, pertussis and poliomyelitis. The ATAGI recommends that, when appropriate, this product may also be used for either catch-up of the primary schedule or as a booster dose in

children aged <10 years. The ATAGI also recommends that the primary schedule may be commenced at 6 weeks of age, if required.

The product information for Tripacel states that this vaccine is indicated for use in a 3-dose primary schedule from the age of 2 months to 12 months and may also be used as a booster dose for children from 15 months to 8 years of age who have previously been vaccinated against diphtheria, tetanus and pertussis. The ATAGI recommends that, when appropriate, this product may also be used for either catch-up of the primary schedule or as a booster dose in children aged <10 years. The ATAGI also recommends that the primary schedule may be commenced at 6 weeks of age, if required.

The product information for Pediacel states that this vaccine is indicated for primary immunisation of infants from the age of 6 weeks and may also be used as a booster dose for children from 15 to 20 months of age who have previously been vaccinated against diphtheria, tetanus, pertussis, poliomyelitis and *Haemophilus influenzae* type b. The ATAGI recommends that, when appropriate, this product may also be used for either catch-up of the primary schedule or as a booster dose in children aged <10 years.

The product information for ADT Booster states that this vaccine is indicated for use as a booster dose only in children aged ≥5 years and adults who have previously received at least 3 doses of diphtheria and tetanus vaccines. The ATAGI recommends instead that, where a dT vaccine is required, ADT Booster can be used, including for primary immunisation against diphtheria and tetanus (for any person ≥10 years of age).

The product information for Adacel and Boostrix (reduced antigen content dTpa) states that these vaccines are indicated for booster doses only. The ATAGI recommends instead that, when a 3-dose primary course of diphtheria/tetanus toxoids is given to an adolescent/adult, dTpa should replace the 1st dose of dT, with 2 subsequent doses of dT. If dT is *not* available, dTpa can be used for all 3 primary doses, but this is *not* routinely recommended.

The product information for Adacel and Boostrix states that there is no recommendation regarding the timing and frequency of booster doses against pertussis in adults; however, the ATAGI recommends that pregnant or post-partum women can receive a booster dose every 5 years and that other adults in contact with infants and/or at increased risk from pertussis can receive a booster dose every 10 years.

The product information for Boostrix, Boostrix-IPV and Adacel states that dTpa-containing vaccine should not be given within 5 years of a tetanus toxoid-containing vaccine. The product information for Adacel Polio states that dTpa-containing vaccine should not be given within 3 years of a tetanus toxoid-containing vaccine. The ATAGI recommends instead that, if protection against pertussis is required, dTpa-containing vaccines can be administered at any time following receipt of a dT-containing vaccine.

The product information for Boostrix, Boostrix-IPV, Infanrix hexa and Infanrix IPV states that these vaccines are contraindicated in children with encephalopathy of unknown aetiology or with neurologic complications occurring within 7 days following a vaccine dose. The ATAGI recommends instead that the only contraindication is a history of anaphylaxis to a previous dose or to any of the vaccine components.

References

A full reference list is available on the electronic *Handbook* or website www.immunise.health.gov.au

4.3 *HAEMOPHILUS INFLUENZAE* TYPE B

4.3.1 Bacteriology

Haemophilus influenzae is a Gram-negative coccobacillus that is a normal part of upper respiratory tract flora. It can be isolated in two forms: capsular and non-capsular. Strains isolated from respiratory tract specimens, such as sputum and middle ear or sinus fluid, usually do not have a capsule, and are known as non-typeable *Haemophilus influenzae* (NTHi). Six capsular types (a to f) have been described and, before the introduction of vaccination against *Haemophilus influenzae* type b (Hib), almost all *H. influenzae* isolates from sterile sites (blood, cerebrospinal fluid, joint or pleural fluid) were of the b capsular type.[1]

Before Hib immunisation, invasive disease caused by Hib rarely occurred after the age of 5 years. This was because the prevalence of antibody to Hib progressively increased from the age of 2 years, thought to be related to exposure to Hib (or cross-reacting organisms) colonising the nasopharynx or other sites. Children <2 years of age are usually unable to mount an antibody response to the type b capsular polysaccharide, even after invasive disease.[2]

4.3.2 Clinical features

Clinical categories of invasive disease caused by Hib include meningitis, epiglottitis and a range of other infections such as septic arthritis, cellulitis and pneumonia.[3] Hib is rarely isolated from the blood without a focal infection such as the above being evident or developing subsequently. The classical clinical signs of meningitis – neck stiffness and photophobia – are often not detected in infants, who present with drowsiness, poor feeding and high fever. Epiglottitis (inflammation of the epiglottis) presents with respiratory obstruction, associated with soft stridor and often drooling in a pale, febrile, anxious child who remains upright to maximise his or her airway. Meningitis and epiglottitis are almost invariably fatal without appropriate treatment. The case-fatality rate for Hib meningitis in developed countries is at least 3% even with treatment, and 15 to 30% of survivors have permanent neurological sequelae.[1] There are no specific clinical features of any of the focal infections due to Hib that enable them to be differentiated from those due to other organisms. However, before the introduction of Hib vaccines, epiglottitis was due to Hib in over 95% of cases.[4] Non-typeable *Haemophilus influenzae* strains may occasionally cause invasive disease, but are a common cause of otitis media in children and bronchitis in adults.[2] Hib vaccines are not effective in preventing NTHi infections.

4.3.3 Epidemiology

Since Hib vaccines were included in the routine vaccination schedule in 1993, there has been a reduction of more than 95% in notified cases of Hib disease. In 1992 alone, 549 Hib cases were reported; in contrast, during the 2 years from January 2006 to December 2007, a total of 39 Hib infections were notified in Australia, giving an average annual notification rate of 0.09 per 100 000

population.[5-7] The reduction in the incidence of Hib disease following routine vaccination has been particularly marked in Indigenous children, although absolute rates remain substantially higher than those in the non-Indigenous population.[8-10] Similar impressive reductions in Hib disease have been seen in other countries with routine childhood vaccination.[11,12] Since Hib disease has become relatively rare, cases of epiglottitis can no longer be assumed to be due to *H. influenzae* type b and, moreover, even when *H. influenzae* is isolated from a normally sterile site, it may not be type b. Thus, laboratory confirmation of *H. influenzae* infection and serotype should always be sought before vaccination failure is assumed.[13,14]

4.3.4 Vaccines

Four types of conjugate Hib vaccines have been developed, each containing the Hib capsular polysaccharide polyribosylribitol phosphate (PRP) conjugated to a different carrier protein. Of these, PRP-OMP (conjugated to the outer membrane protein of *Neisseria meningitidis*), PRP-T (conjugated to tetanus toxoid) and HbOC (conjugated to a mutant diphtheria toxoid) elicit antibody responses associated with protection of children against Hib. The fourth vaccine type, PRP-D (conjugated to diphtheria toxoid), was less immunogenic and found to be poorly protective in high-risk populations, such as Indigenous children.[15] PRP-T has subsequently been included in a number of combination vaccines, including DTPa-hepB-IPV-Hib and Hib-MenCCV.

In Australia, the differing epidemiology of invasive Hib disease by ethnicity and region has determined the recommendations for Hib vaccine choice (see 3.1 *Vaccination for Aboriginal and Torres Strait Islander people*). There have been four distinct eras of implementation of the Hib vaccination program for Australian children, which are described in detail elsewhere.[10]

Some Hib combination vaccines containing acellular pertussis are known to produce lower Hib antibody responses than similar formulations containing whole-cell pertussis.[16] When administered according to the United Kingdom's schedule as 3 primary doses at 2, 3 and 4 months of age without a booster, their use has been associated with an increased risk of vaccine failure.[17] In other European countries that routinely give a 4th dose around the time of the 1st birthday, as Australia does, no loss of effectiveness has been observed.[18,19]

Monovalent Hib vaccines

- ***Act-HIB*** – Sanofi Pasteur Pty Ltd (PRP-T). Lyophilised powder in a monodose vial with a pre-filled diluent syringe. Each 0.5 mL reconstituted dose contains 10 µg Hib capsular polysaccharide (polyribosyl-ribitol-phosphate [PRP]) conjugated to 18–30 µg tetanus protein.

- ***Hiberix*** – GlaxoSmithKline (PRP-T). Lyophilised pellet in a monodose vial with separate diluent. Each 0.5 mL reconstituted dose contains 10 µg Hib capsular polysaccharide (PRP) conjugated to 30 µg tetanus toxoid; lactose.
- ***Liquid PedvaxHIB*** – CSL Limited/Merck & Co Inc (PRP-OMP). Each 0.5 mL monodose vial contains 7.5 µg Hib capsular polysaccharide (PRP) conjugated to 125 µg *Neisseria meningitidis* outer membrane protein (OMP) complex; 225 µg aluminium as aluminium hydroxide; 35 µg borax.

Combination vaccines that contain Hib

- ***Infanrix hexa*** – GlaxoSmithKline (DTPa-hepB-IPV-Hib; diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus-*Haemophilus influenzae* type b [PRP-T]). The vaccine consists of *both* a 0.5 mL pre-filled syringe containing ≥30 IU diphtheria toxoid, ≥40 IU tetanus toxoid, 25 µg pertussis toxoid (PT), 25 µg filamentous haemagglutinin (FHA), 8 µg pertactin (PRN), 10 µg recombinant HBsAg, 40 D-antigen units inactivated poliovirus type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett), adsorbed onto aluminium hydroxide/phosphate; traces of formaldehyde, polysorbate 80, polysorbate 20, polymyxin and neomycin; *and* a vial containing a lyophilised pellet of 10 µg purified Hib capsular polysaccharide (PRP) conjugated to 20–40 µg tetanus toxoid. May contain yeast proteins.
- ***Menitorix*** – GlaxoSmithKline (Hib-MenCCV; *Haemophilus influenzae* type b [PRP-T]-meningococcal serogroup C–tetanus toxoid conjugate). Lyophilised powder in a monodose vial with a pre-filled diluent syringe. Each 0.5 mL reconstituted dose contains 5 µg Hib capsular polysaccharide (PRP) conjugated to 12.5 µg tetanus toxoid, and 5 µg *Neisseria meningitidis* serogroup C polysaccharide conjugated to 5 µg tetanus toxoid; traces of trometamol and sucrose.
- ***Pediacel*** – Sanofi Pasteur Pty Ltd (DTPa-IPV-Hib; diphtheria-tetanus-acellular pertussis-inactivated poliovirus-*Haemophilus influenzae* type b [PRP-T]). Each 0.5 mL monodose vial contains ≥30 IU diphtheria toxoid, ≥40 IU tetanus toxoid, 20 µg PT, 20 µg FHA, 3 µg PRN, 5 µg pertussis fimbriae (FIM) 2+3, 40 D-antigen units inactivated poliovirus type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett), 10 µg Hib capsular polysaccharide (PRP) conjugated to 20 µg tetanus protein; 1.5 mg aluminium phosphate; ≤50 ng bovine serum albumin; phenoxyethanol as preservative; traces of formaldehyde, glutaraldehyde, polysorbate 80, polymyxin, neomycin and streptomycin.

4.3.5 Transport, storage and handling

Transport according to *National vaccine storage guidelines: Strive for 5*.[20] Store at +2°C to +8°C. Do not freeze. Protect from light.

Act-HIB *must be reconstituted* by adding the entire contents of the diluent syringe to the vial and shaking until the powder is completely dissolved. Reconstituted vaccine must be used immediately.

Hiberix *must be reconstituted* by adding the entire contents of the diluent container to the vial and shaking until the pellet is completely dissolved. Reconstituted vaccine should be used as soon as practicable. If storage is necessary, hold at +2°C to +8°C for not more than 24 hours.

Infanrix hexa *must be reconstituted* by adding the entire contents of the syringe to the vial and shaking until the pellet is completely dissolved. Reconstituted vaccine should be used as soon as practicable. If storage is necessary, hold at room temperature for not more than 8 hours.

Menitorix *must be reconstituted* by adding the entire contents of the diluent syringe to the vial and shaking until the powder is completely dissolved. Reconstituted vaccine should be used as soon as practicable. If storage is necessary, hold at +2°C to +8°C for not more than 24 hours.

4.3.6 Dosage and administration

The dose of all Hib-containing vaccines is 0.5 mL to be given by IM injection.

Co-administration with other vaccines

All Hib-containing vaccines may be administered in separate sites on the same day as any of the other childhood vaccines such as pneumococcal conjugate, meningococcal serogroup C conjugate (MenCCV), hepatitis B, DTPa-containing and inactivated poliomyelitis vaccine (IPV) (or IPV-containing) vaccines.

No or minimal immunologic interference has been observed when children are vaccinated with pneumococcal conjugate vaccines (7vPCV – Prevenar; 13vPCV – Prevenar 13; or 10vPCV – Synflorix) and PRP-T-containing hexavalent vaccine (Infanrix hexa) at the same immunisation visit.[21-24]

Interchangeability of Hib vaccines

Where possible, the same brand of Hib-containing vaccine should be used for all primary doses. If different Hib-containing vaccines (i.e. PRP-OMP and PRP-T vaccines) are used in the primary series, then 3 doses (of any Hib-containing vaccine) are required at 2, 4 and 6 months of age, with a booster of a Hib-containing vaccine at 12 months of age. For booster doses and in children >15 months of age, regardless of previous Hib vaccinations, a single dose of any Hib-containing vaccine is sufficient for protection.

4.3.7 Recommendations

Infants

A Hib-containing vaccine is recommended for all infants from 2 months of age. PRP-T-containing Hib vaccines require 3 primary doses, at 2, 4 and 6 months of age, followed by a booster dose at 12 months of age. Immunisation using PRP-OMP-containing Hib vaccine only requires 2 primary doses, at ages 2 and 4 months, followed by a booster at 12 months of age.

The 1st dose of a Hib-containing vaccine can be given as early as 6 weeks of age. If the 1st dose is given at 6 weeks of age, the next scheduled doses should still be given at 4 months and 6 months of age.

Booster doses

A single booster dose of Hib vaccine is recommended at 12 months of age (see 'Infants' above). This booster dose can be administered using either the monovalent Hib vaccine or, where meningococcal serogroup C vaccination is also scheduled, the combined Hib-meningococcal serogroup C conjugate vaccine (Hib-MenCCV).

Children aged >15 months and up to 59 months of age at presentation who have not received a primary course of a Hib or Hib-containing vaccine will only require 1 dose of vaccine as catch-up, irrespective of the number of previous doses administered. There should be a minimum 2-month interval between their last dose and the catch-up dose. Catch-up for Hib vaccination for children up to 59 months of age is outlined in Table 2.1.8 *Catch-up schedule for Hib vaccination for children <5 years of age* in 2.1.5 *Catch-up*.

Preterm infants

Preterm infants can be immunised according to their chronological age, without correction for prematurity (see 3.3.2 *Vaccination of women who are planning pregnancy, pregnant or breastfeeding, and preterm infants*). For PRP-T-containing Hib vaccines, including Infanrix hexa, no change in the usual schedule is required. Preterm infants have been shown to produce good antibody responses to all the antigens in Infanrix hexa following administration at 2, 4 and 6 months of age, although the responses to hepatitis B and Hib are not quite as high as in full-term infants.[25]

If a PRP-OMP-containing Hib vaccine is used for the primary doses in an extremely preterm and/or low-birth-weight baby (<28 weeks gestation or <1500 g birth weight), an additional dose should be given at 6 months of age; that is, doses should be given at 2, 4, 6 and 12 months of age.

Persons with functional or anatomical asplenia

Hib is an uncommon cause of post-splenectomy sepsis in adults and children. A single dose of Hib vaccine is recommended for persons with functional or anatomical asplenia who were not fully vaccinated in early childhood

according to the recommendations above and Table 2.1.8 *Catch-up schedule for Hib vaccination for children <5 years of age*. If vaccination is required, the dose should, where possible, be given 2 weeks before a planned splenectomy or at approximately 1 week following an emergency splenectomy. Subsequent booster doses of Hib vaccine are not required.[26] For all recommendations for persons with functional or anatomical asplenia, see 3.3.3 *Vaccination of immunocompromised persons*, Table 3.3.5 *Recommendations for vaccination in persons with functional or anatomical asplenia*.

Allogeneic and autologous haematopoietic stem cell transplant recipients

Allogeneic and autologous haematopoietic stem cell transplant (HSCT) recipients should also be given Hib vaccine post transplant. Three doses of Hib conjugate vaccine should be administered to HSCT recipients at 6, 8 and 12 months after transplant. See 3.3.3 *Vaccination of immunocompromised persons*, Table 3.3.3 *Recommendations for revaccination following HSCT in children and adults, irrespective of previous immunisation history*.

4.3.8 Pregnancy and breastfeeding

Hib vaccine is not routinely recommended for pregnant or breastfeeding women. However, for women who have functional or anatomical asplenia refer to 'Persons with functional or anatomical asplenia' above.

Refer to 3.3 *Groups with special vaccination requirements*, Table 3.3.1 *Recommendations for vaccination in pregnancy* for more information.

4.3.9 Contraindications

The only absolute contraindications to Hib-containing vaccines are:

- anaphylaxis following a previous dose of any Hib-containing vaccine
- anaphylaxis following any vaccine component.

4.3.10 Adverse events

Swelling and redness at the injection site after the 1st dose are common and have been reported in up to 5% of vaccinated children. Fever in up to 2% has also been reported. These adverse events usually appear within 3 to 4 hours of vaccination and resolve completely within 24 hours. The incidence of these adverse events declines with subsequent doses, so it is recommended that the course of vaccination be completed regardless.

4.3.11 Public health management of invasive Hib disease

Haemophilus influenzae type b is a notifiable disease in all states and territories in Australia.

Further instructions about the public health management of Hib, including management of cases of invasive Hib disease and their contacts, should be obtained from state/territory public health authorities (see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*).

4.3.12 Variations from product information

The product information for Infanrix hexa states that this vaccine is indicated for primary immunisation of infants from the age of 6 weeks. The ATAGI recommends that this vaccine may also be used for catch-up of the primary schedule in children <10 years of age.

The product information for Infanrix hexa states that these vaccines are contraindicated in children with encephalopathy of unknown aetiology or with neurologic complications occurring within 7 days following a vaccine dose. The ATAGI recommends instead that the only contraindication is a history of anaphylaxis to a previous dose or to any of the vaccine components.

The product information for Act-HIB, Hiberix and Liquid PedvaxHIB states that these vaccines are indicated for use in children aged 2 months to 5 years. The ATAGI also recommends administration of Hib vaccine to older people with asplenia or following either allogeneic or autologous haematopoietic stem cell transplantation.

The product information for Pediacel states that this vaccine is indicated for primary immunisation of infants from the age of 6 weeks and may also be used as a booster dose for children from 15 to 20 months of age who have previously been vaccinated against diphtheria, tetanus, pertussis, poliomyelitis and *Haemophilus influenzae* type b. The ATAGI recommends that, when appropriate, this product may also be used for either catch-up of the primary schedule or as a booster dose in children aged <10 years.

References

A full reference list is available on the electronic *Handbook* or website www.immunise.health.gov.au

4.4 HEPATITIS A

4.4.1 Virology

Hepatitis A is an acute infection of the liver caused by the hepatitis A virus (HAV), a picornavirus (a small single-stranded RNA virus).[1] The virus survives well in the environment outside of the human host. It persists on hands for several hours and in food kept at room temperature for considerably longer, and is relatively resistant to heat and freezing.

4.4.2 Clinical features

Hepatitis A is an infection of humans; there is no animal reservoir.[1] HAV is predominantly transmitted by the faecal–oral route. The infecting dose is unknown, but it is presumed to be low. The incubation period of hepatitis A is 15 to 50 days, with a mean of about 28 days.[2] HAV is excreted in faeces for up to 2 weeks before the onset of illness and for at least 1 week afterwards.[1]

In young children, HAV usually causes either an asymptomatic infection or a very mild illness without jaundice; adults are more likely to have symptomatic infection (over 70%).[2] Patients with symptomatic illness typically have a 4- to 10-day prodrome of systemic (fever, malaise, weakness and anorexia) and gastrointestinal (nausea and vomiting) symptoms. Dark urine is usually the first specific manifestation of acute hepatitis A infection, followed a day or two later by jaundice and pale faeces.[2] The prodromal symptoms tend to wane with the onset of jaundice, although the anorexia and malaise may persist; pruritus and localised hepatic discomfort or pain may follow.[1] The duration of illness varies, but most patients feel better and have normal, or near normal, liver function tests within a month of the onset of illness.[3] Complications of hepatitis A are uncommon but include, on rare occasions, fulminant hepatitis.[4] The case-fatality rate of hepatitis A increases with age.[2] Hepatitis A does not cause chronic liver disease. Relapse has been found in up to 10% of cases, but recovery is universal. HAV does not cause chronic infection and immunity after infection is life-long.[2] Diagnosis of hepatitis A is made by detecting anti-HAV IgM in serum during the acute illness. Anti-HAV IgM is invariably present by the time the patient presents and persists for 3 to 6 months after the acute illness.[1] Serum anti-HAV IgG alone indicates past infection (or possibly immunisation) and therefore immunity; it probably persists for life.[1]

4.4.3 Epidemiology

Hepatitis A was a considerable public health problem in Australia in the 1990s. During this time, numerous outbreaks occurred in child day-care centres and preschools,[5] Indigenous communities,[6] communities of men who have sex with men,[7] schools and residential facilities for the disabled,[8] and communities of persons who inject drugs.[7] A very large outbreak of hepatitis A, associated with the consumption of raw oysters, occurred in New South Wales in 1997 and there was a large outbreak associated with semidried tomatoes during 2009.[9,10]

In recent years, hepatitis A notifications and hospitalisations have been low with a downward trend.[11] This has been accompanied by an increasing proportion of cases related to travel to countries where hepatitis A is endemic.[12-14] Advocacy for hepatitis A vaccination of travellers and those at increased risk because of lifestyle or occupation remains a priority, as does the hepatitis A vaccination program for Aboriginal and Torres Strait Islander children. Established initially in north Queensland in 1999 for Indigenous children aged 18 months,[6] the hepatitis A vaccination program was expanded in 2005 to include all Indigenous children aged ≤2 years in the Northern Territory, Queensland, South Australia and Western Australia, contributing substantially to the decline in notifications.[15,16] In north Queensland, most Indigenous children >2 years of age have now been immunised against hepatitis A. However, it is important to note that Indigenous children remain at considerably greater risk – not only of acquiring hepatitis A, but also for being hospitalised with the infection – than non-Indigenous children.[11,17] This is particularly true for Indigenous children residing in other regions of Queensland, the Northern Territory, South Australia and Western Australia. (See also 3.1 *Vaccination for Aboriginal and Torres Strait Islander people*.)

4.4.4 Vaccines

Monovalent hepatitis A vaccines

- ***Avaxim*** – Sanofi Pasteur Pty Ltd (formaldehyde-inactivated hepatitis A virus [GBM strain]). Each 0.5 mL pre-filled syringe contains 160 antigen units of hepatitis A virus (HAV) antigens inactivated by formaldehyde; 0.3 mg aluminium as aluminium hydroxide; 2.5 µL phenoxyethanol; 12.5 µg formaldehyde; traces of neomycin and bovine serum albumin.
- ***Havrix Junior*** – GlaxoSmithKline (formaldehyde-inactivated hepatitis A virus [HM175 strain]). Each 0.5 mL monodose vial or pre-filled syringe contains 720 ELISA units of HAV antigens; 0.25 mg aluminium as aluminium hydroxide; traces of formaldehyde, neomycin and polysorbate 20.
- ***Havrix 1440*** – GlaxoSmithKline (formaldehyde-inactivated hepatitis A virus [HM175 strain]). Each 1.0 mL monodose vial or pre-filled syringe contains 1440 ELISA units of HAV antigens; 0.5 mg aluminium as aluminium hydroxide; traces of formaldehyde, neomycin and polysorbate 20.

- ***Vaqta Paediatric/Adolescent formulation*** – CSL Limited/Merck & Co Inc (formaldehyde-inactivated hepatitis A virus [CR326F strain]). Each 0.5 mL monodose vial or pre-filled syringe contains approximately 25 units (U) of hepatitis A virus protein; 0.225 mg aluminium as aluminium hydroxide; 35 µg borax; traces of formaldehyde, neomycin and bovine serum albumin.
- ***Vaqta Adult formulation*** – CSL Limited/Merck & Co Inc (formaldehyde-inactivated hepatitis A virus [CR326F strain]). Each 1.0 mL monodose vial or pre-filled syringe contains approximately 50 U of hepatitis A virus protein; 0.45 mg aluminium as aluminium hydroxide; 70 µg borax; traces of formaldehyde, neomycin and bovine serum albumin.

Combination vaccines that contain hepatitis A

- ***Twinrix Junior (360/10)*** – GlaxoSmithKline (formaldehyde-inactivated hepatitis A virus [HM175 strain] and recombinant hepatitis B vaccine). Each 0.5 mL monodose vial or pre-filled syringe contains 360 ELISA units of HAV antigens, 10 µg recombinant DNA hepatitis B surface antigen protein; 0.225 mg aluminium as aluminium phosphate/hydroxide; traces of formaldehyde, neomycin, trometamol and polysorbate 20. May contain yeast proteins.
- ***Twinrix (720/20)*** – GlaxoSmithKline (formaldehyde-inactivated hepatitis A virus [HM175 strain] and recombinant hepatitis B vaccine). Each 1.0 mL monodose vial or pre-filled syringe contains 720 ELISA units of HAV antigens, 20 µg recombinant DNA hepatitis B surface antigen protein; 0.45 mg aluminium as aluminium phosphate/hydroxide; traces of formaldehyde, neomycin, trometamol and polysorbate 20. May contain yeast proteins.
- ***Vivaxim*** – Sanofi Pasteur Pty Ltd (formaldehyde-inactivated hepatitis A virus [GBM strain] and typhoid Vi capsular polysaccharide). Supplied in a dual-chamber syringe which enables the two vaccines to be mixed just before administration. Each 1.0 mL dose of mixed vaccine contains 160 ELISA units of inactivated hepatitis A virus antigens, 25 µg purified typhoid Vi capsular polysaccharide strain Ty2; 0.3 mg aluminium as aluminium hydroxide; 2.5 µL phenoxyethanol; 12.5 µg formaldehyde; traces of neomycin, bovine serum albumin and polysorbate 80.

Inactivated hepatitis A vaccines are prepared from HAV harvested from human diploid cell cultures, which are then purified by ultrafiltration and chromatography, inactivated by formaldehyde, and adsorbed onto aluminium hydroxide adjuvant. Although the vaccines are prepared from differing strains of HAV, there is only one known serotype; immunity induced by a particular strain probably provides protection against all strains.[1]

Inactivated hepatitis A vaccines induce HAV antibodies (anti-HAV) at titres many-fold greater than are provided by the recommended dose of normal human immunoglobulin. Although the vaccines are highly immunogenic (see below), antibody titres are usually below the detection limits of the routinely available commercial tests for anti-HAV.[1] *Therefore, serological testing to assess immunity after vaccination against hepatitis A is neither necessary nor appropriate*. Likewise, it is also inappropriate to undertake testing if an individual cannot recall if he/she has been vaccinated against hepatitis A in the past; if no vaccination records are available, vaccination should be advised. However, certain groups of people should be screened for natural immunity to hepatitis A to avoid unnecessary vaccination: those born before 1950; those who spent their early childhood in endemic areas; and those with an unexplained previous episode of hepatitis or jaundice. In addition, it is necessary to test for other causes of hepatitis, in particular hepatitis B, in those with unexplained jaundice.

Hepatitis A vaccines are highly immunogenic in both children and adults, with virtually universal seroconversion 4 weeks after vaccination.[1,18,19] Two randomised clinical trials conducted in the early 1990s showed that the vaccines have a very high protective efficacy, approaching 100%.[20,21] This finding is supported by the apparent eradication of hepatitis A from Indigenous communities in north Queensland and the Northern Territory since the introduction of the vaccination program in those regions.[6,16]

The duration of immunity, and therefore protection, following vaccination is not certain. However, vaccine-induced anti-HAV probably persists for many years. There is no current evidence that booster doses are required; in healthy individuals, it is quite possible that they will never be required.[22]

4.4.5 Transport, storage and handling

Transport according to *National vaccine storage guidelines: Strive for 5*.[23]
Store at +2°C to +8°C. Do not freeze.

4.4.6 Dosage and administration

Inactivated hepatitis A vaccines are to be given by IM injection.
The recommended doses and schedules are shown in Table 4.4.1.

Table 4.4.1: Recommended doses and schedules for use of inactivated hepatitis A and hepatitis A combination vaccines*

Vaccine	Age of vaccine recipient (years)	Dose (HAV antigen)	Volume per dose (mL)	Number of doses	Vaccination schedule
Monovalent hepatitis A vaccines					
Avaxim	≥2	160 ELISA U	0.5	2	1st dose: day 0 (day of vaccination) 2nd dose: 6 to 12 months after 1st dose
Havrix Junior	2–<16	720 ELISA U	0.5	2	1st dose: day 0 (day of vaccination) 2nd dose: 6 to 12 months after 1st dose
Havrix 1440	≥16	1440 ELISA U	1.0	2	1st dose: day 0 (day of vaccination) 2nd dose: 6 to 12 months after 1st dose
Vaqta Paediatric/ Adolescent	1–<18	25 U	0.5	2	1st dose: day 0 (day of vaccination) 2nd dose: 6 to 18 months after 1st dose
Vaqta Adult	≥18	50 U	1.0	2	1st dose: day 0 (day of vaccination) 2nd dose: 6 to 18 months after 1st dose
Combination hepatitis A/hepatitis B vaccines					
Twinrix Junior (360/10)	1–<16	360 ELISA U	0.5	3	1st dose: day 0 (day of vaccination) 2nd dose: 1 month after 1st dose 3rd dose: 6 months after 1st dose
Twinrix (720/20)†	1–<16	720 ELISA U	1.0	2	1st dose: day 0 (day of vaccination) 2nd dose: 6 to 12 months after 1st dose
Twinrix (720/20)	≥16	720 ELISA U	1.0	3	1st dose: day 0 (day of vaccination) 2nd dose: 1 month after 1st dose 3rd dose: 6 months after 1st dose
Twinrix (720/20)	≥16	720 ELISA U	1.0	4	1st dose: day 0 (day of vaccination) 2nd dose: 7 days after 1st dose 3rd dose: 21 days after 1st dose 4th dose: 12 months after 1st dose *Note*: This accelerated schedule is not suitable for all circumstances.‡
Combination hepatitis A/typhoid vaccine					
Vivaxim	≥16	160 ELISA U	1.0	1 (+ 1 monovalent hepatitis A vaccine)	1st dose: single dose of Vivaxim (mixed vaccine) on day 0 (day of vaccination) 2nd dose: for long-term protection against hepatitis A, a 2nd dose of hepatitis A-containing vaccine (monovalent hepatitis A vaccine) should be given between 6 and 36 months after the dose of Vivaxim

* For more information on combination hepatitis A/hepatitis B vaccines and schedules, see also 4.5 *Hepatitis B*.

† This schedule should not be used for persons who require prompt protection against hepatitis B, for example, if there is close contact with a person known to be chronically infected with hepatitis B.

‡ This 'accelerated' schedule should be used only if there is very limited time before departure to either moderately or highly endemic regions (see also 4.5 *Hepatitis B*, 'Accelerated schedules').

Co-administration with other vaccines

Hepatitis A vaccines are inactivated vaccines and can be administered either simultaneously with, or at any time before or after, all other vaccines relevant to international travel.[24]

Combination hepatitis A/hepatitis B vaccines can be administered simultaneously with, or at any time before or after, all other vaccines relevant to international travel.

The combination hepatitis A/typhoid vaccine can be administered simultaneously with, or at any time before or after, all other vaccines relevant to international travel.

Interchangeability of hepatitis A vaccines

Although the manufacturers use slightly different production methods and quantify the HAV antigen content in their respective vaccines differently, the hepatitis A vaccines of the different manufacturers used in 'equivalent' schedules in Table 4.4.1 can be considered interchangeable, when given in a 2-dose course. As there is only one brand of combination hepatitis A/hepatitis B vaccine, interchangeability is not relevant. (See also 'Recommendations for the use of combination hepatitis A/hepatitis B vaccines' in 4.4.7 *Recommendations* below.)

4.4.7 Recommendations

Hepatitis A vaccination is recommended for persons with an increased risk of acquiring hepatitis A and/or who are at increased risk of severe disease. Serological testing for immunity to hepatitis A from previous infection is not usually required prior to vaccination, but may be indicated in some circumstances (see 'Serological testing for hepatitis A immunity from infection and/or vaccination' below).

When vaccination against both hepatitis A and hepatitis B (or hepatitis A and typhoid) is indicated, combination vaccines may be used, as described below.

Recommendations for hepatitis A vaccine

Hepatitis A vaccination is recommended for the following groups:

Aboriginal and Torres Strait Islander children residing in the Northern Territory, Queensland, South Australia and Western Australia

Two doses of hepatitis A vaccine are required for Aboriginal and Torres Strait Islander children living in these jurisdictions, due to the increased risk for hepatitis A in this population (see 4.4.3 *Epidemiology* above). Vaccination for these children should commence in the 2nd year of life, with the 1st dose given between 12 and 18 months of age, and the 2nd dose given between 18 and 24 months of age. The recommended interval between doses is 6 months (see Table 4.4.1). State/territory health authorities should be contacted about local hepatitis A vaccination schedules, including catch-up.

Travellers (≥1 year of age) to hepatitis A endemic areas

Travellers to (≥1 year of age), and expatriates living in, moderately to highly endemic areas for hepatitis A should receive hepatitis A vaccine.[25] A single dose of a monovalent hepatitis A vaccine provides protective levels of anti-HAV for at least a year;[1] a 2nd dose is recommended 6 to 12 months following the 1st dose, to increase the duration of protection (see Table 4.4.1).

Persons whose occupation puts them at increased risk of acquiring hepatitis A

Persons whose occupation puts them at increased risk of acquiring hepatitis A include: persons who live or work in rural and remote Indigenous communities and/or persons who regularly provide care for Aboriginal and Torres Strait Islander children in the Northern Territory, Queensland, South Australia and Western Australia; staff working in early childhood education and care; carers of persons with developmental disabilities; and plumbers or sewage workers. See also 3.3 *Groups with special vaccination requirements*, Table 3.3.7 *Recommended vaccinations for persons at increased risk of certain occupationally acquired vaccine-preventable diseases*.

Persons whose lifestyle puts them at increased risk of acquiring hepatitis A

Persons who engage in anal intercourse, men who have sex with men, persons who inject drugs (including inmates of correctional facilities) and sex industry workers are at increased risk of acquiring hepatitis A.[26] See also 3.3 *Groups with special vaccination requirements*.

Persons with developmental disabilities

Vaccination is recommended for persons with developmental disabilities, and susceptible carers, who attend both residential and non-residential facilities for persons with developmental disabilities. Although conditions/measures to limit the likelihood of hepatitis A transmission in such facilities have improved in recent decades, outbreaks of hepatitis A can occur in these settings.[26]

Persons with chronic liver disease, liver solid organ transplant recipients and/or those chronically infected with either hepatitis B or hepatitis C viruses

Hepatitis A vaccination is recommended for persons with chronic liver disease of any aetiology.[2,26] Those with chronic liver disease of mild to moderate severity mount a satisfactory immune response following vaccination, but those with end-stage liver disease do not respond as well, and liver transplant recipients may not respond at all.[27,28] Nevertheless, all those with chronic liver disease who are non-immune to hepatitis A should be vaccinated, preferably as early in the course of the disease as possible.

Vaccination is recommended for persons with chronic hepatitis C and hepatitis B infection because of the high case-fatality rate among these persons if they acquire hepatitis A.[2]

Recommendations for the use of combination hepatitis A/hepatitis B vaccines

Combination hepatitis A/hepatitis B vaccines should be considered for susceptible persons in whom both hepatitis A and hepatitis B vaccines are recommended. Vaccination is usually provided in a 3-dose schedule (see Table 4.4.1). Twinrix (720/20) can be administered in a 2-dose regimen in persons 1 to <16 years of age (see Table 4.4.1); however, this regimen should not be used in those who require prompt protection against hepatitis B, for example, if there is close contact with a person known to be chronically infected with hepatitis B. If a combination hepatitis A/hepatitis B vaccine is not available, monovalent hepatitis A and hepatitis B vaccines can be administered simultaneously (in separate syringes at separate sites) (see 'Interchangeability of hepatitis A vaccines' above). The use of schedules mixing combination hepatitis A/hepatitis B vaccines with the respective monovalent vaccines is not routinely recommended.

Persons in whom combination hepatitis A/hepatitis B vaccines may be suitable for use include:

- travellers to, and expatriates living in, moderately to highly endemic areas (for hepatitis A and B)

  The combination hepatitis A/hepatitis B vaccine is recommended in a 3-dose schedule, administered prior to travel. Twinrix (720/20) can be administered according to a 'rapid' schedule if there is limited time before departure.[29] This consists of a single dose on each of days 0, 7 and 21, followed by a 4th dose 12 months after the 1st dose. It is important that a 4th dose be given to ensure longer-term protection (see Table 4.4.1).
- persons whose lifestyle puts them at increased risk of hepatitis A and hepatitis B (sexually active men who have sex with men, sex industry workers, persons who inject drugs and inmates of correctional facilities)
- persons who attend or work at residential or non-residential facilities for people with developmental disabilities
- persons with occupational risks of exposure to both hepatitis A and hepatitis B
- persons with chronic liver disease and/or hepatitis C
- solid organ transplant liver recipients or solid organ transplant recipients who have chronic liver disease (see Table 3.3.2 *Recommendations for vaccinations for solid organ transplant (SOT) recipients*).

See 'Recommendations for hepatitis A vaccine' above and 4.5 *Hepatitis B* for more details. See also 3.3 *Groups with special vaccination requirements*.

Recommendations for the use of combination hepatitis A/typhoid vaccine

The combination hepatitis A/typhoid vaccine (see Table 4.4.1) is recommended as an option for all persons ≥16 years of age who intend travelling to developing countries where there is an increased risk of acquiring hepatitis A and typhoid

fever. This combination is particularly useful for those already immunised against hepatitis B.

To provide longer-term protection against hepatitis A, a single dose of a monovalent adult formulation hepatitis A vaccine administered between 6 and 36 months after the single dose of combination hepatitis A/typhoid vaccine is required (see Table 4.4.1). If there is a continued risk of typhoid infection, a booster dose of parenteral typhoid Vi polysaccharide vaccine is required 3 years after the single dose of combination hepatitis A/typhoid vaccine. The combination hepatitis A/typhoid vaccine may be used as a 'booster' vaccine for hepatitis A if a person received a previous dose of a monovalent adult formulation hepatitis A vaccine; this should be given at a minimum interval of 6 months after the 1st dose of hepatitis A vaccine.

Serological testing for hepatitis A immunity from infection and/or vaccination

Serological testing for immunity to hepatitis A is not recommended before routine administration of hepatitis A vaccine to those in most of the categories above, for example, Aboriginal and Torres Strait Islander children or travellers. However, previous infection with hepatitis A is more likely to have occurred in persons born before 1950, those who spent their early childhood in an endemic area, and those with an unexplained previous episode of hepatitis or jaundice. In such persons, testing for total hepatitis A antibodies or anti-HAV IgG may be indicated, and, if positive, indicates immunity to hepatitis A. Such persons do not need hepatitis A vaccination.

Interpretation of the results of serological testing may be enhanced by discussion with the laboratory that performed the test, ensuring that relevant clinical information is provided.

Serological testing following vaccination is not routinely required.

4.4.8 Pregnancy and breastfeeding

Hepatitis A vaccine is not routinely recommended for pregnant or breastfeeding women, but can be given where vaccination is considered necessary (see 4.4.7 *Recommendations* above).

Refer to 3.3 *Groups with special vaccination requirements*, Table 3.3.1 *Recommendations for vaccination in pregnancy* for more information.

4.4.9 Contraindications

The only absolute contraindications to hepatitis A vaccines are:

- anaphylaxis following a previous dose of any hepatitis A vaccine
- anaphylaxis following any vaccine component.

Combination vaccines containing the hepatitis B component are contraindicated in persons with a history of anaphylaxis to yeast.

4.4.10 Adverse events

The most common adverse events following administration of hepatitis A vaccines are mild local events of a short duration, probably caused by the aluminium hydroxide adjuvant. About 15% of adults report headache and approximately 5% report malaise or fatigue following vaccination.[26] Up to 20% of children who receive either Havrix or Vaqta experience soreness at the injection site. In both adults and children, systemic adverse events such as headache and fever are much less common than local adverse events.[26]

Hepatitis A vaccines do not affect liver enzyme levels. They can be safely given to persons with HIV infection, and do not adversely affect either the HIV load or $CD4^+$ cell count.[30]

4.4.11 Public health management of hepatitis A

Hepatitis A is a notifiable disease in all states and territories in Australia. Detailed information regarding the management of hepatitis A cases and contacts can be found in the national guidelines for control of hepatitis A[31] (www.health.gov.au/cdnasongs).

Further instructions can also be obtained from state/territory public health authorities (see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*).

Post-exposure prophylaxis using hepatitis A vaccine or normal human immunoglobulin (NHIG) can be used to prevent secondary cases in close contacts of hepatitis A cases. However, vaccination is recommended in preference to NHIG for use in post-exposure prophylaxis in persons ≥12 months of age who are immunocompetent (see Part 5 *Passive immunisation*).[31]

4.4.12 Variations from product information

None.

References

A full reference list is available on the electronic *Handbook* or website www.immunise.health.gov.au

4.5 HEPATITIS B

4.5.1 Virology

Hepatitis B virus (HBV) contains circular, partially double-stranded DNA. The outer surface of the virus is glycolipid, which contains the hepatitis B surface antigen (HBsAg). Other important antigenic components are the hepatitis B core antigen (HBcAg) and hepatitis B e antigen (HBeAg). HBcAg is not detectable in serum, but can be detected in liver tissue in persons with acute or chronic hepatitis B infection. HBeAg, and antibodies against HBeAg (anti-HBe) or the HBcAg (anti-HBc), are serological markers of HBV infection. Antibodies against HBsAg (anti-HBs) indicate immunity, which may result from either natural infection or immunisation (in which case there would not be any markers of HBV infection). Persistence of HBsAg denotes infectivity, which is greater if HBeAg and/or HBV DNA are also positive.[1] Occult hepatitis B infection is characterised by the presence of HBV DNA in the liver (with or without detectable HBV DNA in the serum) and negative HBsAg.[2]

4.5.2 Clinical features

In approximately 30 to 50% of adults, infection causes symptomatic acute hepatitis, but in neonates and young children, particularly those <1 year of age, initial infection is usually asymptomatic.[3,4] The incubation period is usually 45 to 180 days and the period of communicability extends from several weeks before the onset of acute illness usually to the end of the period of acute illness. Acute illness is clinically indistinguishable from other forms of hepatitis, and symptoms include fever, jaundice, malaise, anorexia, nausea and vomiting, abdominal pain (especially in the right upper quadrant), myalgia, and the passage of dark-coloured urine and light-coloured stools. Jaundice may be preceded by an acute febrile illness with arthralgia or arthritis and rash, most typical of hepatitis B. During recovery, malaise and fatigue may persist for many weeks. Fulminant hepatitis occurs in up to 1% of acute cases.[1,5]

Following acute infection, approximately 1 to 10% of persons infected in adulthood,[4,6] but up to 90% of those infected in early infancy,[6] become chronically infected with hepatitis B. Persons chronically infected with HBV are identified by the long-term presence (longer than 6 months) of circulating HBsAg.[1,5] Those with occult infection may reactivate HBV infection if they become immunocompromised.

Persons with chronic HBV infection are capable of transmitting the disease, including mother-to-child peripartum transmission, though they often remain asymptomatic and may not be aware that they are infected. Most of the serious complications associated with hepatitis B occur in the context of chronic HBV infection, which is associated in up to 25% of cases with premature mortality due to cirrhosis and/or hepatocellular carcinoma.[1]

4.5.3 Epidemiology

The prevalence of chronic HBV infection differs in different parts of the world, and may be quite variable within countries. The prevalence of chronic HBV infection varies from less than 0.5% among Caucasians in the United States, northern Europe and Australia, 1 to 5% in the Mediterranean countries, parts of eastern Europe, Africa, Central and South America, up to greater than 10% in many sub-Saharan African, East and Southeast Asian and Pacific island populations.[7-10] In regions of moderate to high prevalence of HBsAg (where ≥2% of the population is HBsAg-positive), infections are mainly acquired perinatally or in early childhood.[1]

Chronic infection and its sequelae, including cirrhosis and hepatocellular carcinoma, contribute to the majority of HBV disease burden in Australia. In recent decades, the burden from such disease has been increasing, concurrent with the increasing number of immigrants from regions of high HBV prevalence.[11] Aboriginal and Torres Strait Islander people, and migrants born in Asia and Pacific islands, North Africa, Middle Eastern and Mediterranean countries, have a significantly increased prevalence of chronic HBV infection compared with the rest of the Australian-born population.[12,13] First-generation immigrants of culturally and linguistically diverse background, who are mostly from countries of high HBV endemicity, usually retain the prevalence of chronic HBV infection of their country of origin. Other population groups with an increased prevalence of markers of HBV infection include patients with HIV infection, persons who used injected drugs between 1980 and 1990, and household contacts of someone diagnosed with hepatitis between 1980 and 1990.[13] Notification of chronic HBV infection depends on levels of hepatitis B testing and reporting, and a substantial proportion of persons with chronic HBV infection remain undiagnosed. It has been estimated by mathematical modelling that, in 2010, about 170 000 people were living with HBV infection in Australia, with about 335 deaths due to HBV infection in that year.[14]

Newly acquired cases of HBV infection in Australia mostly occur in young adults, through injecting drug use, skin penetration procedures or sexual contact.[15] Between 2006 and 2010, the notification rate of newly acquired hepatitis B in Australia ranged from 1.0 to 1.4 per 100 000 population. Since 2001, the rate of diagnosis of newly acquired infections has declined substantially among people aged 15–29 years and has remained relatively stable among people aged ≥30 years.[14-16] However, some new HBV infections are asymptomatic and may go undetected.

Similar to chronic infection, higher rates of notified cases of newly acquired hepatitis B, or hospitalisation due to acute hepatitis B, have been reported among Aboriginal and Torres Strait Islander people compared with the general Australian population.[17,18] In one United States study, adults with diabetes mellitus had a greater chance of developing acute hepatitis B disease than

the general population;[19] however, there are no published Australian studies examining this.

Transmission of HBV may result from inoculation through broken or penetrated skin, or by mucosal contact with blood or other body fluids (mainly vaginal fluids and semen) from an infectious person. There are four major routes of HBV transmission:

- perinatal transmission from infected mother to neonate (vertical transmission), usually occurring at or around the time of birth
- parenteral or mucosal exposure to infected blood and other bodily fluids; common scenarios include:
  - » sharing of contaminated equipment that penetrates the skin, such as needles (among persons who inject drugs), tattoo equipment, body-piercing equipment, acupuncture equipment and razor blades
  - » needle-stick injury, for example, in a healthcare setting
  - » contact between infective body fluids and mucous membranes
- sexual contact (including vaginal or anal intercourse, although the latter is associated with a higher risk)
- non-sexual contact with an infected person (horizontal transmission), including household transmission, for example, child-to-child transmission through contact between open sores or wounds.

In Australia, screening of blood and organ donors using nucleic acid amplification testing has virtually eliminated the risk of transmission of hepatitis B through blood transfusion and organ transplants.[20,21] Saliva may contain levels of virus that are likely to be infective only if inoculated directly into tissue (ocular or mucous membranes). The risk of transmission by inadvertent inoculation by other means, such as by toothbrush, razor etc., or through close personal contact in households in which one or more infected persons reside, is low but not negligible.[22-29]

The strategy for prevention of hepatitis B through immunisation in Australia commenced in the early 1980s, with vaccination programs targeting individuals with increased risk of HBV exposure, including infants at particular risk of infection at birth. Universal infant vaccination commenced in the Northern Territory in 1990. A universal hepatitis B vaccination program was recommended for infants and adolescents in 1996. The adolescent program commenced in some states and territories in 1997 and the universal infant program, which includes a dose given at birth, began nationally in 2000. The adolescent program will continue until those immunised for hepatitis B in the infant program reach adolescence.

4.5.4 Vaccines

Monovalent hepatitis B vaccines

- ***Engerix-B*** – GlaxoSmithKline (recombinant DNA hepatitis B vaccine). ***Adult formulation*** – Each 1.0 mL monodose vial or pre-filled syringe contains 20 µg recombinant hepatitis B surface antigen (HBsAg) protein, adsorbed onto 0.5 mg aluminium as aluminium hydroxide. ***Paediatric formulation*** – Each 0.5 mL monodose vial or pre-filled syringe contains 10 µg HBsAg protein, adsorbed onto 0.25 mg aluminium as aluminium hydroxide.
  Both formulations may contain yeast proteins.
- ***H-B-Vax II*** – CSL Limited/Merck & Co Inc (recombinant DNA hepatitis B vaccine). ***Adult formulation*** – Each 1.0 mL monodose vial or pre-filled syringe contains 10 µg recombinant HBsAg protein, adsorbed onto 0.5 mg aluminium hydroxide. ***Paediatric formulation*** – Each 0.5 mL monodose vial or pre-filled syringe contains 5 µg recombinant HBsAg protein, adsorbed onto 0.25 mg aluminium hydroxide. ***Dialysis formulation*** – Each 1.0 mL monodose vial contains 40 µg recombinant HBsAg protein, adsorbed onto 0.5 mg aluminium hydroxide.
  All formulations may contain yeast proteins.

Combination vaccines that contain hepatitis B

- ***Infanrix hexa*** – GlaxoSmithKline (DTPa-hepB-IPV-Hib; diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus-*Haemophilus influenzae* type b). The vaccine consists of *both* a 0.5 mL pre-filled syringe containing ≥30 IU diphtheria toxoid, ≥40 IU tetanus toxoid, 25 µg pertussis toxoid, 25 µg filamentous haemagglutinin, 8 µg pertactin, 10 µg recombinant HBsAg, 40 D-antigen units inactivated poliovirus type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett), adsorbed onto aluminium hydroxide/phosphate; traces of formaldehyde, polysorbate 80, polysorbate 20, polymyxin and neomycin; *and* a vial containing a lyophilised pellet of 10 µg purified Hib capsular polysaccharide (PRP) conjugated to 20–40 µg tetanus toxoid. May contain yeast proteins.
- ***Twinrix Junior (360/10)*** – GlaxoSmithKline (formaldehyde-inactivated hepatitis A virus [HM175 strain] and recombinant hepatitis B vaccine). Each 0.5 mL monodose vial or pre-filled syringe contains 360 ELISA units of HAV antigens, 10 µg recombinant DNA hepatitis B surface

antigen protein; 0.225 mg aluminium as aluminium phosphate/hydroxide; traces of formaldehyde, neomycin, trometamol and polysorbate 20. May contain yeast proteins.

- ***Twinrix (720/20)*** – GlaxoSmithKline (formaldehyde-inactivated hepatitis A virus [HM175 strain] and recombinant hepatitis B vaccine). Each 1.0 mL monodose vial or pre-filled syringe contains 720 ELISA units of HAV antigens, 20 µg recombinant DNA hepatitis B surface antigen protein; 0.45 mg aluminium as aluminium phosphate/hydroxide; traces of formaldehyde, neomycin, trometamol and polysorbate 20. May contain yeast proteins.

Hepatitis B vaccines are prepared using recombinant technology. After purification, the HBsAg protein is adsorbed onto elemental aluminium (as hydroxide and/or phosphate). Hepatitis B vaccines may contain up to 1% yeast proteins (but no yeast DNA).

The Engerix-B and the H-B-Vax II vaccines are manufactured by different processes, and the HBsAg content of an 'equivalent' dose of these 2 vaccines is different. Studies of hepatitis B vaccines have been conducted using different schedules and intervals for different age groups. Acceptable schedules are shown in Table 4.5.1 and are described below.

The standard 3-dose schedule and variations

Neonates, children and young adults aged <20 years

The Australian infant schedule consists of a dose of monovalent hepatitis B vaccine given at birth, followed by 3 doses of a hepatitis B-containing combination vaccine, given at 2, 4 and 6 months of age (see 'Infants and young children' in 4.5.7 *Recommendations* below). If an infant did not receive the birth dose within the 1st 7 days of life, catch-up of that dose is *not* necessary. Such infants then only require 3 doses of a hepatitis B-containing combination vaccine, given at 2, 4 and 6 months of age. For infants, the final dose of the primary course should not be administered before reaching 24 weeks of age.[30]

This schedule (of birth dose, followed by hepatitis B-containing vaccine at 2, 4, and 6 months of age) has been shown to be equally immunogenic when compared with giving monovalent hepatitis B vaccine in a 3-dose schedule at birth, 1–2 months and 6–18 months of age; this hepatitis B vaccine schedule is often used overseas.[31-33] Children born overseas who have received hepatitis B vaccine in this 3-dose schedule can also be considered to have completed the primary vaccination course.

For older children and young adults aged <20 years (who have not received hepatitis B vaccination earlier in life) a 3-dose schedule of the *paediatric* formulation (0.5 mL) of monovalent hepatitis B vaccine can be used (at times 0, 1 and 6 months), as per Table 4.5.1. Immunogenicity studies suggest there can be some flexibility of the vaccination schedule intervals for monovalent hepatitis B vaccines. The use of longer time intervals between doses does not impair the immunogenicity of hepatitis B vaccine, especially in adolescents and young children.[34,35] For children, aged ≥1 year, the minimum interval between the 1st and 3rd doses of a 3-dose primary schedule is 4 months. A shortened 3-dose schedule provided at either 0, 1, 4 months or 0, 2, 4 months is acceptable for children and adolescents aged <20 years.[30] (See also 2.1.5 *Catch-up*.)

Adults aged ≥20 years

For adults, monovalent hepatitis B vaccine *adult* formulation (1.0 mL) is given in a 3-dose schedule at times 0, 1 and 6 months (see Table 4.5.1). There is some flexibility regarding the interval between the doses. The proportion of vaccine recipients attaining a seroprotective anti-HBs antibody level (≥10 mIU/mL), generally measured at 1–2 months post vaccination, is comparable between adults who received their 3rd dose at 4–6 months after the 1st dose and those who received their 3rd dose 6 months or more after the 1st.[36] Increasing the interval between the 1st and 2nd doses has little effect on the final antibody level attained, but a longer interval between the 2nd and 3rd doses is associated with a higher final antibody level.[37-39] However, for those who may be exposed to hepatitis B, delaying the 3rd dose may increase the risk of acquiring HBV infection. No published studies support an interval of less than 4 months between the 1st and the 3rd doses in a 3-dose schedule.

Thus, for a shortened 3-dose schedule to attain comparable antibody levels to the standard 3-dose schedule, all three of the following minimum interval requirements must be satisfied:

- the *minimum interval* between the 1st and 2nd doses is 1 month,
- the *minimum interval* between the 2nd and 3rd doses is 2 months, and
- the *minimum interval* between the 1st and 3rd doses is 4 months (or 16 weeks).

That is, either a 0, 1, 4 month or a 0, 2, 4 month interval schedule is an acceptable 3-dose schedule for adults.[40]

Note that the interval between the 1st and 3rd doses has been shortened to less than 4 months in studies of *4-dose* accelerated schedules, with the aim to achieve a higher seroprotective antibody level sooner. However, as antibody levels are substantially lower after 3 accelerated doses than after the standard 3-dose schedule,[39] a 4th dose is required (see 'Accelerated schedules' below and Table 4.5.1).

The standard 3-dose schedule induces protective levels of neutralising antibody against hepatitis B virus in more than 90% of adults. The frequency

of seroconversion increases progressively from approximately 35% after the 1st dose to more than 90% after the 3rd dose. There is evidence of immunity in most vaccine recipients after administration of 2 doses of a 3-dose schedule. However, the 3rd dose is necessary to increase the percentage of responders and to provide long-term protection.

Alternative 2-dose schedule for adolescents

Several studies have demonstrated that adolescents 11–15 years of age who receive 2 doses of adult formulation monovalent hepatitis B vaccine 4 to 6 months apart develop similar protective antibody levels to those vaccinated using paediatric formulations in the standard 3-dose schedule.[41-43]

Using a 2-dose schedule for the 11–15 years age group may improve compliance and will provide comparable immunogenicity to that of a 3-dose paediatric schedule. Adolescents (11–15 years of age) can be vaccinated with the adult formulation of either H-B-Vax II or Engerix-B in a 2-dose schedule (see Table 4.5.1).

Table 4.5.1: Recommended schedules for use of monovalent hepatitis B and hepatitis B combination vaccines

Vaccine	Age of vaccine recipient	Dose (HBsAg protein)	Volume per dose (mL)	Number of doses	Recommended schedule intervals*†
Recommended infant schedule					
Engerix-B (paediatric formulation) or H-B-Vax II (paediatric formulation)	birth	10 µg (Engerix-B) or 5 µg (H-B-Vax II)	0.5	1	Birth (if not given at birth, may be given up to 7 days of age)
Combination hepatitis B-containing vaccine (e.g. Infanrix hexa DTPa-hepB-IPV-Hib)	2, 4 and 6‡ months	10 µg	0.5	3	1st dose: 2 months of age 2nd dose: 4 months of age (2 months after 1st dose) 3rd dose‡: 6 months of age (2 months after 2nd dose)
Monovalent hepatitis B vaccines – standard 3-dose schedule					
Engerix-B (paediatric formulation)	<20 years	10 µg	0.5	3	1st dose: day 0 (day of vaccination) 2nd dose: 1 month after 1st dose 3rd dose: 6 months after 1st dose
Engerix-B (adult formulation)	≥20 years	20 µg	1.0	3	1st dose: day 0 (day of vaccination) 2nd dose: 1 month after 1st dose 3rd dose: 6 months after 1st dose
H-B-Vax II (paediatric formulation)	<20 years	5 µg	0.5	3	1st dose: day 0 (day of vaccination) 2nd dose: 1 month after 1st dose 3rd dose: 6 months after 1st dose

Vaccine	Age of vaccine recipient	Dose (HBsAg protein)	Volume per dose (mL)	Number of doses	Recommended schedule intervals*†
Monovalent hepatitis B vaccines – standard 3-dose schedule					
H-B-Vax II (adult formulation)	≥20 years	10 µg	1.0	3	1st dose: day 0 (day of vaccination) 2nd dose: 1 month after 1st dose 3rd dose: 6 months after 1st dose
H-B-Vax II (dialysis formulation)	≥20 years	40 µg	1.0	3	1st dose: day 0 (day of vaccination) 2nd dose: 1 month after 1st dose 3rd dose: 6 months after 1st dose
Monovalent hepatitis B vaccines – 2-dose schedule ONLY for adolescents aged 11–15 years					
Engerix-B (adult formulation)	11–15 years	20 µg	1.0	2	1st dose: day 0 (day of vaccination) 2nd dose: 6 months after 1st dose
H-B-Vax II (adult formulation)	11–15 years	10 µg	1.0	2	1st dose: day 0 (day of vaccination) 2nd dose: between 4 and 6 months after 1st dose
Combination hepatitis A/hepatitis B vaccines					
Twinrix (720/20)§	1–<16 years	20 µg	1.0	2	1st dose: day 0 (day of vaccination) 2nd dose: between 6 and 12 months after 1st dose (2-dose schedule)
Twinrix Junior (360/10)	1–<16 years	10 µg	0.5	3	1st dose: day 0 (day of vaccination) 2nd dose: 1 month after 1st dose 3rd dose: 6 months after 1st dose
Twinrix (720/20)	≥16 years	20 µg	1.0	3	1st dose: day 0 (day of vaccination) 2nd dose: 1 month after 1st dose 3rd dose: 6 months after 1st dose

* For minimum intervals, see text above.

† In these schedules, the 'day 0' dose refers to the day when the 1st dose is given (i.e. day 0 of the vaccination course), not the age of the recipient. For infant vaccination, where the 1st dose is a 'birth dose' it is indicated as so.

‡ The final dose of the primary course should not be administered before reaching 24 weeks of age.

§ This schedule should not be used for those who require prompt protection against hepatitis B, for example, if there is close contact with a person known to be chronically infected with hepatitis B.

Accelerated schedules

Engerix-B (monovalent hepatitis B vaccine, paediatric and adult) and Twinrix (720/20) (combination hepatitis A/hepatitis B vaccine) are also registered for use in accelerated schedules, which consist of 4 doses in total (see Table 4.5.2). Accelerated schedules result in a high proportion of adolescents and adults attaining a seroprotective anti-HBs antibody level (≥10 mIU/mL) in the early

months following commencement of the schedule. However, multiple studies have consistently shown that antibody levels are substantially lower at month 7, after 3 accelerated doses, than after the standard 3-dose schedule (0, 1, 6 months).[39] Also, some studies, in particular among persons who inject drugs and/or inmates of correctional facilities, have shown a lower proportion of subjects attaining the seroprotective antibody level after 3 doses of an accelerated schedule than after the standard 3-dose schedule.[39,44,45] After the 4th dose of an accelerated schedule, administered at 12 months, anti-HBs antibody levels are higher or comparable to those after a standard 3-dose schedule. Hence, it is important for long-term protection that a 4th dose be administered at 12 months to complete an accelerated schedule.

Accelerated schedules should only be used for those persons with an imminent risk of exposure, such as those intending to travel to hepatitis B endemic areas with a very limited time before departure. As higher seroprotective rates after the 3rd dose of an accelerated 4-dose schedule are seen after the 0, 1, 2, 12 months schedule than after the 0, 7, 21 days, 12 months schedule, it is recommended that the latter schedule only be used in exceptional circumstances.

Table 4.5.2: Accelerated hepatitis B vaccination schedules (for persons with imminent risk of exposure)

Vaccine	Age of vaccine recipient (years)	Dose (HBsAg protein)	Volume (mL)	Number of doses	Recommended schedule minimum interval
Engerix-B (paediatric formulation)	<20	10 µg	0.5	4	1st dose: day 0 (day of vaccination) 2nd dose: 1 month after 1st dose 3rd dose: 2 months after 1st dose 4th dose: 12 months after 1st dose
Engerix-B (adult formulation)	≥20	20 µg	1.0	4	1st dose: day 0 (day of vaccination) 2nd dose: 1 month after 1st dose 3rd dose: 2 months after 1st dose 4th dose: 12 months after 1st dose *or* 1st dose: day 0 (day of vaccination) 2nd dose: 7 days after 1st dose 3rd dose: 21 days after 1st dose 4th dose: 12 months after 1st dose
Twinrix (720/20)	≥16	20 µg	1.0	4	1st dose: day 0 (day of vaccination) 2nd dose: 7 days after 1st dose 3rd dose: 21 days after 1st dose 4th dose: 12 months after 1st dose

Combination hepatitis A/hepatitis B vaccine schedules

The schedules for combination hepatitis A/hepatitis B vaccines are shown in Table 4.5.1 (and 4.4 *Hepatitis A*). Three-dose schedules for adults and children aged <16 years are acceptable; however, a 2-dose schedule in children 1–15 years of age, using Twinrix (720/20), also results in protective antibody levels for both hepatitis A and hepatitis B. An accelerated schedule for combination hepatitis A/hepatitis B vaccine in those aged ≥16 years is shown in Table 4.5.2. The appropriate use of accelerated schedules is discussed above.

The use of mixed vaccine schedules using both the combination hepatitis A/hepatitis B vaccine and monovalent hepatitis B vaccines is not routinely recommended. Generally, use of the same brand of vaccine is recommended. (See also 'Interchangeability of hepatitis B vaccines' in 4.5.6 *Dosage and administration* below.)

4.5.5 Transport, storage and handling

Transport according to *National vaccine storage guidelines: Strive for 5*.[46] Store at +2°C to +8°C. Do not freeze.

Infanrix hexa *must be reconstituted* by adding the entire contents of the syringe to the vial and shaking until the pellet is completely dissolved. Reconstituted vaccine should be used as soon as practicable. If storage is necessary, hold at room temperature for not more than 8 hours.

4.5.6 Dosage and administration

The schedules for hepatitis B vaccines and for combination hepatitis A/hepatitis B vaccines are shown in Table 4.5.1. For combination hepatitis A/hepatitis B vaccines, see also 4.4 *Hepatitis A*.

The dose of Engerix-B and H-B-Vax II (paediatric formulations) and Twinrix Junior (360/10) is 0.5 mL, to be given by IM injection.

The dose of Engerix-B and H-B-Vax II (adult formulations) and Twinrix (720/20) is 1.0 mL, to be given by IM injection.

The dose of Infanrix hexa is 0.5 mL, to be given by IM injection.

Hepatitis B and combination hepatitis A/hepatitis B vaccines can generally be co-administered simultaneously with, or at any time before or after, all other vaccines.

Interchangeability of hepatitis B vaccines

The Engerix-B and H-B-Vax II vaccines are manufactured by different processes, and the HBsAg content of an 'equivalent' dose is different. Although switching of vaccine brands is not recommended, in cases where the brand of vaccine used for previous doses is not known, another age-appropriate 'equivalent' dose brand (see Table 4.5.1) may be used. For example, a study in healthy neonates demonstrated comparable high levels of immunogenicity between two different

mixed regimens that used two monovalent hepatitis B vaccines from different manufacturers.[47] As there is only one brand of combination hepatitis A/hepatitis B vaccine, interchangeability is not relevant. (See also 'Combination hepatitis A/hepatitis B vaccine schedules' in 4.5.4 *Vaccines* above.)

4.5.7 Recommendations

Infants and young children

The recommended hepatitis B vaccine schedule for infants from birth is shown in Table 4.5.1. A birth dose of monovalent paediatric formulation hepatitis B vaccine is recommended for all newborn infants. Following this birth dose, 3 doses of a hepatitis-B-containing combination vaccine (usually provided as DTPa-hepB-IPV-Hib) are recommended for all children, at 2, 4 and 6 months of age. Thus, a total of 4 doses of hepatitis B vaccine are provided in the 1st year of life. The 1st dose of a hepatitis B-containing combination vaccine can be given as early as 6 weeks of age. If the 1st dose is given at 6 weeks of age, the next scheduled doses should still be given at 4 months and 6 months of age.

If an infant has not received a birth dose within the 1st 7 days of life, a primary 3-dose course of a hepatitis B-containing combination vaccine should be given, at 2, 4 and 6 months of age; catch-up of the birth dose is *not* necessary. Irrespective of whether a birth dose was given, the infant should not be given the final dose before 24 weeks of age.

The rationale for recommending the birth dose for all newborn infants is not only to prevent vertical transmission from a mother with chronic hepatitis B infection (recognising that there may be errors or delays in maternal testing, reporting, communication or appropriate response), but also to prevent horizontal transmission to the infant in the first months of life from persons with chronic hepatitis B infection who are household or other close contacts.[48] The birth dose should be given as soon as the baby is medically stable, and preferably within 24 hours of birth. Every effort should be made to administer the vaccine before discharge from the obstetric hospital or delivery unit. All newborns of mothers known to have chronic hepatitis B infection *must* be given a birth dose of hepatitis B vaccine *and* hepatitis B immunoglobulin (HBIG) (see 'Management of infants born to mothers who are HBsAg-positive' below).

Although it is not routinely recommended in Australia, infants or toddlers who have received a 3-dose schedule of monovalent vaccine (often given overseas) with doses at birth, 1–2 months of age and ≥6 months of age can also be considered fully vaccinated. The important consideration is that there should have been an interval of at least 2 months between the 2nd and 3rd doses, and that the final dose should not be administered before 24 weeks of age (see also 4.5.4 *Vaccines* above).

Management of infants born to mothers who are HBsAg-positive

Routine antenatal screening of pregnant women for HBsAg is recommended to enable appropriate management to prevent newborn infants developing HBV infection (see 4.5.2 *Clinical features* and 4.5.3 *Epidemiology* above).[49-51] It also enables appropriate follow-up and management of mothers who have chronic HBV infection, identification of the HBV immune status of other household members, and protection of those who are susceptible to HBV infection.

Infants born to HBsAg-positive mothers should be given HBIG and a dose of monovalent hepatitis B vaccine on the day of birth, concurrently but in separate thighs. The dose of HBIG is 100 IU, to be given by IM injection. It is preferable to administer HBIG immediately after birth (preferably within 12 hours of birth and certainly within 48 hours) as its efficacy decreases markedly if given more than 48 hours after birth.

The dose of monovalent hepatitis B vaccine should be given to the infant preferably within 24 hours of birth, and definitely within 7 days. This regimen results in seroconversion rates of more than 90% in neonates, even with concurrent administration of HBIG. Vaccination should not be delayed beyond 7 days after birth, as vaccination alone has been shown to be reasonably effective in preventing infection, provided it is given early.[52] Three subsequent doses of a hepatitis B-containing vaccine should be given, at 2, 4 and 6 months of age, so that the infant receives a total of 4 doses of hepatitis B-containing vaccines.

Anti-HBs antibody and HBsAg levels should be measured in infants born to mothers with chronic hepatitis B infection 3 to 12 months after completing the primary vaccine course. Testing should not be performed before 9 months of age to avoid detection of anti-HBs antibodies from HBIG given at birth. If anti-HBs antibody levels are adequate (≥10 mIU/mL) and HBsAg is negative, then the infant is considered to be protected[30] (see 'Serological testing following hepatitis B vaccination' below). If the anti-HBs level is <10 mIU/mL, then the possibility of HBV infection should be investigated.[51] Expert advice regarding revaccination and/or further testing should be sought for such children.

Preterm and low-birth-weight infants

Low-birth-weight preterm newborn infants do not respond as well to hepatitis B-containing vaccines as full-term infants.[53-55] Thus, for low-birth-weight infants (<2000 g) and/or infants born at <32 weeks gestation (irrespective of weight), it is recommended to give the vaccine in a 4-dose schedule at 0 (birth), 2, 4 and 6 months of age, followed by either:

- measuring the anti-HBs antibody level at 7 months of age, and if the antibody titre is <10 mIU/mL, giving a booster at 12 months of age (due to a better immunogenic response at this age compared with a younger age); or
- giving a booster of a hepatitis B-containing vaccine at 12 months of age (without measuring the antibody titre).

HIV-positive and immunocompromised children

All HIV-positive and immunocompromised children should be age-appropriately vaccinated against hepatitis B.

HIV-positive children should receive 3 doses of hepatitis B vaccine using an adult formulation (i.e. double the standard recommended dose for children). In a limited number of studies, paediatric haemodialysis patients have demonstrated improved response when given higher doses in a 3-dose schedule.[56,57]

For specific hepatitis B recommendations for immunocompromised children, see 3.3.3 *Vaccination of immunocompromised persons*.

Adolescents

Vaccination of adolescents 10–13 years of age is recommended for all those in this age group who have not already received a primary course of hepatitis B vaccine. Refer to your state/territory health authority for further information about hepatitis B vaccine for this age group (see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*).

As the risk in Australian schools is very low,[58] vaccination of classroom contacts of hepatitis B cases is seldom indicated. Nevertheless, vaccination of all children and adolescents should be encouraged.

A 2-dose schedule of hepatitis B vaccine using the adult formulation of either of the available monovalent vaccines should be considered for adolescents aged 11–15 years who are to receive hepatitis B vaccination (see Table 4.5.1 and 4.5.4 *Vaccines* above). A 2-dose schedule increases compliance and thus protection in this age group.

Adolescents who did not receive an age-appropriate completed course of vaccination should be identified and offered catch-up vaccination, particularly if they fall into one of the risk categories for hepatitis B infection, discussed under 'Adults' below.

Adults

Hepatitis B vaccination is recommended for the following groups of adults because they are either at a higher risk of acquiring hepatitis B infection and/or at higher risk of severe disease. Serological testing for previous or chronic hepatitis B infection may be indicated in many circumstances (see 'Serological testing prior to hepatitis B vaccination' below). See also 3.3 *Groups with special vaccination requirements*.

When vaccination against both hepatitis B and hepatitis A is indicated, the combination hepatitis A/hepatitis B vaccines may be used. See Tables 4.5.1 and 4.5.2 above and 'Recommendations for the use of combination hepatitis A/hepatitis B vaccines' below.

Household or other close (household-like) contacts of persons with hepatitis B

There is a low, but definite, risk of transmission from a person with acute or chronic hepatitis B to household or other close residential contacts (e.g. students or asylum seekers sharing residential facilities). This can be reduced by avoiding contact with blood or other body fluids and not sharing items that may penetrate the skin (such as combs, nail brushes, toothbrushes and razors). Immunisation of susceptible household-like contacts is strongly recommended. This includes household members of the adoptive family if the adopted child is known to have chronic hepatitis B infection.

Sexual contacts of persons with hepatitis B

Susceptible sexual partners of persons with acute hepatitis B should be offered post-exposure HBIG and hepatitis B vaccination; both should be initiated within 14 days of the last sexual contact (see 4.5.11 *Public health management of hepatitis B* below and Table 4.5.3). Susceptible partners of those with chronic HBV infection should also be offered vaccination.

Hepatitis B is relatively common in clients of sexual health services and vaccination should be offered to susceptible persons at the time of first attendance.

Susceptible, sexually active men who have sex with men should be vaccinated. The combination hepatitis A/hepatitis B vaccine may be appropriate for men who have sex with men, if they are not immune to either disease, as they are at increased risk of both conditions (see 'Recommendations for the use of combination hepatitis A/hepatitis B vaccines' below).

Migrants from hepatitis B endemic countries

Migrants from hepatitis B endemic countries have a higher likelihood of having been previously infected with hepatitis B and of having a close household contact with chronic hepatitis B infection. Such persons should be offered testing for hepatitis B, and vaccination if appropriate. (See also 3.3.8 *Vaccination of migrants to Australia*.) Areas of high endemicity, indicated by high seroprevalence of HBsAg, include most of East and Southeast Asia (except Japan), Pacific island groups, parts of central Asia and the Middle East, the Amazon Basin, and sub-Saharan Africa.[59]

Aboriginal and Torres Strait Islander people

There is an increased risk of acquiring new HBV infection among Aboriginal and Torres Strait Islander people compared with other Australians.[17,18] Although many younger Aboriginal and Torres Strait Islander people, especially children and adolescents, would have been eligible for, and have received, hepatitis B vaccination through population-wide vaccination programs, it is recommended that Aboriginal and Torres Strait Islander people have their risks and vaccination status for hepatitis B reviewed, be offered testing for previous hepatitis B infection, and be offered vaccination if non-immune. (See also 3.1 *Vaccination for Aboriginal and Torres Strait Islander people*.)

Adult haemodialysis patients and patients with severely impaired renal function in whom dialysis is anticipated

Dialysis patients, and patients with severely impaired renal function in whom dialysis is anticipated, may be at increased risk of acquiring hepatitis B infection and also respond less well to vaccination. These patients should be given a larger than usual dose of hepatitis B vaccine.

Adult haemodialysis or pre-dialysis patients should be given either:

- 1.0 mL of Engerix-B adult formulation (20 µg) in each arm at each schedule point (i.e. effectively giving a double dose on each occasion) in a 4-dose schedule at 0, 1, 2 and 6 months;[60] or
- a single dose of H-B-Vax II dialysis formulation (40 µg) on each occasion in a 3-dose schedule at 0, 1 and 6 months.

Solid organ and haematopoietic stem cell transplant recipients

If seronegative for hepatitis B, solid organ transplant recipients should be vaccinated before transplantation as they may be at increased risk of infection from the transplanted organ.[61] Haematopoietic stem cell transplant recipients should be revaccinated following transplantation, due to the loss of immune memory that often follows the transplant procedure. (See also 3.3.3 *Vaccination of immunocompromised persons*.)

HIV-positive adults and other immunocompromised adults

HIV-positive adults, and other immunocompromised adults, may be at increased risk of acquiring hepatitis B infection and also respond less well to vaccination. Limited studies in HIV1-positive adults have demonstrated an improved and accelerated serological response to a schedule that consists of 4 double doses, comprising two injections of the standard adult dose (using Engerix-B) on each occasion, at times 0, 1, 2 and 6 months.[62,63]

Persons with chronic liver disease and/or hepatitis C

Hepatitis B vaccination is recommended for those in this category who are seronegative for hepatitis B, because of the risk of severe liver disease following infection with hepatitis B.[64]

Persons who inject drugs

Persons who inject drugs should be tested, and be vaccinated if they have not previously been infected with HBV.

Recipients of certain blood products

Screening of all blood donors for HBV using HBsAg and nucleic acid amplification tests has greatly decreased the incidence of transfusion-related hepatitis B virus infection. Since 2010, nucleic acid testing has been introduced nationally to improve detection of hepatitis B infection in donated blood, mainly through reduction of the infectious window period when acute hepatitis B infection may not be detected using HBsAg, but also through detecting persons

with occult hepatitis B infection. This further reduces the residual risk of hepatitis B transmission through transfusion in Australia, from approximately 1 in 739 000 to less than 1 in 1 million.[65] However, persons with clotting disorders who receive blood product concentrates, persons with recurrent transfusion requirements, and persons with underlying immunocompromise[66] have an elevated risk of hepatitis B virus infection, and should therefore be vaccinated.

Persons with developmental disabilities

Vaccination is recommended for persons who attend either residential or non-residential day-care facilities for persons with developmental disabilities. This is due to the high prevalence of markers indicating past or current infection in persons in these settings, including an HBsAg prevalence of >10%.[67-69]

Inmates of correctional facilities

Inmates are at increased risk of hepatitis B infection because of the prevalence of chronic hepatitis B among inmates, and the potential for unprotected sexual intercourse, injecting drug use and amateur tattooing in correctional facilities. Therefore, they should be offered the opportunity to be screened for hepatitis B upon incarceration, as part of the preventive health program for blood-borne viruses, and vaccinated if susceptible.

Sex industry workers

Sex industry workers are one of the population groups at higher risk of HBV infection. They have been specifically identified as an important population on which to focus for the prevention of hepatitis B transmission.[70] They are at a particularly high risk if they engage in unprotected sex.

Persons at occupational risk

The risk to persons in certain occupations differs considerably from setting to setting in different parts of Australia. However, it is recommended that all staff directly involved in patient care and/or the handling of human tissue, blood or body fluids should be vaccinated. In addition, standard precautions against exposure to human tissue, blood or body fluids should be used as a matter of routine.[71]

Other occupations where the risk of acquiring hepatitis B is increased include:

- police, members of the armed forces, emergency services staff and staff of correctional facilities; these persons should be vaccinated if they are assigned to duties that may involve exposure to human tissue, blood or body fluids
- funeral workers, embalmers and other workers who have regular contact with human tissue, blood or body fluids and/or used needles or syringes
- staff involved in both residential and non-residential care of persons with developmental disabilities, due to the high prevalence of markers of past or current infection in persons in this setting[67-69]
- workers who perform skin penetration procedures (e.g. tattooists, body-piercers).

Staff of child day-care centres will normally be at minimal risk of hepatitis B. If advice on risk is sought, the enquiry should be directed to the local public health authority.

Contact sports generally carry a low risk of hepatitis B infection. However, age-appropriate hepatitis B vaccination is recommended.

Travellers to hepatitis B endemic areas

Persons travelling to regions of intermediate or high endemicity, either long-term or for frequent short terms, or who are likely to undertake activities that increase their risks of exposure to HBV during travel, should be vaccinated.[59] (See also 3.2 *Vaccination for international travel*.)

Recommendations for the use of combination hepatitis A/hepatitis B vaccines

Combination hepatitis A/hepatitis B vaccines should be considered for susceptible persons in whom both hepatitis A and hepatitis B vaccines are recommended, including:

- travellers to, and expatriates living in, moderately to highly endemic areas for hepatitis A and B
- persons whose lifestyle puts them at increased risk of hepatitis A and hepatitis B (sexually active men who have sex with men, sex industry workers, persons who inject drugs and inmates of correctional facilities)
- persons who attend or work at residential or non-residential facilities for people with developmental disabilities
- persons with occupational risks of exposure to both hepatitis A and hepatitis B
- persons with chronic liver disease and/or hepatitis C
- solid organ transplant liver recipients or solid organ transplant recipients who have chronic liver disease (see Table 3.3.2 *Recommendations for vaccinations for solid organ transplant (SOT) recipients*).

If a combination hepatitis A/hepatitis B vaccine is not available, monovalent hepatitis A and hepatitis B vaccines can be administered simultaneously (in separate syringes at separate sites) (see 'Interchangeability of hepatitis B vaccines' above).

See 4.5.7 *Recommendations* above and 4.4 *Hepatitis A* for more details. See also 3.3 *Groups with special vaccination requirements*.

Booster doses

Booster doses of hepatitis B vaccine (after completion of a primary course by a recommended schedule) are not recommended for immunocompetent persons. This applies to children and adults, including healthcare workers and dentists.[72-78] This is because there is good evidence that a completed primary course of hepatitis B vaccination provides long-lasting protection. Even though vaccine-induced antibody levels may decline with time and may become undetectable,

immune memory persists and is thought to result in a protective immune response on re-exposure.[79] However, booster doses are recommended for persons who are immunocompromised, in particular those with either HIV infection or renal failure. The time for boosting in such persons should be decided by regular monitoring of anti-HBs levels at 6- to 12-monthly intervals.[72]

Serological testing prior to hepatitis B vaccination

Routine antenatal screening of all pregnant women for HBsAg is recommended to allow appropriate measures to be implemented to prevent newborn infants developing chronic HBV infection[49-51] (see 'Management of infants born to mothers who are HBsAg-positive' above).

Serological testing for evidence of past (or current) hepatitis B infection prior to vaccination may be warranted for certain older children, adolescents and adults. This is particularly so for those at increased risk of acquiring hepatitis B infection, such as persons who inject drugs, sex industry workers, immunocompromised persons, and those living in communities with higher prevalence of HBV, including migrant communities and Aboriginal and Torres Strait Islander people. Serological testing enables identification of persons who were infected by HBV, to facilitate timely appropriate clinical management and prevention of onward transmission, hence reducing population impact of HBV infection. Testing also identifies those who are susceptible to HBV infection and, as such, should be offered vaccination if they continue to have a high exposure risk (see 4.5.7 *Recommendations* above).[70] Testing for immunity to hepatitis A infection (and vaccination of susceptible at-risk persons with combination hepatitis A/hepatitis B vaccines) may also be indicated for some population groups at increased risk of hepatitis A exposure (see 4.4 *Hepatitis A*).

Interpretation of the results of serological testing may be enhanced by discussion with the laboratory that performed the test, ensuring that relevant clinical information is provided.

Serological testing following hepatitis B vaccination

Anti-HBs antibody and HBsAg levels should be measured in infants born to mothers with chronic hepatitis B infection 3 to 12 months after completing the primary vaccine course (for more information see 'Management of infants born to mothers who are HBsAg-positive' above).

Other than for infants born to mothers with chronic hepatitis B infection, post-vaccination serological testing is recommended 4 to 8 weeks after completion of the primary course for persons in the following categories:

- those at significant occupational risk (e.g. healthcare workers whose work involves frequent exposure to human tissue, blood or body fluids)
- those at risk of severe or complicated HBV disease (e.g. persons who are immunocompromised, and persons with pre-existing liver disease not related to hepatitis B)

- those in whom a poor response to hepatitis B vaccination may occur (e.g. haemodialysis patients, persons with bleeding disorders vaccinated via the SC route)
- sexual partners and household, or other close household-like, contacts of persons who are infected with hepatitis B.[30]

For these individuals, if adequate anti-HBs levels (≥10 mIU/mL) are not reached on serological testing 4 to 8 weeks after the 3rd dose, the possibility of HBV infection, including chronic HBV infection, should be investigated by testing for serological markers, including HBsAg and anti-HBc antibodies. In select cases in which hepatitis B infection is suspected, HBV nucleic acid testing may also be indicated, and expert advice regarding further management should be sought. If there are no markers of HBV infection, the individual should be managed as a non-responder to hepatitis B vaccination (see 'Non-responders to primary vaccination' below).

If persons who are at significant risk of hepatitis B (such as healthcare workers) were not tested for anti-HBs within 4 to 8 weeks after completion of the documented primary course, they should still undergo serological testing to ensure immunity. If, on testing, they have an anti-HBs level of <10 mIU/mL, they should be given a single booster dose (4th dose) of vaccine. Persons with immune memory established from effective prior vaccination should respond to this booster dose. Anti-HBs should be checked 4 weeks later, and if the anti-HBs level remains <10 mIU/mL, the possibility of HBV infection should be investigated (and, if excluded, the person should be managed as a non-responder to vaccination, see below). If the anti-HBs level is ≥10 mIU/mL, the person can be regarded as immune.

Non-responders to primary vaccination

A non-responder is a person without HBV infection who has a documented history of an age-appropriate primary course of hepatitis B vaccine, but with a current anti-HBs level <10 mIU/mL. There are a number of potential options for non-responders. Persons who do not respond to the primary vaccination course, and in whom chronic HBV infection has been excluded, should be offered further doses.

As discussed above, in 'Serological testing following hepatitis B vaccination', a single booster dose (4th dose) of vaccine can be given to confirm non-responder status. Persons who are non-responders after being given the booster/4th dose (and in whom HBV infection has been excluded) should have 2 further doses of hepatitis B vaccine at monthly intervals, and be re-tested for anti-HBs levels at least 4 weeks after the last dose. The booster/4th dose that was received could be counted as the 1st of the 3 repeat doses, as recommended for non-responders. A few small studies have reported attainment of seroprotection in non-responders with high-dose formulations or double-dose administration for a 4th, or subsequent, dose of hepatitis B vaccination, but there is no consistent evidence

to suggest that a higher proportion of subjects would respond with these higher-dose regimens.[80-82]

For HBsAg-negative healthcare workers who are non-responders to a primary course of vaccination and to subsequent additional IM doses (≥5 doses in total), some small observational studies report that some individuals may respond to the vaccine administered intradermally.[83-85] Engerix-B (0.25 mL [5 µg] per dose) was used in these studies, giving up to 4 doses.[83] Younger age and longer duration (≥6 months) since the last IM dose may be associated with greater probability of response.[84] If an intradermal dose(s) is given, it is recommended that the anti-HBs levels be measured before each subsequent dose to assess for seroconversion.

Persistent non-responders should be informed that they should be considered not protected against hepatitis B and should minimise exposures. They should also be informed about the need for HBIG within 72 hours of parenteral or mucosal exposure to HBV (see Table 4.5.3).

4.5.8 Pregnancy and breastfeeding

Hepatitis B vaccine is not routinely recommended for pregnant or breastfeeding women. However, the WHO states that neither pregnancy nor breastfeeding is a contraindication to the use of this vaccine.[86]

Refer to 3.3 *Groups with special vaccination requirements*, Table 3.3.1 *Recommendations for vaccination in pregnancy* for more information.

4.5.9 Contraindications

The only absolute contraindications to hepatitis B vaccines are:

- anaphylaxis following a previous dose of any hepatitis B vaccine
- anaphylaxis following any vaccine component.

In particular, hepatitis B vaccines are contraindicated in persons with a history of anaphylaxis to yeast.

4.5.10 Adverse events

Extensive experience indicates that the birth dose of hepatitis B vaccine is very well tolerated by newborn infants. It does not interfere with either the establishment or maintenance of breastfeeding, and it is not associated with an increased risk of either fever, medical investigation for sepsis, or serious outcomes in newborns who were vaccinated compared with the unvaccinated.[87-89]

Adverse events after hepatitis B vaccination are transient and minor, and include soreness at the injection site (5%), fever (usually low grade; 2–3%), nausea, dizziness, malaise, myalgia and arthralgia. Fever can be expected in some neonates following immunisation with hepatitis B vaccine (0.6–3.7%).

Anaphylaxis has been reported very rarely in adults, notably in yeast-sensitive individuals.[90] Although various adverse events such as demyelinating diseases,

Guillain-Barré syndrome and arthritis have been reported, there is no evidence of a causal relationship with hepatitis B vaccination.[90,91]

The World Health Organization Global Advisory Committee on Vaccine Safety states that 'multiple studies and review panels have concluded that there is no link between MS [multiple sclerosis] and hepatitis B vaccination'.[92,93]

The vaccine produces neither therapeutic effects nor adverse events in persons with chronic HBV infection. It is also safe, though of no additional benefit, in those already immune to hepatitis B through past natural infection.

4.5.11 Public health management of hepatitis B

Acute hepatitis B and newly identified chronic hepatitis B are notifiable diseases in all states and territories in Australia.

Further instructions about the public health management of hepatitis B, including management of cases of acute hepatitis B and newly identified chronic hepatitis B, and their contacts, should be obtained from state/territory public health authorities (see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*).

Following significant exposure (percutaneous, ocular or mucous membrane) to blood or to potentially blood-contaminated secretions, where feasible, the source individual should be tested for HBsAg as soon as possible.

If the person exposed has not been previously vaccinated against hepatitis B, their anti-HBs level, and anti-HBc and HBsAg status, should be determined immediately. If the person exposed is anti-HBs and anti-HBc negative (non-immune) and the source is either HBsAg-positive or cannot be identified and tested rapidly, a single dose of HBIG should be administered according to the recommendations in Table 4.5.3. The dose of HBIG is 100 IU for children weighing up to 30 kg (about 5 years of age) and 400 IU for all others. Hepatitis B vaccine must also be given as soon as possible, with further doses as recommended in Table 4.5.3.

For previously vaccinated persons exposed to either an HBsAg-positive source or a source whose hepatitis B status cannot be determined, post-exposure prophylaxis is not necessary if there was a documented protective response (anti-HBs level ≥10 mIU/mL) at any time after vaccination. If the response to previous vaccination is unknown, the anti-HBs level should be determined as quickly as possible. If the anti-HBs level is <10 mIU/mL and there is no evidence of HBV infection, HBIG and HBV vaccine should be administered as per Table 4.5.3.

All healthcare workers should be immunised against hepatitis B. Completion of a full course of hepatitis B vaccination is strongly recommended for any non-immune healthcare worker who has sustained a needle-stick injury or other potential hepatitis B exposure.

Table 4.5.3: Post-exposure prophylaxis for non-immune persons exposed to a HBsAg-positive source

Type of exposure	Hepatitis B immunoglobulin		Vaccine	
Perinatal (exposure of babies during and after birth)*	100 IU, by IM injection	Single dose immediately after birth (preferably within 12 hours of birth and certainly within 48 hours)	0.5 mL, by IM injection	Immediately after birth (preferably within 24 hours, no later than 7 days),† then at 2, 4 and 6 months of age
Percutaneous, ocular or mucous membrane	400 IU, by IM injection 100 IU, if body weight <30 kg	Single dose within 72 hours of exposure	0.5 mL or 1 mL (depending on age), by IM injection	Within 7 days‡ of exposure and at 1 and 6 months after 1st dose
Sexual	400 IU, by IM injection	Single dose within 72 hours of last sexual contact‡	0.5 mL or 1 mL (depending on age), by IM injection	Within 14 days‡ and at 1 and 6 months after 1st dose

* See also 'Management of infants born to mothers who are HBsAg-positive' above.

† The 1st dose can be given at the same time as HBIG, but should be administered at a separate site. Administration as soon as possible after exposure is preferred.

‡ There is limited evidence for efficacy if given within 14 days of contact; however, administration as soon as possible after exposure is preferred.

- ***Hepatitis B Immunoglobulin-VF*** – CSL Limited. 160 mg/mL immunoglobulin (mainly IgG) prepared from human plasma containing high levels of antibody to surface antigen of the hepatitis B virus. Single vials contain 100 IU or 400 IU hepatitis B antibody, with the actual volume stated on the label on the vial. Also contains glycine.

Hepatitis B immunoglobulin (HBIG) is prepared from plasma donated through routine blood bank collection. Samples are selected on the basis that they contain high levels of anti-HBs antibodies. As stocks of HBIG are very limited, use should be strictly reserved for those who are at high risk, such as babies born to mothers with chronic HBV infection and non-immune persons who are exposed through occupational exposure to the blood of unidentified persons or to persons who are chronically infected with hepatitis B or whose hepatitis status cannot be ascertained in time.[86] Requests should be directed to the Australian Red Cross Blood Service in your state/territory (see 5.1.1 *Availability of immunoglobulins* in Part 5 *Passive immunisation*).

4.5.12 Variations from product information

The product information for Infanrix hexa states that this vaccine is indicated for primary immunisation of infants from the age of 6 weeks. The ATAGI recommends that this vaccine may also be used for catch-up of the primary schedule in children <10 years of age.

The product information for Infanrix hexa states that this vaccine is contraindicated in children with encephalopathy of unknown aetiology or with neurologic complications occurring within 7 days following a vaccine dose. The ATAGI recommends instead that the only contraindication is a history of anaphylaxis to a previous dose or to any of the vaccine components.

References

A full reference list is available on the electronic *Handbook* or website www.immunise.health.gov.au

4.6 HUMAN PAPILLOMAVIRUS

4.6.1 Virology

Human papillomaviruses (HPVs) are small, non-enveloped viruses with circular double-stranded DNA. HPVs infect and replicate primarily within cutaneous and mucosal epithelial tissues.

More than 100 HPV genotypes have been identified based on sequence variations in the major genes. They differ in their preferred site of infection; approximately 40 HPV types infect the anogenital tract. Some HPV types, including types 16, 18, 31, 33, 35, 45, 52 and 58, are designated as 'high-risk', as they are causally associated with the development of cancer. Other HPV types, including types 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81 and 89, have been classified as 'low-risk' and are predominantly associated with non-malignant lesions, such as genital warts. The other types are uncommon and their associations with disease are undetermined, but they are not currently believed to be significant causes of cancer.[1,2]

4.6.2 Clinical features

Transmission of anogenital HPV occurs primarily through sexual intercourse; however, virus transmission can less commonly occur following non-penetrative sexual contact.[3] Perinatal transmission of HPV can cause laryngeal infection in infants, rarely resulting in recurrent respiratory papillomatosis.[4] HPV infection is often subclinical, but, dependent upon the infecting HPV genotype, may result in lesions that include cutaneous warts, genital warts, respiratory papillomatosis (low-risk HPV types), and dysplasias and cancers of the cervix, vulva, vagina, penis, anus, and the oral cavity and oropharynx (high-risk HPV types). Most genital HPV infections are cleared (no longer detectable via HPV DNA testing) within 12 to 24 months. In about 3 to 10% of infections, the virus persists. Persons with persistent HPV infection constitute the at-risk group for development of HPV-associated cancers.[5-7]

The causal link between persistent cervical HPV infection and cervical cancer is well established. The strength of association between HPV infection and other cancers varies by site and oncogenic HPV type.[8]

Cellular changes that occur in the cervix as a result of HPV infection are referred to as cervical intraepithelial neoplasia (CIN). The majority of these changes regress, but a minority will progress to cervical cancer. Malignant transformation in the cervix usually occurs 10 to 20 years following infection with high-risk HPV types, but has been reported to occur in less than 2 years.[9]

The clinical features of other HPV-associated cancers and their precursor lesions in the anogenital region and oropharynx vary, and also depend on the anatomical site. The process of progression of HPV-associated precursor lesions to cancers in these sites is less well understood than the process in the cervix. Anogenital warts may present as painless lumps, or with local tenderness, itching or

bleeding. Recurrent respiratory papillomatosis is a potentially fatal condition that usually occurs in childhood, characterised by multiple warty excrescences on the mucosal surface of the respiratory tract.[10]

4.6.3 Epidemiology

Infection with HPV is very common in both men and women, with initial infection occurring close to the time of sexual debut. It is estimated that up to 79% of the general population will be infected with at least one genital type of HPV at some time in their lives.[11,12] A greater number of sexual partners is consistently found to be associated with an increased risk of HPV acquisition.[12] HPV infection rates differ between geographic regions, and estimated population prevalence of HPV also varies depending on the anatomical site and the lesions sampled. About two-thirds of Australian women aged 15–20 years participating in cervical screening had HPV DNA detected in cervical samples collected for cytology.[13]

Certain population subgroups are identified to be at increased risk of HPV infection and HPV-associated diseases, compared with the general population. Infection with multiple HPV genotypes and longer time to clear infection are commonly observed in men who have sex with men (MSM).[14-16] In addition, the prevalence of high-risk HPV types is significantly higher in HIV-positive MSM than in MSM who are HIV-negative.[14] Persons who are immunocompromised (due to disease or medical treatment) are at increased risk of HPV-related disease.[12]

In a serosurvey conducted in Australia in 2006, 24% of females and 18% of males aged 0–69 years were seropositive to at least one of the four HPV types 6, 11, 16 and 18[17] – noting that fewer than 60% of women, and an even lower proportion of men, who are infected with HPV develop antibodies.[18-20] The onset age of seropositivity for HPV in this study was 10–14 years in females and 15–19 years in males. The average age of sexual debut for both males and females in Australia was 16 years, as reported in 2000–2002.[21] A more recent national survey in 2008 reported that about 80% of senior secondary school children (aged approximately 15–19 years) acknowledged having engaged in some form of sexual activity that may transmit HPV.[22]

Persistent HPV infection is the necessary precursor for the development of all cervical cancers.[23] Worldwide, approximately 70% of cervical cancers contain HPV-16 DNA and 16% contain HPV-18 DNA.[24,25] Australian data indicate that HPV-16 and HPV-18 are responsible for approximately 60% and 20%, respectively, of cervical cancers, and 37% and 8%, respectively, of high-grade cervical abnormalities.[26,27] In Australia, cervical cancer ranked 22nd in the overall cancer disease burden in 2008 and now occurs predominantly in women unscreened or under-screened through the National Cervical Screening Program.[28,29] In 2007, the age-standardised incidence rate of cervical cancer in Australia was 6.8 per 100 000, and the mortality rate was 1.8 deaths per 100 000

women. The prevalence of high-risk HPV types 16 and 18, detected when cervical samples collected for cytology were tested for HPV DNA, was similar between Indigenous and non-Indigenous women.[13] However, the incidence rate of cervical cancer in Aboriginal and Torres Strait Islander women is almost 3 times higher than in non-Indigenous Australian women, an indication of lower participation rates in cervical screening programs by Indigenous Australians and greater prevalence of cofactors for cervical cancer such as smoking, earlier and more pregnancies, and lower socioeconomic status.[13,28,30] Indigenous women are 5 times more likely to die from cervical cancer than non-Indigenous women.[28] Also, Australians in remote and very remote areas have 1.5 times higher cervical cancer incidence than those living in major cities.[28]

The proportion of cancers of other anogenital sites that is attributable to HPV ranges from approximately 40% for vulval cancers to approximately 85% for anal cancers. More than 85% of these HPV-associated cancers have evidence of infection due to the high-risk HPV types 16 and 18.[31-36]

In Australia in 2007, incidence rates of vulval and vaginal cancers in women were 2.6 per 100 000 (n=276) and 0.65 per 100 000 (n=69), respectively.[28] The incidence rate of penile cancer was 0.8 per 100 000. The age-standardised incidence rate for anal cancer was 1.3 per 100 000; however, a slightly higher incidence was observed in females than in males. Overall, anal cancer incidence has been steadily increasing over the past few decades; however, the increase has been greater in males than in females.[31,34] The mortality rates for vulval, vaginal, penile and anal cancers were all less than 0.6 per 100 000.[28]

MSM have a significantly higher incidence of high-grade anal intraepithelial neoplasia and anal cancer than the general population. Overseas studies have found a greater than 30-fold higher incidence of anal cancer in MSM than in other men.[37,38]

There is wide variability in the reported proportions of oropharyngeal cancers associated with HPV, ranging from 12% to 63%, and a lower proportion of oral cancers.[39-41] Of the cancers at these sites that are HPV-positive, HPV-16 and/or HPV-18 account for more than 85%. In Australia, similar to the United States and other western countries, there has been a steady increase in the burden of HPV-positive oropharyngeal cancers (mainly attributable to cancers of the base of the tongue and tonsils) over the past few decades.[31,39,42-45]

The population incidence of benign HPV-associated lesions, such as anogenital warts, is much higher than the incidence of HPV-associated cancers. In Australia, the estimated annual incidence of anogenital warts in 2000–2006 was 206 per 100 000 in males and 231 per 100 000 in females. The age group of peak incidence was 25–29 years for men (rate 740 per 100 000) and 20–24 years for women (rate 861 per 100 000).[46] In Australia, 4.0% of men and 4.4% of women aged 16–59 years reported ever being diagnosed with genital warts,[47] and the estimated cumulative lifetime risk of genital warts was 10%.[48,49] The estimated incidence of

anogenital warts in MSM is about 10 times higher than in the general population, with a third of HIV-negative MSM reporting a history of these lesions.[46,50] HPV types 6 and 11 are associated with 90% of genital warts.[51,52]

Recurrent respiratory papillomatosis is a rare (incidence approximately 3.5 per 100 000) and predominantly childhood disease that is associated with HPV types 6 and 11 in 100% of cases.[52-54]

In 2007, the HPV Vaccination Program, funded under the NIP, was introduced. This initially included universal vaccination of girls aged approximately 12–13 years, delivered through an ongoing school-based program. It also included a catch-up program for females up to 26 years of age, which ceased at the end of 2009. In 2013, the program will be extended to include HPV vaccine for boys aged approximately 12–13 years, together with a 2-year catch-up program for Year 9 boys. Although the impact of HPV vaccination on cancer incidence will take decades to occur, early surveillance data have shown an impact on the incidence of genital warts and CIN in the years following the introduction of the female vaccination program.[55-58] A study including eight sexual health centres showed a 59% decrease in the proportion of vaccine-eligible female first-time clinic attendees diagnosed with genital warts.[56] This study also demonstrated that vaccination of females results in some herd immunity benefits to males, with a significant decline in the diagnosis of genital warts observed in unvaccinated males of the same age.[55,56,58] In addition to reduction in genital warts, Victorian data have demonstrated a 48% decline in the incidence of high-grade cervical abnormalities in girls aged <18 years in the years after the introduction of the HPV Vaccination Program.[57] National cervical screening data are also indicating a decline in high-grade lesions diagnosed in women aged <20 years.[29]

4.6.4 Vaccines

There are two HPV vaccines registered for use in Australia: the bivalent vaccine (2vHPV; Cervarix), which contains virus-like particles (VLPs) of HPV types 16 and 18; and the quadrivalent vaccine (4vHPV; Gardasil), which contains VLPs of HPV types 16, 18, 6 and 11. VLPs are not infectious and do not replicate or cause cellular abnormalities.[59,60]

- ***Cervarix*** – GlaxoSmithKline (recombinant protein particulate [VLP] vaccine containing the major capsid [L1] protein of HPV types 16 and 18; 2vHPV). Each 0.5 mL monodose vial or pre-filled syringe contains 20 µg HPV-16 L1 protein and 20 µg HPV-18 L1 protein, adjuvanted with AS04 (comprised of 0.5 mg aluminium hydroxide and 50 µg 3-O-desacyl-4'-monophosphoryl lipid A [MPL]).

- ***Gardasil*** – CSL Limited/Merck & Co Inc (recombinant protein particulate [VLP] vaccine containing the major capsid [L1] protein of HPV types 6, 11, 16 and 18; 4vHPV). Each 0.5 mL monodose vial or pre-filled syringe contains 20 µg HPV-6 L1 protein, 40 µg HPV-11 L1 protein, 40 µg HPV-16 L1 protein and 20 µg HPV-18 L1 protein, adsorbed onto 0.225 mg of aluminium as aluminium hydroxyphosphate sulphate; 0.780 mg L-histidine; 50 µg polysorbate 80; 35 µg sodium borate. May also contain yeast proteins.

The 2vHPV and 4vHPV vaccines have been assessed in females in a number of international clinical trials. When given as a 3-dose series, HPV vaccines elicit a neutralising antibody level many times higher than the level observed following natural infection.[61,62] Overall, seroconversion occurs in 97 to 100% of those vaccinated.[63-65] In women who are naïve to HPV types 16 and 18 prior to vaccination, both vaccines are highly effective at preventing type-specific persistent infection and related cervical disease (approximately 90 to 100%).[66-71] The 4vHPV vaccine also has established efficacy (100%; 95% CI: 94–100%) against external anogenital and vaginal lesions (genital warts, and vulval, vaginal, perineal and perianal dysplasias) associated with HPV types 6, 11, 16 or 18 in women.

In women who are vaccinated irrespective of their baseline HPV status (i.e. women who may have pre-existing HPV infection), vaccine efficacy is lower than observed in HPV-naïve women, indicating reduced vaccine effectiveness among women who are already sexually active. This is because both HPV vaccines are prophylactic vaccines (i.e. preventing primary HPV infection). Vaccination will not treat an existing HPV infection or prevent disease that may be caused by an existing HPV vaccine-type infection.[63,72,73] However, vaccination may still provide benefit for sexually active women by protecting them against new infections with other vaccine-preventable HPV types.

The efficacy of 4vHPV in males aged 16–26 years has been demonstrated in one clinical trial.[74] Vaccination was greater than 85% protective against persistent anogenital infection and external genital lesions due to vaccine HPV types among HPV-naïve participants. Among HPV-naïve MSM participants within the clinical trial, vaccine efficacy was 95% against intra-anal HPV infection and 75% against high-grade anal intraepithelial neoplasia from vaccine HPV types. Efficacy of 2vHPV vaccine in males has not been assessed to date; however, the vaccine has demonstrated safety and immunogenicity in males aged 10–18 years.[75]

There is some evidence of HPV vaccine providing some cross-protection to disease due to other HPV types in women: 4vHPV vaccine against cervical

disease due to HPV types 31 and 45[76] and 2vHPV vaccine against cervical disease due to HPV types 31, 33, 45 and 51.[77] However, the level of protection is less than for the vaccine HPV types and the durability of any such protection is unknown.

Efficacy of HPV vaccines in females or males <16 years of age was not assessed in pre-market trials due to the genital sampling requirements of such studies. However, the antibody responses observed in pre-adolescent and adolescent females and males (>9 years of age) were greater than those in adult women and men, in whom clinical efficacy has been demonstrated for both the 4vHPV and 2vHPV vaccines.

It is not certain how long immunity following HPV vaccination persists, or whether a booster dose after the primary course will ever be required. However, long-term population-based follow-up studies to assess this are underway.[78] In clinical trials, vaccine efficacy has been demonstrated up to at least 5 years for 4vHPV vaccine and 9.4 years for 2vHPV vaccine in women, with no breakthrough disease due to vaccine HPV types.[61,79,80]

Variations in vaccination schedules for both HPV vaccines are being assessed in clinical trials. A recent study showed a lesser immune response in a schedule with a dose interval of 12 months between each of the 3 doses of 4vHPV vaccine compared with schedules with dose intervals of 6 months or less between each of the doses.[81] However, a recent study of 2vHPV following an alternative schedule (0, 1 and 12 months) demonstrated that the immunogenicity of vaccine HPV types was non-inferior following this schedule, compared with the standard schedule (measured 1 month after the final dose).[82] Two-dose schedules of both 2vHPV and 4vHPV are also being studied.[83,84]

4.6.5 Transport, storage and handling

Transport according to *National vaccine storage guidelines: Strive for 5*.[85] Store at +2°C to +8°C. Do not freeze. Protect from light.

4.6.6 Dosage and administration

The dose of both HPV vaccines is 0.5 mL to be given by IM injection.

The primary vaccination course for both HPV vaccines consists of 3 doses.

The recommended schedule for the 2vHPV vaccine is at times 0 (the day the 1st dose is given), 1 and 6 months. The 2vHPV vaccine is registered for use in females aged 10–45 years. The 2vHPV vaccine is not registered for use in males of any age.

The recommended schedule for the 4vHPV vaccine is at times 0 (the day the 1st dose is given), 2 and 6 months. The 4vHPV vaccine is registered for use in females aged 9–45 years and in males aged 9–26 years. However, there are no theoretical concerns that the efficacy or safety of 4vHPV vaccine in males up to the age of 45 years will differ significantly from females of the same age or younger males.

If scheduled doses have been missed, there is no need to repeat earlier doses. The missed dose(s) should be given as soon as is practicable, making efforts to complete doses within 12 months.

Where vaccines have been administered at less than the minimum intervals (see Table 2.1.12 *Catch-up schedule for persons ≥10 years of age (for vaccines recommended on a population level)*), contact your state or territory health department for guidance. See also Chief Medical Officer Guidance available at www.health.gov.au/internet/immunise/publishing.nsf/Content/cmo-full-advice-hpv-cnt.

Co-administration with other vaccines

Both HPV vaccines can be given concomitantly with reduced antigen content diphtheria-tetanus-acellular pertussis (dTpa) or diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis vaccine (dTpa-IPV), and hepatitis B vaccine (monovalent).[86-90] There are no clinical data regarding concomitant administration of either HPV vaccine with varicella vaccine, but there are no theoretical concerns about safety or efficacy of the vaccines if they are given simultaneously, using different injection sites.

Interchangeability of human papillomavirus vaccines

There are currently no clinical data available on the interchangeability of the two HPV vaccines. However, from first principles, acceptable antibody levels and protection against HPV-16 and 18 (the types that are shared by both these vaccines and that are the dominant causes of cervical cancer) would be expected following a combination schedule.

It is recommended that an HPV vaccination course commenced with one vaccine should, wherever possible, be completed with that vaccine and according to its recommended schedule.

Where the course includes a combination of the two HPV vaccines, either inadvertently or because of an adverse event following one vaccine, the person is considered to be fully immunised against HPV-16 and 18 disease if a total of 3 doses of HPV vaccine have been given, provided that the minimum interval requirements between the doses are satisfied. Every effort should be made to complete a 3-dose schedule for effective protection against disease due to each of the vaccine HPV types.

4.6.7 Recommendations

Neither HPV vaccine is registered or recommended for use in children <9 years of age.

Females

Both the 4vHPV and 2vHPV vaccines are recommended for use in females for prevention of persistent infection and anogenital disease caused by HPV types 16 and 18. The 4vHPV vaccine also provides protection against vaccine-type genital warts (which are mostly caused by HPV types 6 and 11). (See also 4.6.4 *Vaccines* above.)

Children and adolescents aged 9–18 years

HPV vaccine is recommended for females 9–18 years of age. The optimal age for administering the HPV vaccine is approximately 11–13 years, as most females in this age group would not have commenced sexual activity and so would be naïve to all HPV types. Vaccination only provides protection against vaccine-type disease if the vaccine is delivered prior to acquisition of that HPV type. Therefore, the decision to vaccinate older adolescent females, who may have already commenced sexual activities, should follow an assessment of the potential benefits, based on their likely previous HPV exposure and future risks of HPV exposure.

Either of the HPV vaccines can be used for adolescent females. The 2vHPV vaccine is only registered for use in girls ≥10 years of age.

Adults aged ≥19 years

Vaccination of all women in this age group is not routinely recommended, as many are likely to have been exposed to one or more vaccine HPV types through sexual activity (see 4.6.3 *Epidemiology* above).

However, some adult females may gain an individual benefit from HPV vaccination. The decision to vaccinate older females should take into account their likelihood of previous exposure to HPV and their future risks of HPV exposure.

Males

The 4vHPV vaccine is recommended for use in males for prevention of persistent infection and anogenital disease caused by HPV types 6, 11, 16 and 18. The 4vHPV vaccine also provides protection against vaccine-type genital warts (which are mostly caused by HPV types 6 and 11). (See also 4.6.4 *Vaccines* above.)

Children and adolescents aged 9–18 years

The 4vHPV vaccine is recommended for males 9–18 years of age. The optimal age for administering the 4vHPV vaccine is approximately 11–13 years, as most males in this age group would not have commenced sexual activity and so would be naïve to all HPV types. Vaccination only provides protection against vaccine-type disease if the vaccine is delivered prior to acquisition of that HPV type. Therefore, the decision to vaccinate older adolescent males, who may have already commenced sexual activities, should follow an assessment of the potential benefits, based on their likely previous HPV exposure and future risks of HPV exposure.

Adults aged ≥19 years

Vaccination of all men in this age group is not routinely recommended as many are likely to have been exposed to one or more vaccine HPV types through sexual activity (see 4.6.3 *Epidemiology* above).

However, some adult males may gain an individual benefit from HPV vaccination. The decision to vaccinate older males should take into account their likelihood of previous exposure to HPV and their future risks of HPV exposure.

Men who have sex with men

The 4vHPV vaccine is recommended for men who have sex with men (MSM) who have not previously been vaccinated with 3 doses of HPV vaccine. The decision to vaccinate males in this group should take into account their likelihood of previous exposure to HPV and their future risks of HPV exposure. Overall, MSM are at increased risk of persistent HPV infection and associated disease (independent of HIV status or the presence of other immunocompromising conditions).[14,38] In addition, at the population level, MSM are less likely to benefit from herd immunity attained from HPV vaccination of females. The safety and efficacy of 4vHPV vaccine has been demonstrated in MSM participants in a randomised clinical trial (see 4.6.4 *Vaccines* above).

Persons who are immunocompromised

HPV vaccine is recommended for adult men and women who are immunocompromised due to medical conditions (including HIV infection) or treatment. The decision to vaccinate immunocompromised persons should take into account their likelihood of previous exposure to HPV, their future risks of HPV exposure, and the extent and duration of their immunocompromise (see 3.3.3 *Vaccination of immunocompromised persons*). Immunocompromised adolescents who have not yet been vaccinated with 3 doses of HPV vaccine should be offered catch-up vaccination. This is based on evidence that persons who are immunocompromised are more likely to develop a persistent HPV infection and to subsequently progress to HPV-related disease.[14,91]

There are currently no clinical trial data demonstrating the efficacy of either of the HPV vaccines in immunocompromised participants. However, 4vHPV has been shown to be well tolerated and immunogenic in HIV-infected males and women with systemic lupus erythematosus.[92-94] As HPV vaccines are not live viral vaccines, there are no specific safety concerns regarding administration to immunocompromised persons (see 3.3.3 *Vaccination of immunocompromised persons*).

Cervical screening in vaccinated females

For all sexually active women, regular cervical screening remains an important preventive measure against cervical disease (refer to the National Cervical Screening Program at www.cancerscreening.gov.au). Vaccination is not an alternative to cervical screening but is a complementary preventive measure, as HPV types other than those included in the current vaccines have the potential to cause cervical cancer. Likewise cervical screening is not an alternative to HPV vaccination. Both are recommended.

Cervical screening detects histopathological changes. It is not recommended to test for the presence of HPV virus or antibody routinely as a way of determining whether HPV vaccination is indicated.

For women who have recently been diagnosed with cervical dysplasia, or have been treated for this in the past, HPV vaccine will have no impact on current disease, but may prevent future dysplasia due to different HPV types included in the vaccine.

4.6.8 Pregnancy and breastfeeding

HPV vaccines are not recommended for pregnant women.

Women who become pregnant after starting the HPV vaccination course should withhold getting further doses of the HPV vaccine while pregnant, and receive the remaining doses of the course after pregnancy.

Females who inadvertently receive a dose of HPV vaccine around the time of conception or during pregnancy should be informed of the body of evidence supporting lack of harm from vaccine administration in this setting. Among women who became pregnant during the course of 4vHPV vaccine clinical trials (despite recommendations for participants to avoid pregnancy), the overall proportions of pregnancies that resulted in an adverse outcome (spontaneous abortion, late fetal death, infant with congenital anomalies) were similar among 4vHPV vaccine recipients and placebo or control vaccine recipients. Although one clinical trial raised the possibility of an association between 4vHPV vaccine administered within 30 days following the estimated date of conception and an increased incidence of congenital anomalies in the infant, those conditions were relatively common and unrelated.[72] Pooled analyses from multiple clinical trials have not confirmed such an association.[95]

Pooled analysis of women who became pregnant during clinical trials showed that, overall, there were no differences in pregnancy outcomes between 2vHPV vaccine and control vaccine recipients.[96,97]

HPV vaccines can be given to breastfeeding women. Among breastfeeding mothers in the clinical studies of 4vHPV vaccine, the rates of adverse events in the mother and the breastfeeding infant were comparable between 4vHPV vaccine and control vaccination groups.[98] The effect on breastfed infants of the administration of 2vHPV vaccine to their mothers has not been evaluated directly in clinical studies, but breastfeeding is not considered a contraindication for receiving the 2vHPV vaccine.

Refer to 3.3 *Groups with special vaccination requirements*, Table 3.3.1 *Recommendations for vaccination in pregnancy* for more information.

4.6.9 Contraindications

The only absolute contraindications to HPV vaccines are:

- anaphylaxis following a previous dose of either HPV vaccine
- anaphylaxis following any vaccine component.

In particular, the 4vHPV vaccine is contraindicated in persons with a history of anaphylaxis to yeast.

4.6.10 Adverse events

Both the 2vHPV and 4vHPV vaccines are generally safe and well tolerated.

For both vaccines, injection site pain was the most commonly reported adverse event (approximately 80% of recipients), followed by swelling and erythema (20–30% for each). Injection site reactions were more commonly reported in vaccine recipients than in recipients of aluminium-containing placebo or control vaccines in clinical trials. Systemic reactions were also very common following both vaccines, occurring in up to about 30% of recipients. The most common adverse events included headache, fatigue, fever and myalgia. In most of the clinical trials, the frequencies of most of these common systemic adverse events were comparable between the HPV vaccine and the control vaccine recipients. Meta-analyses on pooled data from multiple clinical trials on both the 2vHPV and 4vHPV vaccines have shown no increase in the risk of serious adverse events among vaccine recipients compared with control recipients.[99,100]

For both vaccines, the safety profile and the spectrum of adverse events following immunisation in males were similar to those reported in females of corresponding age groups,[74,75,101,102] although some of the studies were not direct comparison studies.

Post-marketing passive surveillance of HPV vaccine use in the United States has identified syncope (fainting) as one of the most common adverse events reported following 4vHPV vaccine in adolescent and young adult females.[103] A small proportion (about 10%) of syncopal episodes resulted in a fall with head injury.[103] Similar or higher rates of syncope have been reported in other countries, through different surveillance mechanisms.[104,105] However, a prospective adverse events surveillance study in the United States, based on over 600 000 records of vaccine doses administered, did not find any increased risk of syncope with 4vHPV vaccination compared to the expected rate following non-4vHPV vaccination in youths and adults.[106] Syncope (fainting) may follow any vaccination, especially in adolescents and young adults, but is preventable through appropriate precautions. (See also 2.3.2 *Adverse events following immunisation*). In an Australian study, 22 subjects (including 14 with syncope and 8 with syncopal seizure following 4vHPV vaccination) were reviewed in a Victorian clinic and received further doses while supine; no recurrence of syncope occurred.[104]

Anaphylaxis and other suspected hypersensitivity reactions, including skin rash, after 4vHPV vaccine have also been reported. The estimated incidence

rate of anaphylaxis following 4vHPV vaccine in Australia, as at June 2010, was 2.6 anaphylaxis episodes per million doses of vaccine distributed, which was within the rate range for other vaccines given to children and adolescents in international studies.[107] A prospective surveillance study in the United States did not find any increased risk of anaphylaxis or allergic reactions with 4vHPV vaccination compared to the expected rate following childhood vaccines.[106]

4.6.11 Variations from product information

The product information for the 4vHPV vaccine, Gardasil, states that this vaccine is indicated for use in males up to 26 years of age and females up to 45 years of age. The product information for the 2vHPV vaccine, Cervarix, states that this vaccine is indicated for use in females up to 45 years of age and is not registered for use in males of any age. The ATAGI instead recommends that some males aged >26 years, such as MSM and those who are immunocompromised, who are likely to derive an individual benefit from HPV vaccination, can be vaccinated with 4vHPV. The ATAGI also recommends that some females aged >45 years, such as those who are immunocompromised, can be vaccinated with either 2vHPV or 4vHPV, based on their individual risk of future HPV exposure and disease.

References

A full reference list is available on the electronic *Handbook* or website www.immunise.health.gov.au

4.7 INFLUENZA

4.7.1 Virology

The influenza viruses are single-stranded RNA orthomyxoviruses. They are classified antigenically as types A, B or C, but only influenza A and B are clinically important in human disease.[1] Influenza viruses possess two surface glycoprotein antigens: the haemagglutinin (H), which is involved in cell attachment during infection, and the neuraminidase (N), which facilitates the release of newly synthesised virus from the cell. Influenza A viruses can be classified into subtypes based on differences in these surface antigens, whereas influenza B cannot. Antibody against the surface antigens, particularly the haemagglutinin, reduces infection or severe illness due to influenza.

Both influenza A and influenza B viruses undergo frequent changes in their surface antigens, involving stepwise mutations of genes coding for H and N glycoproteins. This results in cumulative changes in influenza antigens, or 'antigenic drift', which is responsible for the annual outbreaks and epidemics of influenza and is the reason that the composition of influenza vaccines requires annual review. 'Antigenic shift', defined as a dramatic change in influenza A H (and other) antigen, occurs occasionally and unpredictably and can cause pandemic influenza.[1] Pandemic subtypes arise following antigenic shift, which is due to direct adaptation to humans of an avian or animal virus, or to this adaptation occurring by genetic reassortment (mixing) with a human virus.

4.7.2 Clinical features

Influenza is transmitted from person to person by virus-containing respiratory aerosols produced during coughing or sneezing, or by direct contact with respiratory secretions.[1,2] Influenza virus infection causes a wide spectrum of disease, from no or minimal symptoms, to respiratory illness with systemic features, to multisystem complications and death from primary viral or secondary bacterial pneumonia. Severe disease is more likely with advanced age; lack of previous exposure to antigenically related influenza virus; greater virulence of the viral strain; chronic conditions, such as heart or lung disease, renal failure, diabetes and chronic neurological conditions; immunocompromise; pregnancy; and smoking. In pandemics, severe disease may also occur in otherwise healthy young adults. Annual attack rates in the general community are typically 5 to 10%, but may be up to 20% in some years. In households and 'closed' populations, attack rates may be 2 to 3 times higher.[3,4] However, as asymptomatic or mild influenza illness is common and symptoms are non-specific, a large proportion of influenza infections are not detected.

In adults, the onset of illness due to influenza is often abrupt, usually after an incubation period of 1 to 3 days, and includes systemic features such as malaise, feverishness, chills, headache, anorexia and myalgia. These may be accompanied by a cough, nasal discharge and sneezing. Fever is a prominent sign of infection

and peaks at the height of the systemic illness. Symptoms are similar for influenza A and B viruses. However, infections due to influenza A (H3N2) strains are more likely to lead to severe morbidity and increased mortality than influenza B or seasonal influenza A (H1N1) strains.[1,2]

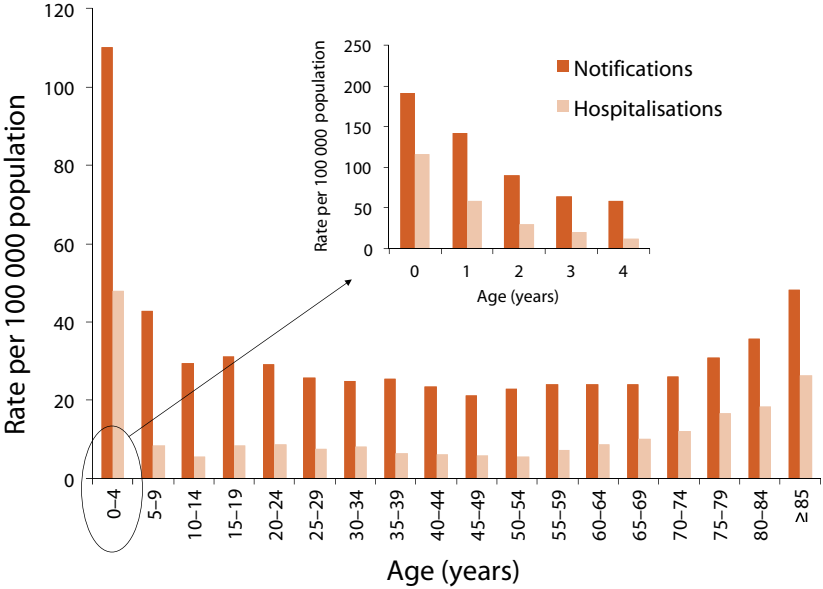
The clinical features of influenza in infants and children are similar to those in adults. However, temperatures may be higher in children (and may result in febrile convulsions in this susceptible age group), and otitis media and gastrointestinal manifestations are more prominent.[5] Infection in young infants may be associated with more non-specific symptoms.[5,6]

Complications of influenza include: acute bronchitis, croup, acute otitis media, pneumonia (both primary viral and secondary bacterial pneumonia), cardiovascular complications including myocarditis and pericarditis, post-infectious encephalitis, Reye syndrome, and various haematological abnormalities. Primary viral pneumonia occurs rarely, but secondary bacterial pneumonia is a frequent complication in persons whose medical condition makes them vulnerable to the disease. Such persons are at high risk in epidemics and may die of pneumonia or cardiac decompensation.

4.7.3 Epidemiology

In most years, minor or major epidemics of type A or type B influenza occur, usually during the winter months in temperate regions. In Australia, although an average of 85 deaths and approximately 4000 hospitalisations directly attributed to influenza are notified annually, it has long been recognised that this is a substantial underestimate of the impact of influenza.[7] It is estimated that there are an average of over 13 500 hospitalisations due to influenza per year in Australia and over 3000 deaths per year in Australians aged over 50 years alone.[8] Influenza activity varies from year to year and is dependent on the circulating virus and the susceptibility of the population.[8,9] For example, there were over 10 000 confirmed cases of influenza reported to the National Notifiable Diseases Surveillance System in the first half of 2011, compared with approximately 1570 for the same period in 2010.[2] Laboratory testing for influenza has also increased in recent years. In Australia, like other developed countries, the highest influenza burden is seen in the elderly and in children <5 years of age (Figure 4.7.1).[9-11] During annual epidemics of influenza, mortality rises, especially among the elderly and people with chronic diseases, and there is increased morbidity, increased rates of hospitalisation for pneumonia, and exacerbation of chronic diseases in association with influenza.[12,13]

Figure 4.7.1: Influenza notification rates 2006–2007* and hospitalisation rates 2005–2007,* Australia, by age group[9]



* Notifications where the month of diagnosis was between January 2006 and December 2007; hospitalisations where the month of separation was between July 2005 and 30 June 2007. These data are prior to the appearance of the pandemic A(H1N1)pdm09 virus in 2009.

Three pandemics were recognised in the 20th century, in 1918 (H1N1), 1957 (H2N2) and 1968 (H3N2). Each of these pandemic strains replaced the previously circulating influenza A subtype and went on to circulate as seasonal influenza. In 1977, the A (H1N1) re-emerged in the human population and, since then, A (H1N1) and A (H3N2) have co-circulated with influenza B. Recently, the avian influenza A virus subtypes, H5N1 and H9N2, have caused human infections. The most notable of these is the A (H5N1) subtype, which has become established in domestic poultry throughout Southeast Asia and has spread to Europe and Africa in either wild birds or domestic poultry. Although growing numbers of people have contracted the virus by contact with birds and there is a high mortality rate (≥50%), there has been no evidence of ongoing person-to-person transmission.

In 2009, the World Health Organization (WHO) declared a pandemic of a novel subtype A (H1N1) influenza virus, A(H1N1)pdm09, which originated in swine; the pandemic started in Mexico and the United States in April 2009. In August 2010, the WHO reported that more than 214 countries and overseas territories or

communities reported laboratory-confirmed cases of A(H1N1)pdm09 (pH1N1) influenza, including more than 18 000 deaths.[14] In Australia, a total of 44 403 confirmed cases of pH1N1 influenza occurred between May 2009 and November 2010, including 6767 cases in 2010. A total of 213 pandemic influenza-associated deaths were reported, 22 of which occurred in 2010.[15]

Evidence from multiple outbreak sites demonstrated that the A(H1N1)pdm09 virus rapidly established itself and was the dominant influenza strain in most parts of the world. The clinical picture of pH1N1 influenza appeared to be largely consistent across all countries, with most affected persons experiencing moderate illness. Risk factors for severe disease included obesity, pregnancy, diabetes mellitus and, in Australia, being of Aboriginal or Torres Strait Islander descent (see 3.1 *Vaccination for Aboriginal and Torres Strait Islander people*). Although influenza can cause very severe and fatal illness, particularly in the elderly, the impact of pH1N1 influenza in younger healthy adults and in pregnant women was proportionally greater than normal seasonal outbreaks, even though the absolute number of such cases remained low. During the last quarter of 2009, Australia introduced a non-adjuvanted, inactivated, egg-derived, monovalent A(H1N1)pdm09 vaccine for administration to all persons aged ≥6 months (Panvax, CSL Limited). Expired monovalent vaccine supplies were withdrawn in December 2010.[16] In Australia, there was ongoing summer activity of A(H1N1) pdm09 in late 2009, and the virus continued to circulate in 2010 and 2011, replacing the previously circulating seasonal H1N1 strain.[2] The A(H1N1)pdm09 strain was included in trivalent seasonal influenza vaccine formulations used in the southern hemisphere in 2010, 2011 and 2012.

4.7.4 Vaccines

The administration of influenza vaccine to persons at risk of complications of infection is the single most important measure in preventing or attenuating influenza infection and preventing mortality. After vaccination, most adults develop antibody levels that are likely to protect them against the strains of virus represented in the vaccine. In addition, there is likely to be protection against many related influenza variants. Infants, the very elderly, and persons who are immunocompromised may develop lower post-vaccination antibody levels. Under these circumstances, influenza vaccine may be more effective in preventing lower respiratory tract involvement or other complications of influenza than in preventing influenza infection.

Always check annual seasonal influenza vaccine availability statements on www.immunise.health.gov.au. Vaccines and age eligibility change from year to year.

Vaccines for intramuscular administration

Children aged ≥6 months and adults (see Table 4.7.1 for dosage information for different age groups)

- ***Agrippal*** – Novartis Vaccines and Diagnostics Pty Ltd (inactivated influenza virus). Each 0.5 mL pre-filled syringe contains 15 µg haemagglutinin of each of the three recommended strains. May contain traces of kanamycin, neomycin, formaldehyde, barium sulphate, cetrimonium bromide (CTAB), polysorbate 80 and egg protein.
- ***Fluarix*** – GlaxoSmithKline (inactivated influenza virus). Each 0.5 mL pre-filled syringe contains 15 µg haemagglutinin of each of the three recommended strains. May contain traces of formaldehyde, gentamicin, polysorbate 80, octoxinol 10 and egg protein.
- ***Influvac*** – Abbott Products Pty Ltd (inactivated influenza virus). Each 0.5 mL pre-filled syringe contains 15 µg haemagglutinin of each of the three recommended strains. May contain traces of formaldehyde, CTAB, polysorbate 80, gentamicin and egg protein.
- ***Influvac Junior*** (6 months to <3 years) – Abbott Products Pty Ltd (inactivated influenza virus). Each 0.25 mL pre-filled syringe contains 7.5 µg haemagglutinin of each of the three recommended strains. May contain traces of formaldehyde, CTAB, polysorbate 80, gentamicin and egg protein.
- ***Vaxigrip*** – Sanofi Pasteur Pty Ltd (inactivated influenza virus). Each 0.5 mL pre-filled syringe contains 15 µg haemagglutinin of each of the three recommended strains. May contain traces of formaldehyde, octoxinol 9, neomycin and egg protein.
- ***Vaxigrip Junior*** (6 months to <3 years) – Sanofi Pasteur Pty Ltd (inactivated influenza virus). Each 0.25 mL pre-filled syringe contains 7.5 µg haemagglutinin of each of the three recommended strains. May contain traces of formaldehyde, octoxinol 9, neomycin and egg protein.

Children aged ≥10 years* and adults (see Table 4.7.1 for dosage information)

- ***Fluvax*** – CSL Limited (inactivated influenza virus).* Each 0.5 mL pre-filled syringe contains 15 µg haemagglutinin of each of the three recommended strains. May contain traces of neomycin, polymyxin B, β-propiolactone, sodium taurodeoxycholate and egg protein.

Adults aged ≥65 years

- ***Fluad*** – Novartis Vaccines and Diagnostics Pty Ltd (inactivated influenza virus). Each 0.5 mL pre-filled syringe contains 15 µg haemagglutinin of each of the three recommended strains, adjuvanted with MF59C.1 (which contains squalene and polysorbate 80). May contain traces of kanamycin, neomycin, formaldehyde, barium sulphate, CTAB and egg protein.

Vaccines for intradermal administration

Adults aged 18–59 years

- ***Intanza 9 µg*** – Sanofi Pasteur Pty Ltd (inactivated influenza virus). Each 0.1 mL pre-filled purpose-designed Micro-Injection System contains 9 µg haemagglutinin of each of the three recommended strains. May contain traces of formaldehyde, octoxinol 9, neomycin and egg protein.

Adults aged ≥60 years

- ***Intanza 15 µg*** – Sanofi Pasteur Pty Ltd (inactivated influenza virus). Each 0.1 mL pre-filled purpose-designed Micro-Injection System contains 15 µg haemagglutinin of each of the three recommended strains. May contain traces of formaldehyde, octoxinol 9, neomycin and egg protein.

* Fluvax (CSL Limited) is registered by the Therapeutic Goods Administration (TGA) for administration in children ≥5 years of age; however, it is not recommended for use in children <10 years of age (see 4.7.11 *Adverse events* and 4.7.13 *Variations from product information* below).

The composition of vaccines for use in Australia is determined annually by the Australian Influenza Vaccine Committee.[17] Influenza vaccines normally contain three recommended strains of virus, two influenza A subtypes and influenza B, representing currently circulating viruses. The included strains may differ from those selected for use in the northern hemisphere influenza vaccine formulation. The final trivalent influenza vaccine contains 15 µg of viral haemagglutinin (or 9 µg in Intanza 9 µg), the principal surface antigen, for each virus strain. Vaccines specifically packaged for use in children aged ≥6 months to <3 years contain

7.5 µg of viral haemagglutinin (in a 0.25 mL dose) of each of the same three strains found in the adult formulations.

All the influenza vaccines currently available in Australia are either split virion or subunit vaccines prepared from purified inactivated influenza virus that has been cultivated in embryonated hens' eggs. Split virion and subunit vaccines are generally considered to be equivalent with respect to safety, and both are substantially free of the systemic reactions sometimes induced by whole virus vaccines. One exception is Fluvax (CSL Limited), which in 2010 resulted in higher rates of adverse events, specifically fevers and febrile convulsions, in children aged <5 years, in comparison with other influenza vaccines (see 4.7.11 *Adverse events* below).[17] Because influenza vaccine viruses are cultivated in embryonated hens' eggs, these vaccines may contain traces of egg-derived proteins. Manufacturing processes vary by manufacturer, and different chemicals (formaldehyde or β-propiolactone) may be used to inactivate the virus. The product information for each vaccine should be consulted for specific information. (See also 'Vaccination of persons with a known egg allergy' in 3.3.1 *Vaccination of persons who have had an adverse event following immunisation*.)

Two intradermally administered influenza vaccines from the same manufacturer (Intanza 9 µg for use in adults aged 18–59 years and Intanza 15 µg for use in adults aged ≥60 years) have been registered in Australia since 2009. These vaccines are presented in a purpose-designed syringe, the Micro-Injection System, which will deliver 0.1 mL of vaccine to the dermis. These vaccines demonstrate comparable immunogenicity to influenza vaccines administered intramuscularly and are likely to have similar efficacy.

Live attenuated intranasal influenza vaccine(s) are not currently registered in Australia and, worldwide, are not as widely used as the currently available inactivated influenza vaccines.[18,19]

The efficacy and effectiveness of different split virion and subunit influenza vaccines are generally considered equivalent. The efficacy and effectiveness of influenza vaccine depends primarily on the age and immunocompetence of the vaccine recipient and the degree of similarity between the virus strains in the vaccine and those circulating in the community.[13,20-27] In children, the burden of influenza is well documented, but there is less evidence for vaccine efficacy, particularly in children aged <2 years.[22] There have been few vaccine effectiveness studies undertaken in very young infants and toddlers and these studies are difficult to compare due to differences in vaccine formulations and inclusion and exclusion criteria, and the measurement of different clinical endpoints.[28] A recent study has suggested that, during a season with good vaccine match, vaccine effectiveness was between 60 and 85% in children ranging in age from 6 months to <6 years.[28] When vaccine match was poor, vaccine effectiveness ranged from zero to about 60%.[28] A recent systematic review estimated the overall efficacy of inactivated vaccines against laboratory-confirmed influenza in healthy adults <65 years of age to be 59%, although

efficacy varied by influenza season.[29] The efficacy of inactivated influenza vaccine against influenza-like illness in persons ≥65 years of age living in the community is estimated to be 43% when viral circulation is high, although there have been few randomised controlled trials of influenza vaccine in elderly people.[30] A systematic review assessing vaccine effectiveness estimated that during periods of high virus circulation, when vaccine match is good, influenza vaccination is approximately 45% effective against hospitalisations due to influenza and pneumonia and 60% effective against all-cause mortality in persons aged >65 years in nursing home settings.[30]

Currently available influenza vaccines confer protection for about a year. Low levels of protection may persist for a further year, if the prevalent strain remains the same or undergoes only minor antigenic drift.[13,27] Continuing protection requires annual vaccination with vaccine containing the most recent strains.

4.7.5 Transport, storage and handling

Transport according to *National vaccine storage guidelines: Strive for 5*.[31] Store at +2°C to +8°C. Do not freeze. Protect from light.

At the end of each year, influenza vaccines should be appropriately discarded to avoid inadvertently using a product with incorrect formulation in the following year.

4.7.6 Dosage and administration

Vaccines registered by the TGA, and the ages for which they are indicated, can change from year to year. Always check annual seasonal influenza vaccine availability statements on www.immunise.health.gov.au, and consult individual product information.

Influenza vaccines available in Australia for IM use are presented in pre-filled syringes, of either 0.5 mL or 0.25 mL. The dose of vaccine to be administered varies by age, with children aged 6 months to <3 years requiring a 0.25 mL dose. See Table 4.7.1 for the recommended doses of influenza vaccine for different age groups. Some 0.5 mL syringes have a graduated mark to indicate where the plunger can be depressed to provide a 0.25 mL dose, if indicated.

Shake the pre-filled syringe vigorously before injection. Most influenza vaccines should be given by IM injection. However, if administered by SC injection, the vaccine does not need to be re-administered. The IM route causes fewer local reactions and is preferred over the SC route.[32]

Intradermal influenza vaccines are presented in a purpose-designed syringe containing 0.1 mL of vaccine, the Micro-Injection System, and do not require mixing before administration. They should be administered according to manufacturer's instructions.

Table 4.7.1: Recommended doses of influenza vaccine

Age	Dose	Number of doses (first year of vaccination)	Number of doses* (subsequent years)
6 months to <3 years	0.25 mL	2†	1
3 to 9 years	0.5 mL	2†	1
≥10 years	0.5 mL	1‡	1

* If a child 6 months to ≤9 years of age receiving influenza vaccine for the first time inadvertently does not receive the 2nd dose within the same year, he/she should have 2 doses administered the following year.[33-35]

† Two doses, at least 4 weeks apart, are recommended for children aged ≤9 years who are receiving influenza vaccine for the first time. The same vial should not be re-used for the 2 doses.[31]

‡ Two doses, at least 4 weeks apart, are recommended for immunocompromised persons receiving influenza vaccine for the first time (see 3.3 *Groups with special vaccination requirements*). The same vial should not be re-used for the 2 doses.

Vaccination is best undertaken in autumn, in anticipation of winter outbreaks of influenza. However, vaccination can be given as early as February if vaccine is available, particularly for the northern areas of Queensland and in the Northern Territory where the seasonality of influenza differs from the southern states. In autumn, the opportunities to provide influenza vaccination to persons at increased risk of influenza should not be missed during visits for routine medical care.

As full protection is usually achieved within 10 to 14 days and there is evidence of increased immunity within a few days, vaccination can still be offered to adults and children after influenza virus activity has been documented in the community.

Co-administration with other vaccines

Influenza vaccine can be administered concurrently with other vaccines, including pneumococcal polysaccharide vaccine and all scheduled childhood vaccines. However, parents/carers of infants or children who are recommended to receive both influenza vaccine and 13-valent pneumococcal conjugate vaccine (13vPCV) should be advised of the increased risk of fever following concomitant administration of these vaccines (see 4.7.10 *Precautions* below and 4.13 *Pneumococcal disease*).

4.7.7 Recommendations

Annual influenza vaccination is recommended for any person ≥6 months of age for whom it is desired to reduce the likelihood of becoming ill with influenza.[5,6,36,37]

Influenza vaccination is strongly recommended and should be actively promoted for the groups discussed below.

All adults aged ≥65 years

There is evidence that influenza vaccine reduces hospitalisations from influenza and pneumonia and all-cause mortality in adults ≥65 years of age.[30] (See also 4.7.4 *Vaccines* above.)

Persons at increased risk of complications from influenza infection

Persons aged ≥6 months with conditions predisposing to severe influenza,[7] such as:

- *Pregnancy* – Pregnant women (and women planning pregnancy) are recommended to be immunised against influenza because they are at increased risk of morbidity and mortality from influenza and because there is good evidence that influenza immunisation in pregnancy is safe and effective.[38-45] The risk to the mother of complications from influenza increases in the later stages of pregnancy.[38-42,46-50] There is also a growing body of evidence showing that influenza vaccination of pregnant women protects infants against influenza for the first 6 months after birth.[39,51,52] Most evidence around infant protection is from studies of maternal influenza vaccination in the second or third trimester.[38-42,46-51] Influenza vaccination is thought to provide protection for up to a year, but there is limited evidence that immunity may start to wane from 4 months following immunisation. Although it is recommended that all pregnant women should be immunised as early as possible in pregnancy,[53] the precise timing of vaccination will depend on the time of the year, vaccine availability, influenza seasonality, gestation of pregnancy and the likely duration of immunity. (See also 4.7.8 *Pregnancy and breastfeeding* below.)
- *Cardiac disease*, including cyanotic congenital heart disease, coronary artery disease and congestive heart failure – Influenza causes increased morbidity and mortality in children with congenital heart disease and adults with coronary artery disease and congestive heart failure.[37,54-57]
- *Down syndrome* – Persons with Down syndrome should receive annual seasonal influenza vaccine whether or not they have congenital heart disease. This is due to the presence of anatomical abnormalities, which put them at increased risk of upper respiratory tract infections, as well as a high prevalence of other medical conditions that put them at increased risk of severe influenza.[56]
- *Obesity* – Persons with significant obesity, defined as a BMI ≥30 kg/m^2, with or without other underlying conditions, have been identified as being at increased risk for hospitalisation with respiratory complications following influenza.[37] This risk was particularly apparent during the 2009–2010 pandemic.[58,59]

- *Chronic respiratory* conditions, including:
  - » Suppurative lung disease, bronchiectasis and cystic fibrosis[37,55] – Patients with these diseases are at greatly increased risk from influenza, which may cause irreversible deterioration in lung function.[60]
  - » Chronic obstructive pulmonary disease (COPD) and chronic emphysema[37,61,62] – Data from several studies provide evidence that influenza vaccination has a clinically important protective effect on influenza-related COPD exacerbations, and probably an effect on the total number of exacerbations in COPD patients.[61,62]
  - » Severe asthma – In patients with severe asthma, defined as requiring frequent hospital visits and the use of multiple medications, annual influenza vaccine is an important part of routine care.[37,55] There are insufficient data from randomised controlled trials of influenza vaccine to define efficacy across the whole spectrum of asthma, but influenza can cause severe exacerbations of wheezing, and about 10% of episodes of virus-induced wheezing are attributable to influenza.
- *Chronic neurological conditions* (e.g. multiple sclerosis, spinal cord injuries, seizure disorders or other neuromuscular disorders) – These conditions can compromise respiratory function or the expulsion of respiratory secretions that can then increase the risk for aspiration.[37,55] Influenza vaccination is particularly important for children ≥6 months of age with chronic neurological conditions as these children can experience severe, even fatal, influenza.
- *Immunocompromising conditions* – Persons who are immunocompromised, including those with HIV infection, malignancy or chronic steroid use, are at an increased risk from influenza (see 3.3,3 *Vaccination of immunocompromised persons*).[37,55] They may also have a reduced immune response to the vaccine, although influenza vaccination affords some protection.[63] Influenza vaccination is recommended annually in all oncology patients aged ≥6 months.

  All immunocompromised persons, irrespective of age, who receive influenza vaccine for the first time, are recommended to receive 2 vaccine doses, at least 4 weeks apart, and 1 dose annually thereafter. Where it is known that a new influenza vaccine strain is circulating in the community to which cross-protective immunity in the population is low (such as in the setting of an influenza pandemic), it may be appropriate that immunocompromised persons receive 2 doses of inactivated influenza vaccine, a minimum of 4 weeks apart, to achieve an optimal immune response. For example, in the 2009–2010 H1N1 global influenza pandemic it was shown that seroconversion to influenza vaccination in immunocompromised adolescents and adults was improved following receipt of 2 vaccine doses.[64] Further

information and annual influenza vaccine recommendations are available on the Immunise Australia website (www.imunise.health.gov.au).

While patients with advanced HIV disease and low CD4+ T-lymphocyte counts may not develop protective antibody titres, there is evidence that for those with minimal symptoms and high CD4+ T-lymphocyte counts, protective antibody titres are obtained after influenza vaccination. Influenza vaccine has been shown to reduce the incidence of influenza in HIV-infected patients, and, although viral load may increase transiently, there was no impact on CD4+ count.[63] (See also 3.3 *Groups with special vaccination requirements*, Table 3.3.4.)

- *Other chronic illnesses* requiring regular medical follow-up or hospitalisation in the preceding year, including:
  - » diabetes mellitus[37,55,65]
  - » chronic renal failure[37,55]
  - » alcoholism[66,67]
  - » haemoglobinopathies[55]
  - » chronic inherited metabolic diseases (which includes amino acid disorders, carbohydrate disorders, cholesterol biosynthesis disorders, fatty acid oxidation defects, lactic acidosis, mitochondrial disorders, organic acid disorders, urea cycle disorders, vitamin/cofactor disorders, porphyrias)[37,55]
- *Long-term aspirin therapy in children* (aged 6 months to 10 years) – Such children are at increased risk of Reye syndrome after influenza.[68,69]

Aboriginal and Torres Strait Islander people aged ≥15 years

Annual influenza vaccination is recommended for all Aboriginal and Torres Strait Islander people ≥15 years of age, in view of their substantially increased risk of hospitalisation and death from influenza and pneumonia.[70] (See also 3.1 *Vaccination for Aboriginal and Torres Strait Islander people* and 4.13 *Pneumococcal disease.*)

Children aged <5 years

Young infants and children aged <5 years, particularly Aboriginal and Torres Strait Islander children, are at increased risk for hospitalisation and increased morbidity and mortality following influenza[71-73](see Figure 4.7.1). While many children who have a medical condition are at risk of increased morbidity and mortality following influenza, children without pre-existing medical conditions, particularly those aged <2 years, have also been found to be at increased risk for hospitalisation compared with older children and adults.[71,72,74] Vaccines can be used in children from 6 months of age. Specific brands are registered by the TGA for use in children and these may change from year to year (see 4.7.6 *Dosage and administration* above).

Residents of residential aged care facilities and long-term residential facilities

Annual influenza vaccination is recommended for residents of these facilities, including inmates of correctional facilities, due to high rates of influenza transmission and complications during outbreaks in such facilities.[12,13,62]

Homeless people

The living conditions and prevalence of underlying medical conditions among homeless people will predispose them to complications and transmission of influenza.

Persons who may transmit influenza to persons at increased risk of complications from influenza infection

The following groups of people can potentially transmit influenza to persons at increased risk of complications from influenza infection; vaccination of these groups is therefore recommended to protect those at risk:

- all healthcare providers (particularly those of immunocompromised patients)
- staff (or volunteers) working in nursing homes
- staff (or volunteers) working in long-term care facilities
- household contacts (including children ≥6 months of age) of those in high-risk groups, including providers of home care to persons at risk of high influenza morbidity
- staff working in early childhood education and care
- staff (or volunteers) providing care to homeless people.

Persons involved in the commercial poultry or pork industry or in culling poultry or pigs during confirmed avian or swine influenza activity

Vaccination using the seasonal influenza vaccine composition current at the time is recommended for poultry or piggery workers and others in regular close contact with poultry or pigs during an avian or swine influenza outbreak.[75] Although routine seasonal influenza vaccine does not protect against avian or swine influenza, there is a possibility that a person who is infected at the same time with animal and human strains of influenza virus could act as a vessel for reassortment of the two strains to form a virulent strain, with the potential for spread from human to human (i.e. initiate a pandemic as was the case with swine influenza in 2009).[76] In addition, vaccination can also prevent the transmission of influenza from humans to animals.

Persons providing essential services

Vaccination of those who provide essential community services will minimise disruption of essential activities during influenza outbreaks. Influenza viral infections can place considerable pressure upon both public and private healthcare services (see 3.3 *Groups with special vaccination requirements*, Table 3.3.7 *Recommended vaccinations for persons at increased risk of certain occupationally acquired vaccine-preventable diseases*).

Workers in other industries

Due to the high attack rate of influenza in the general population, influenza vaccination in the workplace can result in benefits such as increased productivity and reduced absenteeism among workers.[77] Employers should consider the benefits of offering influenza vaccine in their individual workplace.

Travellers

Influenza vaccine is particularly relevant if influenza epidemics are occurring at the traveller's destination(s). Travellers in large tourist groups, especially those including older people, those travelling on cruises, and/or those who are likely to be in confined circumstances for days to weeks, are at risk of influenza, either acquired before departure or from travel to areas of the world where influenza is currently circulating. Influenza vaccination is recommended if travelling during the influenza season, especially if it is known before travel that influenza is circulating in the destination region.[78] (See also 3.2 *Vaccination for international travel*.)

4.7.8 Pregnancy and breastfeeding

Influenza vaccination is recommended for pregnant women (see 4.7.7 *Recommendations* above) and is safe to administer during any stage of pregnancy or while breastfeeding.[44,79-81]

Refer to 3.3 *Groups with special vaccination requirements*, Table 3.3.1 *Recommendations for vaccination in pregnancy* for more information.

4.7.9 Contraindications

The only absolute contraindications to influenza vaccines are:

- anaphylaxis following a previous dose of any influenza vaccine
- anaphylaxis following any vaccine component.

See 4.7.10 *Precautions* below for persons with a known egg allergy.

4.7.10 Precautions

Persons with known egg allergy[82-86]

Several recently published reviews, guidelines and reports have indicated that the risk of anaphylaxis associated with influenza vaccination of egg-allergic patients is very low.[82-86] Persons with egg allergy, including anaphylaxis, can be safely vaccinated with influenza vaccines that have less than 1 µg of residual egg ovalbumin per dose.[82,84] Due to changes in influenza vaccine manufacturing, the majority of influenza vaccines currently used contain less than 1 µg of ovalbumin per dose.[82] Note the amount of residual egg ovalbumin may vary from year to year due to manufacturing processes, batches and country of origin.[82,84,85] The product information (PI) of the vaccine to be given should be checked for the vaccine's ovalbumin content prior to vaccine administration. Allergy testing with

influenza vaccine prior to administration is not recommended as there is poor correlation between test results and vaccine tolerance.[82,84-86]

However, there is still a low risk of anaphylaxis, so it is essential that such patients are vaccinated in facilities with staff able to recognise and treat anaphylaxis. Additional information on influenza vaccination of individuals with an allergy to eggs, including risk, dosage and observation period, can be found in the Australasian Society of Clinical Immunology and Allergy (ASCIA) guidelines.[84] (See also 'Vaccination of persons with a known egg allergy' in 3.3.1 *Vaccination of persons who have had an adverse event following immunisation*.)

Persons with a history of Guillain-Barré syndrome

Persons with a history of Guillain-Barré syndrome (GBS) have an increased likelihood in general of developing GBS again, and the chance of them coincidentally developing the syndrome following influenza vaccination may be higher than in persons with no history of GBS.[87] Diagnosis of GBS is complex and must be made by a physician. (See also 4.7.11 *Adverse events* below.)

Children requiring both influenza and 13-valent pneumococcal conjugate vaccine

Parents/carers of infants or children who are recommended to receive both influenza vaccine and 13vPCV should be advised of the slightly higher risk of fever following concomitant administration of these vaccines (see 4.13 *Pneumococcal disease*). Given this relatively low increase in risk, providing 13vPCV and inactivated trivalent influenza vaccine concurrently to children aged 12–23 months is acceptable; however, immunisation service providers should advise parents regarding this, and provide the option of administering these two vaccines on separate days (with an interval of not less than 3 days). In the event that fever occurs following either vaccine, an interval may minimise the risk of increased adverse reactions.

4.7.11 Adverse events

Fever, malaise and myalgia occur commonly, in 1 to 10% of persons who receive influenza vaccination.[88-90] These adverse events may commence within a few hours of vaccination and may last for 1 to 2 days.[88-90] In children <5 years of age, these side effects may be more pronounced. In 2010, an excess of fever and febrile convulsions following influenza vaccination was reported in children aged <5 years, particularly children aged <3 years. This was associated only with one manufacturer's vaccine (Fluvax and Fluvax Junior, CSL Limited); following vaccination with this vaccine, febrile convulsions occurred at a rate of 4.4 per 1000 doses in children <5 years of age.[91] This vaccine is no longer registered for use in children aged <5 years and is not recommended for administration in children aged <10 years (see 4.7.4 *Vaccines* above).[92]

Local adverse events (induration, swelling, redness and pain) occur in more than 10% of vaccine recipients, following IM influenza vaccine administration.[89,90]

Local adverse events (induration, redness, swelling and pruritus) occur more commonly following intradermal influenza vaccine administration. However, most patients report that these events are transient and resolve fully within a few days.[93]

Post-vaccination symptoms may mimic influenza infection, but all currently available influenza vaccines do not contain live virus and so do not cause influenza.

Immediate adverse events (such as hives, angioedema or anaphylaxis) are a rare consequence of influenza vaccination. They probably represent an allergic response to a residual component of the manufacturing process, most likely egg protein.[82,84] Persons with a history of anaphylaxis after eating eggs or a history of a severe allergic reaction following occupational exposure to egg protein may receive influenza vaccination after medical consultation.[82,84]

A small increased risk of GBS was associated historically with one influenza vaccine in the United States in 1976, but, since then, close surveillance has shown that GBS has occurred at a very low rate of up to 1 in 1 million doses of influenza vaccine, if at all.[94] Diagnosis of GBS is complex and must be made by a physician (see 'Uncommon/rare AEFI' in 2.3.2 *Adverse events following immunisation*).

Narcolepsy (sudden sleeping illness) has been described predominantly in the Scandinavian population, in association with adjuvanted pandemic influenza vaccines.[95,96] These vaccines were not used and are not available in Australia.

4.7.12 Public health management of influenza

Laboratory-confirmed cases of influenza are notifiable in all states and territories in Australia. Detailed information regarding the management of influenza cases and contacts can be found in the national guidelines for control of influenza[97] (www.health.gov.au/cdnasongs).

Further instructions about the public health management of influenza can also be obtained from state/territory public health authorities (see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*).

4.7.13 Variations from product information

The product information for influenza vaccines lists allergy to eggs, chicken feathers and/or some food proteins as a contraindication. The ATAGI recommends instead that patients with egg allergies and other allergies can be vaccinated under strict medical supervision, in accordance with ASCIA guidelines.[84]

The product information for Fluvax (CSL Limited) states that this vaccine is registered for use in children ≥5 years of age. However, the ATAGI does not recommend the use of this vaccine in children aged <10 years.

References

A full reference list is available on the electronic *Handbook* or website www.immunise.health.gov.au

4.8 JAPANESE ENCEPHALITIS

4.8.1 Virology

Japanese encephalitis (JE) is caused by a mosquito-borne RNA flavivirus.

4.8.2 Clinical features

The disease is typically an acute neurological illness, characterised by headache, fever, convulsions, focal neurological signs and depressed level of consciousness. It has a high case-fatality rate and there is a high prevalence of neurological sequelae (up to 50%) in those who survive the acute illness.[1] Less commonly, the disease may present as an acute flaccid paralysis.[1] Milder forms include febrile illness with headache, and aseptic meningitis. It is recognised, however, that most infections are asymptomatic; published estimates of the symptomatic to asymptomatic infection ratio vary in different populations from 1:25 to 1:1000.[1]

4.8.3 Epidemiology

JE is a significant public health problem in many parts of Asia, including the Indian subcontinent, Southeast Asia and China.[1] In recent years, however, the disease has extended beyond its traditionally recognised boundaries with, for example, occasional cases in eastern Indonesia, occasional outbreaks in the Torres Strait and 1 case in north Queensland.[2,3] JE is now considered endemic in the Torres Strait region and Papua New Guinea.[2-5] The first ever outbreak of Japanese encephalitis (JE) in Australia occurred in the remote outer islands of the Torres Strait in 1995, with 3 cases, 2 of them fatal. There have been 5 cases to date acquired in Australia. JE virus has only been detected infrequently in sentinel animal surveillance in the outer islands. The sentinel pig surveillance system has been gradually disbanded since 2006, with surveillance of the last remaining herd on Cape York ceasing from the 2011–2012 wet season.

There has not been a case of JE in the Torres Strait since 1998 and the risk of JE has diminished considerably in the outer islands since the mid-1990s. Most communities have relocated pigs well away from homes, and major drainage works on most islands have markedly reduced potential breeding sites for vector mosquitoes. Between 2001 and April 2012, only 4 cases of JE virus infection were notified in Australia.[6]

The JE virus is essentially a zoonosis of pigs and wading birds, and is transmitted between these animals by culicine mosquitoes.[1] The virus replicates, leading to a transient high-level viraemia, within these so-called 'amplifying' hosts, but not within other large vertebrates such as horses and humans.

Indeed, humans are an incidental host, infected when living in close proximity to the enzootic cycle; this usually occurs in rural areas where there is prolific breeding of the vectors in flooded rice fields.[1]

There are two recognised epidemiological patterns of JE.[1] In the temperate or subtropical regions of Asia (northern Thailand, northern Vietnam, Korea, Japan,

Taiwan, China, Nepal and northern India), the disease occurs in epidemics during the summer or wet season months (April to May until September to October). In the tropical regions (most of Southeast Asia, Sri Lanka, southern India), the disease is endemic, occurring throughout the year, but particularly during the wet season.[1] A 2006 study confirmed that JE virus is hyperendemic in Bali, that it causes substantial human illness, and that it circulates year round.[7]

In some countries (Japan, Taiwan, South Korea and some provinces of China), the incidence of JE has declined considerably in recent decades, and it has been eradicated from Singapore. Immunisation, changes in pig husbandry, a reduction in land utilised for rice farming, and improved socioeconomic circumstances have all contributed to these changes.[1] Updated information regarding JE virus activity and/or risk in travel destinations should be sought from a reputable source prior to travel.[8]

4.8.4 Vaccines

- ***Imojev*** – Sanofi Pasteur Pty Ltd (live attenuated Japanese encephalitis virus). Lyophilised powder in a monodose vial with separate diluent. Each 0.5 mL reconstituted dose contains 4.0–5.8 log plaque-forming units (PFU) of live attenuated Japanese encephalitis virus; mannitol; lactose; glutamic acid; potassium hydroxide; histidine; human serum albumin. No adjuvants or antibiotics are added.
- ***JEspect*** – Intercell Biomedical Ltd/CSL Limited (inactivated Japanese encephalitis virus). Each 0.5 mL pre-filled syringe contains 6 µg of purified inactivated Japanese encephalitis virus; 0.25 mg aluminium as aluminium hydroxide. No preservatives or antibiotics are added.

Two JE vaccines, each with different characteristics, are available for use in Australia. The inactivated mouse brain-derived JE vaccine formulation manufactured in Japan, JE-Vax, which was previously used in Australia, is no longer manufactured. Clinical and animal studies have provided evidence in support of an immunological correlate of immunity (established by the World Health Organization as a neutralising antibody titre of ≥1:10). Both currently available JE vaccines were registered on the basis of this serological correlate in lieu of a field efficacy trial.

Imojev is a live attenuated, monovalent viral vaccine produced using recombinant technology. Two genes of the 17D-204 yellow fever vaccine virus have been replaced with two genes, prM and E genes, from the Japanese encephalitis virus strain SA 14-14-2. About 94% of healthy adults aged 18–84 years seroconverted to a strain homologous to that in the Imojev vaccine 14 days after a single vaccine dose.[9] Several clinical trials have demonstrated that, 28 days following vaccination with a single dose of Imojev, protective levels of

neutralising antibodies against the homologous vaccine virus strain are present in 96% of vaccine-naïve children aged 12–24 months[10] and 99% of adults.[9-12] Immunogenicity was non-inferior to that attained after a 3-dose primary course of the inactivated mouse brain-derived JE vaccine[9] that was previously used in Australia. Subjects also seroconverted to various wild-type, non-homologous, JE virus strains (70 to 97% of children aged 12–24 months and 70 to 100% of adults);[10,13] 85% of adults developed neutralising antibodies against all four wild-type strains used for testing.[12] Protective antibody to the vaccine strain was maintained at 6 months after vaccination in 87% of children aged 12–24 months,[10] and 97% of adults.[12] About 93% of adults maintained a protective antibody level to the vaccine strain, and 65% to at least three wild-type strains, 60 months after a single vaccine dose.[12] Establishment of immunological memory in vaccinated adult subjects has also been demonstrated.[13]

Among children aged 2–5 years previously vaccinated with a mouse brain-derived JE vaccine (of whom 86% were seropositive against the vaccine strain and 72 to 81% seropositive against four wild-type strains at baseline), a dose of Imojev produced seroprotective antibody levels against the vaccine strain in 100%, and against all wild-type strains in 99%. Ninety-three per cent of the children seroconverted to the vaccine strain and 90% against all wild-type strains.[10]

JEspect is a Vero cell-derived, inactivated, aluminium-adjuvanted vaccine based on the attenuated SA 14-14-2 JE virus strain. JEspect has equivalent immunogenicity (after 2 doses, given 4 weeks apart) to 3 doses of the previously available mouse brain-derived vaccine, with seroconversion achieved in 98% of subjects.[14] Post-vaccination geometric mean titres (GMT) in JEspect recipients were significantly higher than GMTs attained after a mouse brain-derived vaccine.[14] After a standard 2-dose course, protective levels of neutralising antibodies have been found to persist for 6 months in 95%, for 12 months in 83% and for 24 months in 48% of JEspect-vaccinated subjects in central Europe,[15,16] but in 83%, 58% and 48%, respectively, at these three time points in subjects in western and northern Europe.[17] A suggested plausible explanation for the discrepancy between these two studies is prior vaccination with the tick-borne encephalitis vaccine in a large proportion of subjects in the central European study.[16,17] In an extension of the western and northern European study, those who did not have a seroprotective antibody level at either the 6- or 12-month follow-up point were given a booster dose at 11 and/or 23 months after first vaccination; seropositivity was attained in 100% of these subjects.[17] Another study showed that a booster dose given 15 months after the primary immunisation with 2 doses of JEspect increased the GMT by 5-fold after 4 weeks, and the proportion of subjects with seroprotective antibody levels increased from 69.2% pre booster to 98.5% at 6 and 12 months post booster. Mathematical modelling has predicted that 95% of subjects would maintain seroprotective antibodies for 3.8 years after a booster dose.[18]

A phase II study in 60 Indian children aged 1 to <3 years showed that the vaccine JEspect was safe and immunogenic in this age group.[19] Interim preliminary data from a phase III paediatric study involving 51 children from non-JE endemic countries aged 2 months to <18 years (mean age 12.5 years) suggested that 100% seroconverted to protective levels, and all 18 of those who had had 7 months follow-up from the initial dose maintained protective antibody.[20]

A small study among healthy military personnel observed that the immune response after 4 weeks to 1 dose of JEspect, among those who had previously received at least 3 doses of mouse brain-derived JE vaccine, was non-inferior to the response after 2 doses of JEspect in those who were naïve to JE vaccines.[21] A small study among travellers who had received at least 2 doses of a mouse brain-derived JE vaccine 1 to 21 years previously observed that, 4 to 8 weeks after a single dose of JEspect, a high proportion attained protective antibody levels against both homologous and heterologous strains (98% and 95%, respectively), and these proportions were non-inferior compared to those who received a booster of mouse brain-derived JE vaccine.[22] The duration of antibody response following a single dose of JEspect among those who were primed with mouse brain-derived JE vaccine is currently unknown.

4.8.5 Transport, storage and handling

Transport according to *National vaccine storage guidelines: Strive for 5*.[23] Store at +2°C to +8°C. Do not freeze. Protect from light.

Imojev *must be reconstituted* by adding the entire contents of the diluent container to the vial and shaking until the powder is completely dissolved. Reconstituted vaccine must be used within 1 hour.

4.8.6 Dosage and administration

Imojev is registered for use in persons aged ≥12 months in a single dose.

The dose of Imojev for both children (aged ≥12 months) and adults is 0.5 mL, to be given by SC injection. For individuals aged between 12 and 24 months, the preferred injection site is the anterolateral thigh. For individuals aged >2 years, the deltoid is the recommended injection site.

JEspect is registered for use in individuals aged ≥18 years. However, JEspect can be administered to persons aged ≥12 months in circumstances where an alternative is not available or contraindicated.

JEspect should be given by IM injection into the deltoid. When using JEspect in children aged ≥12 months and <3 years, primary vaccination consists of 2 doses, each of 0.25 mL, according to the following schedule:

- 1st dose at day 0
- 2nd dose 28 days after the 1st dose.

When using JEspect in children aged ≥3 years and adults, primary vaccination consists of 2 doses, each of 0.5 mL, according to the following schedule:

- 1st dose at day 0
- 2nd dose 28 days after the 1st dose.

Do not mix either Japanese encephalitis vaccine with any other vaccine in the same syringe.

Co-administration with other vaccines

Imojev can be given at the same time as the yellow fever vaccine,[24] using separate syringes and separate injection sites.

Co-administration with other vaccines (including other live vaccines) has not been assessed. If Imojev and the yellow fever vaccine or other live vaccines are not given simultaneously, they should be given at least 4 weeks apart.

JEspect can be co-administered with the hepatitis A vaccine.[25] Co-administration with other flavivirus vaccines (including yellow fever vaccine) has not been assessed.

If co-administration of either JE vaccine with other vaccines is indicated, injections should be given in separate limbs.

4.8.7 Recommendations

The two available JE vaccines are registered for different age groups, and have different vaccination schedules, booster dose requirements, and contraindications for use. These factors should be taken into account when deciding the most appropriate vaccine to use.

The dose of Imojev should be administered at least 14 days prior to potential JE virus exposure.

The JEspect vaccine (2-dose) schedule should be completed at least 1 week prior to potential JE virus exposure.

Travellers

JE vaccination is recommended for:

- travellers (≥12 months of age) spending 1 month or more in rural areas of high-risk countries in Asia and Papua New Guinea (see 4.8.3 *Epidemiology* above); however, as JE has occurred in travellers after shorter periods of travel, JE vaccination should be considered for shorter-term travellers, particularly if the travel is during the wet season, or anticipated to be repeated, and/or there is considerable outdoor activity, and/or the accommodation is not mosquito-proof[26]
- all other travellers spending a year or more in Asia (except Singapore), even if much of the stay is in urban areas.

All travellers to Asia (and other tropical regions) must be fully aware of the need to take appropriate measures to avoid mosquito bites.

The risk of JE to travellers to Asia is determined by the season of travel, the regions visited, the duration of travel, the extent of outdoor activity and the extent to which mosquito avoidance measures are taken.[1] Clearly the risk is greater during prolonged travel to rural areas of Asia during the wet season; it is probably negligible during short business trips to urban areas.

Torres Strait Islands

JE vaccination is recommended for:

- all residents (≥12 months of age) of the outer islands in the Torres Strait
- all non-residents (≥12 months of age) who will be living or working on the outer islands of the Torres Strait for a cumulative total of 30 days or more during the wet season (December to May).

Note: The period of greatest risk is from February to March and the vaccination course should be completed before February. Those arriving in the outer islands late in the wet season (i.e. in May) will arrive after the risk period and do not require vaccination. Those visiting the outer islands in the dry season (June to November) do not require vaccination. Those visiting only the inner islands, including Thursday Island, do not require vaccination.

Laboratory personnel

JE vaccination is recommended for all research laboratory personnel who will potentially be exposed to the virus.

Booster doses

Currently there is limited evidence available to inform recommendations regarding the need and appropriate time interval for a booster dose of either Imojev or JEspect.

A booster dose of Imojev is not currently recommended. Preliminary data from a subset of participants in a phase II randomised controlled trial demonstrated considerable persistence of seroprotective antibody levels 60 months following a single dose of Imojev[12] (see 4.8.4 *Vaccines* above).

Some data suggest that if the primary series of JEspect was administered >1 year previously, and there is an ongoing or high risk of JE virus exposure, a booster dose should be offered.[16]

For individuals previously vaccinated with the mouse brain-derived JE vaccine, either Imojev or JEspect can be used for revaccination if there is an ongoing risk of JE virus exposure.

4.8.8 Pregnancy and breastfeeding

Imojev is a live attenuated viral vaccine and is contraindicated in pregnant women. Pregnancy should be avoided for 28 days after vaccination.

There are no data on whether the Imojev vaccine virus is excreted in breast milk; the vaccine should not be given to breastfeeding women.

JEspect vaccine is not routinely recommended for pregnant or breastfeeding women. However, as JE virus infection during the first and second trimesters has been associated with miscarriage, pregnant women at risk of acquiring JE should be offered JE vaccination. Although this inactivated JE vaccine might pose a theoretical risk to the developing fetus, no adverse outcomes of pregnancy have been attributed to vaccination against JE.

No specific data are available regarding the administration of JEspect to breastfeeding women. Breastfeeding women who are at increased risk of acquiring JE should be offered JE vaccination.

Refer to 3.3 *Groups with special vaccination requirements*, Table 3.3.1 *Recommendations for vaccination in pregnancy* for more information.

4.8.9 Contraindications

JE vaccines are contraindicated in persons who have had:

- anaphylaxis following a previous dose of any JE vaccine
- anaphylaxis following any vaccine component.

Imojev is a live attenuated viral vaccine and must not be administered to pregnant or breastfeeding women or to any person who is immunocompromised due to either disease and/or medical treatment.

4.8.10 Precautions

JE vaccines should not be administered during an acute febrile illness.

There are few data on the safety and efficacy of JEspect vaccine in persons who are immunocompromised. Such persons may not mount an adequate immune response, but, as JEspect is an inactivated vaccine, safety and reactogenicity are not expected to be of concern in those who are immunocompromised.

4.8.11 Adverse events

Local reactions and minor systemic reactions are common to very common following vaccination against JE.

In adults, adverse events following Imojev were similar to those in placebo recipients,[9,12] but occurred less often than in recipients of the mouse brain-derived JE vaccine.[9] The most common adverse events in two key studies were injection site pain, headache, fatigue and malaise; most symptoms resolved within 3 days.[9] Similarly, in children aged 12–24 months, the frequency of adverse events after Imojev was comparable to that after the hepatitis A vaccine. About 40% of these subjects reported injection site reactions, including pain (32%), erythema (23%) and swelling (9%), and about 50% reported at least one systemic reaction, including fever (21%), appetite loss (26%), irritability (28%) and abnormal crying (23%). Frequencies of adverse events in children

aged 2–5 years who received Imojev after having been previously vaccinated with the mouse brain-derived vaccine were similar to, or lower than, those seen in children aged 12–24 months not previously vaccinated. All reactions were transient and almost all were mild. Most systemic reactions were mild or moderate, appeared within 7 days of vaccination, and lasted up to 3 days.[10]

In a pooled analysis of over 4000 healthy adults who received at least 1 dose of JEspect, 54% reported injection site reactions, most commonly pain (33%), tenderness (33%) and redness (9%).[27] Headache and myalgia were the most commonly reported systemic adverse events.[17,19,27-29] An earlier analysis found a comparable rate of adverse events in those who received JEspect compared with aluminium-containing placebo.[28] Post-marketing surveillance reported adverse events following JEspect at a rate of about 10 per 100 000 doses distributed; no serious allergic reactions were observed during the first 12 months after marketing approval.[27] The frequencies of adverse events reported following a booster dose were similar to those reported after a primary course.[17,18]

4.8.12 Public health management of Japanese encephalitis

JE virus infection is a notifiable disease in all states and territories in Australia.

Further instructions about the public health management of JE, including management of cases of JE, should be obtained from state/territory public health authorities (see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*)

4.8.13 Variations from product information

JEspect is registered for use in persons aged ≥18 years. The ATAGI recommends that JEspect can be administered to persons aged ≥12 months in circumstances where an alternative is not available or contraindicated. The ATAGI also recommends that children aged ≥12 months to <3 years receive 0.25 mL doses of JEspect.

References

A full reference list is available on the electronic *Handbook* or website www.immunise.health.gov.au

4.9 MEASLES

4.9.1 Virology

Measles is a paramyxovirus, genus *Morbillivirus*. It is an RNA virus with six structural proteins, three complexed to the RNA and three associated with the viral envelope. Two of the envelope proteins, the F (fusion) protein and the H (haemagglutinin) protein, are the most important in pathogenesis. The measles virus can survive for up to 2 hours in air, but is rapidly inactivated by heat, light and extremes of pH.[1,2]

4.9.2 Clinical features

Measles is a highly infectious, acute viral illness spread by respiratory secretions, including aerosol transmission.[1] It is infectious from the beginning of the prodromal period and for up to 4 days after the appearance of the rash. The incubation period is usually 10 to 14 days. The prodrome, lasting 2 to 4 days, is characterised by fever and malaise, followed by a cough, coryza and conjunctivitis. The maculopapular rash typically begins on the face and upper neck, and then becomes generalised.

Measles is often a severe disease, frequently complicated by otitis media (in approximately 9%), pneumonia (in approximately 6%) and diarrhoea (in approximately 8%).[1,2] Acute encephalitis occurs in 1 per 1000 cases, and has a mortality rate of 10 to 15%, with a high proportion of survivors suffering permanent brain damage.[3] Subacute sclerosing panencephalitis (SSPE) is a late complication of measles, occurring on average 7 years after infection in approximately 0.5 to 1 per 100 000 measles cases.[1] SSPE causes progressive brain damage and is always fatal. Complications from measles are more common and more severe in the chronically ill, in children <5 years of age, and in adults.[2] Approximately 60% of deaths from measles are attributed to pneumonia, especially in the young, while complications from encephalitis are more frequently seen in adults.[1,2] Measles infection during pregnancy can result in miscarriage and premature delivery, but has not been associated with congenital malformation.[2] There is no specific therapy for acute measles infection.

4.9.3 Epidemiology

Evidence suggests that endemic measles has been eliminated from Australia, with the absence of a circulating endemic measles strain for several years.[4] However, measles cases in Australia continue to occur, particularly in returning non-immune travellers and their contacts, with measles outbreaks of limited size and duration following importation.[4] In 2005 and 2007, measles notifications and hospitalisations were the lowest recorded in Australia.[5-7] However, there has been a recent increase in imported measles cases in Australia and subsequent outbreaks,[8] highlighting the importance of continued high 2-dose vaccine coverage. High-level vaccination coverage is imperative to maintain measles elimination, with rates for each new birth cohort of >95%

for a single dose and >90% for 2 doses required.[9] A decline in vaccination rates has resulted in a resurgence in endemic transmission in a number of European countries, including the United Kingdom.[10] In 2009, the Australian Childhood Immunisation Register recorded that 94.0% of children aged 2 years had received at least 1 dose of measles-containing vaccine and 80.3% of children aged 5 years had received 2 doses.[11]

National serosurveys in early 1999 (evaluating the 1998 National Measles Control Campaign) and in 2000 showed that those most at risk of measles infection in Australia were infants <12 months of age, 1 to <2-year olds due to delayed vaccine uptake, and persons born in the late 1960s to mid-1980s (especially the 1978–1982 birth cohort).[12-14] Young adults are recognised to be at a greater risk of measles infection as many missed being vaccinated as infants (when vaccine coverage was low), while during their childhood a 2nd dose was not yet recommended and disease exposure was decreasing. They may also have missed catch-up vaccinations during their school years as part of either the Measles Control Campaign (which only targeted primary school-aged children) or the Young Adult Measles Control Campaign (which did not result in high coverage).[15] A high proportion of recent measles cases in Australia have been in unvaccinated young adults.[8,16] Since the Measles Control Campaign, there have been no deaths recorded from measles, with the last measles death recorded in 1995.[5-7,17] Since 1998, 2 deaths have been attributed to SSPE in Australia, 1 in 1999 and 1 in 2004.[6,18]

Global elimination of measles

The World Health Organization (WHO) is overseeing efforts to eliminate measles worldwide through immunisation and surveillance strategies.[19] In 2000, measles was the fifth leading cause of childhood morbidity and mortality worldwide. There were an estimated 770 000 deaths, with more than half of these occurring in Africa.[2,20] Following extensive vaccination campaigns, there was a 78% reduction to 164 000 deaths worldwide in 2008, with the majority of deaths reported in Southeast Asia.[21] In 2003, measles elimination, defined as the absence of endemic measles virus transmission, was included as a regional goal under the Expanded Programme on Immunization (EPI) for the WHO Western Pacific Region, with a target date set for 2012.[22] Considerable progress has been made with an 86% decline in measles cases in the region (excluding China).[22] However, achieving elimination requires continued strengthening of immunisation and surveillance efforts, particularly identification of measles virus genotypes to confirm the absence of an endemic strain. Globally, 10 countries have formally declared measles elimination, including Australia;[4] however, consistent criteria for establishing measles elimination across WHO regions are still being developed.[23]

4.9.4 Vaccines

Monovalent measles vaccine is not available in Australia. Measles vaccination is provided using either measles-mumps-rubella (MMR) or measles-mumps-rubella-varicella (MMRV) vaccines. Two quadrivalent combination vaccines containing live attenuated measles, mumps, rubella and varicella viruses (MMRV) are registered in Australia.

Measles immunity induced by 1-dose vaccination provides long-term immunity in most recipients.[2,24] However, approximately 5% of recipients fail to develop immunity to measles after 1 dose.[25] Following a 2nd vaccine dose, approximately 99% of subjects overall will be immune to measles. Measles vaccine effectiveness studies have found the measles-containing vaccines to be 90 to 95% effective in developed country settings with high vaccination coverage and low incidence of measles.[2] A Cochrane review reported 1-dose vaccine effectiveness to be 95%;[26] however, effectiveness has been demonstrated to be lower, particularly by region (e.g. Asia, Africa) in 1-dose recipients.[27]

Combination MMRV vaccines have been shown in clinical trials, predominantly conducted in children 12 months to 6 years of age, to produce similar rates of seroconversion to all four vaccine components compared with MMR and monovalent varicella vaccines administered concomitantly at separate injection sites.[28-31] In one comparative study assessing seroresponses to a single MMRV vaccine dose in 12–14-month-old children, the seroresponse rates to measles, mumps and rubella were similar, but varicella seroresponses were lower in Priorix-tetra recipients than in ProQuad recipients.[32] However, the clinical significance of this is not clear, particularly for MMRV given after MMR vaccine.[32]

Information on adverse events related to MMR and MMRV vaccines is provided in 4.9.11 *Adverse events* below, and also in 4.22 *Varicella* (for MMRV).

Trivalent measles-mumps-rubella (MMR) vaccines

- ***M-M-R II*** – CSL Limited/Merck & Co Inc (live attenuated measles virus [Enders' attenuated Edmonston strain], mumps virus [Jeryl Lynn B level strain] and rubella virus [Wistar RA 27/3 strain]). Lyophilised pellet in a monodose vial with separate diluent. Each 0.5 mL reconstituted dose contains ≥1000 tissue culture infectious dose 50% ($TCID_{50}$) of Enders' attenuated Edmonston measles virus, ≥12 500 $TCID_{50}$ of the Jeryl Lynn B level mumps virus, and ≥1000 $TCID_{50}$ of the Wistar RA 27/3 rubella virus; sorbitol; sucrose; hydrolysed gelatin; human albumin; fetal bovine serum; neomycin.
- ***Priorix*** – GlaxoSmithKline (live attenuated measles virus [Schwarz strain], mumps virus [RIT 4385 strain, derived from the Jeryl Lynn strain] and rubella virus [Wistar RA 27/3 strain]). Lyophilised pellet

in a monodose vial with a pre-filled diluent syringe. Each 0.5 mL reconstituted dose contains $\geq 10^{3.0}$ cell culture infectious dose 50% ($CCID_{50}$) of the Schwarz measles virus, $\geq 10^{3.7}$ $CCID_{50}$ of the RIT 4385 mumps virus, and $\geq 10^{3.0}$ $CCID_{50}$ of the Wistar RA 27/3 rubella virus; lactose; neomycin; sorbitol; mannitol.

Quadrivalent measles-mumps-rubella-varicella (MMRV) vaccines

- ***Priorix-tetra*** – GlaxoSmithKline (live attenuated measles virus [Schwarz strain], mumps virus [RIT 4385 strain, derived from the Jeryl Lynn strain], rubella virus [Wistar RA 27/3 strain] and varicella-zoster virus [Oka strain]). Lyophilised pellet in a monodose vial with a pre-filled diluent syringe. Each 0.5 mL reconstituted dose contains $\geq 10^{3.0}$ $CCID_{50}$ of the Schwarz measles virus, $\geq 10^{4.4}$ $CCID_{50}$ of the RIT 4385 mumps virus, $\geq 10^{3.0}$ $CCID_{50}$ of the Wistar RA 27/3 rubella virus, and $\geq 10^{3.3}$ plaque-forming units (PFU) of Oka varicella-zoster virus; lactose; neomycin; sorbitol; mannitol.
- ***ProQuad*** – CSL Limited/Merck & Co Inc (live attenuated measles virus [Enders' attenuated Edmonston strain], mumps virus [Jeryl Lynn B level strain], rubella virus [Wistar RA 27/3 strain] and varicella-zoster virus [Oka/Merck strain]). Lyophilised powder in a monodose vial with a pre-filled diluent syringe. Each 0.5 mL reconstituted dose contains $\geq 10^{3.0}$ $TCID_{50}$ of Enders' attenuated Edmonston measles virus, $\geq 10^{4.3}$ $TCID_{50}$ of the Jeryl Lynn B level mumps virus, $\geq 10^{3.0}$ $TCID_{50}$ of the Wistar RA 27/3 rubella virus, and $\geq 10^{3.99}$ PFU of Oka/Merck varicella virus; sucrose; hydrolysed gelatin; urea; sorbitol; monosodium L-glutamate; human albumin; neomycin; residual components of MRC-5 cells; bovine serum albumin.

4.9.5 Transport, storage and handling

Transport according to *National vaccine storage guidelines: Strive for 5*.[33] Store at +2°C to +8°C. Do not freeze. Protect from light.

Both MMR and MMRV vaccines *must be reconstituted* by adding the entire contents of the diluent container to the vial containing the pellet and shaking until the pellet is completely dissolved.

Reconstituted Priorix (MMR), M-M-R II (MMR) and Priorix-tetra (MMRV) vaccines should be used as soon as practicable. If storage is necessary, hold at +2°C to +8°C for not more than 8 hours.

Reconstituted ProQuad (MMRV) vaccine must be used within 30 minutes.

4.9.6 Dosage and administration

The dose of Priorix (MMR) vaccine for both children and adults is 0.5 mL, to be given by either SC or IM injection.

The dose of M-M-R II (MMR) vaccine for both children and adults is 0.5 mL, to be given by SC injection.

For children <14 years of age, the dose of MMRV vaccine is 0.5 mL, to be given by SC injection. Priorix-tetra may also be given by IM injection.[34]

MMRV vaccines are not recommended for use in persons aged ≥14 years.

When 2 doses of MMR-containing vaccine are required, the minimum interval between doses is 4 weeks.

Co-administration with other vaccines

MMR or MMRV vaccines can be given at the same time as other live attenuated parenteral vaccines (e.g. varicella, BCG, yellow fever) or other inactivated vaccines (including DTPa, hepatitis B, Hib, IPV, MenCCV, hepatitis A and pneumococcal conjugate vaccine),[32] using separate syringes and injection sites. If MMR or MMRV vaccine is not given simultaneously with other live attenuated parenteral vaccines, they should be given at least 4 weeks apart.[35,36]

If MMR vaccine is given at the same time as monovalent varicella vaccine (VV), they should be given using separate syringes and injection sites. MMR vaccine and monovalent VV should *not* be mixed together prior to injection.

Separate administration of measles, mumps or rubella vaccine is not available as an alternative to MMR vaccine, although a monovalent varicella vaccine is available (see 4.22 *Varicella*).

Interchangeability of MMR-containing vaccines

In general, the two brands of MMR vaccine can be considered interchangeable, that is, the 2nd MMR dose does not have to be of the same brand as the 1st. The same principle applies to the two available MMRV vaccines,[32] although they are not routinely recommended in a 2-dose schedule.

4.9.7 Recommendations

For additional recommendations associated with MMRV administration to prevent varicella disease, see 4.22 *Varicella*.

Infants aged <12 months

MMR-containing vaccines are not routinely recommended for infants <12 months of age. However, MMR vaccine can be given to children from as early as 9 months of age in certain circumstances, including travel to highly endemic areas and during outbreaks (see 'Travellers' below, and 4.9.12 *Public health management of measles*).

Two doses of measles-containing vaccine should be administered at ≥12 months of age (see 'Children' below). This is because maternal antibodies to measles are known to persist in many infants until approximately 11 months of age and may interfere with active immunisation before 12 months of age.[2] However, there is some evidence that a dose provided at ≥11 months (but prior to 12 months) of age is sufficiently immunogenic; as such, doses given in this timeframe may not need to be repeated in all circumstances (see also Table 2.1.5 *Minimum acceptable age for the 1st dose of scheduled vaccines in infants in special circumstances*).

Children

Two doses of measles-containing vaccine are recommended for all children. The 1st dose should be given at 12 months of age as MMR vaccine. MMRV vaccines are *not* recommended for use as the 1st dose of MMR-containing vaccine in children <4 years of age, due to a small but increased risk of fever and febrile seizures when given as the 1st MMR-containing vaccine dose in this age group (see 4.9.11 *Adverse events* and Table 4.9.1 below).

The 2nd dose of measles-containing vaccine is recommended to be given routinely at 18 months of age as MMRV vaccine. This is to commence from July 2013 once MMRV vaccine(s) are available under the NIP (see Table 4.9.1 below). The recommended age for administration of the 2nd dose of measles-containing vaccine will be moved down from 4 years of age, to provide earlier 2-dose protection against measles, mumps and rubella, and to improve vaccine uptake (see 4.9.3 *Epidemiology* above).

Catch-up vaccination of children who did not receive the 2nd dose of MMR-containing vaccine at 18 months of age can occur at the 4-year-old schedule point, until all relevant children have reached 4 years of age. Use of MMRV vaccine at the 4-year-old schedule point is preferred when varicella vaccination is also indicated (see 4.22 *Varicella*).

Children >12 months of age who have received 1 dose of MMR vaccine can be offered their 2nd dose of MMR-containing vaccine early (if at least 4 weeks after the 1st dose has elapsed) if they are considered at risk of coming in contact with measles[37] (see 4.9.12 *Public health management of measles* below).

If MMRV vaccine is inadvertently administered as dose 1 of MMR-containing vaccine, the dose does not need to be repeated (providing it was given at ≥12 months of age; see also Table 2.1.5 *Minimum acceptable age for the 1st dose of scheduled vaccines in infants in special circumstances*). However, parents/carers should be advised regarding the small but increased risk of fever and febrile seizures (compared with that expected following MMR vaccine).

Table 4.9.1: Recommendations for measles vaccination with (a) measles-mumps-rubella (MMR) (currently available), and (b) once measles-mumps-rubella-varicella (MMRV) vaccines are available from July 2013

Vaccines	Schedule point (age)		
	12 months	18 months	4 years
(a) Only monovalent varicella vaccine available	MMR	VV	MMR*
(b) When MMRV vaccine available (from July 2013)	MMR	MMRV	–

* The 2nd dose of MMR-containing vaccine is recommended to be provided at 18 months of age to improve 2-dose coverage and protection against measles in young children. However, until June 2013, the 2nd dose of MMR vaccine is included under the NIP schedule for administration at 4 years of age. From July 2013, the 2nd dose of MMR vaccine will move to the 18-month NIP schedule point and be provided as MMRV vaccine.

Adults and adolescents

Persons born before 1966

No vaccination is required for persons born before 1966 (unless serological evidence indicates otherwise), as circulating virus and disease were prevalent before this time, suggesting most persons would have acquired immunity from natural infection. However, confirmed cases of measles have occurred in persons born before 1966[7] and, if doubt exists, it may be more expedient to offer vaccination than serological testing. (See also 'Serological testing for immunity to measles' below.)

Persons born during or since 1966

All persons born during or since 1966 who are ≥18 months of age (or, until catch-up following the move of the 2nd NIP dose of measles-containing vaccine to 18 months of age is completed, are ≥4 years of age) should have documented evidence of 2 doses of MMR-containing vaccine (administered at least 4 weeks apart and with both doses administered at ≥12 months of age; see 'Children' above) or have serological evidence of protection for measles, mumps and rubella.

It is recommended that all adolescents and young adults have their vaccination records reviewed to ensure they have received 2 doses of MMR vaccine (see 4.9.3 *Epidemiology* above).

MMRV vaccines are not recommended for use in persons ≥14 years of age, due to a lack of data on safety and immunogenicity/efficacy in this age group. If a dose of MMRV vaccine is inadvertently given to an older person, this dose does not need to be repeated.

Healthcare workers and other occupations

All adolescents and adults (born during or since 1966) should have their vaccination records reviewed to ensure they have received 2 doses of MMR vaccine. This is important for all persons, but especially those working in certain occupations, such as healthcare workers, staff working in early childhood education and care, staff of long-term care facilities and staff of correctional facilities. Those who were born during or since 1966 and are non-immune, or who have only received 1 dose of MMR vaccine, should be vaccinated and have documented evidence of 2 doses of MMR vaccine *or* serological evidence of immunity to measles (see 'Adults and adolescents' above). (See also 3.3 *Groups with special vaccination requirements*, Table 3.3.7 *Recommended vaccinations for persons at increased risk of certain occupationally acquired vaccine-preventable diseases*.)

Travellers

It is especially important that all persons born during or since 1966 have been given 2 doses of measles-containing vaccine (administered at least 4 weeks apart, with both doses administered at ≥12 months of age; see 'Children' above) before embarking on international travel if they do not have evidence of previous receipt of 2 doses of MMR vaccine or serological evidence of protection for measles, mumps and rubella (see 'Adults and adolescents' above).

Infants travelling to countries in which measles is endemic, or where measles outbreaks are occurring, may be given MMR vaccine from as young as 9 months of age, after an individual risk assessment. In these cases, 2 further doses of MMR vaccine are still required. The next dose of MMR vaccine should be given at 12 months of age or 4 weeks after the 1st dose, whichever is later. This should be followed by the routine administration of the next dose of measles-containing vaccine, as MMRV vaccine, at 18 months of age.

Serological testing for immunity to measles

Serological testing for immunity to measles, mumps, rubella or varicella is not recommended before or after routine administration of the 2-dose childhood schedule of these vaccines.

However, serological testing for measles can be performed in cases where a history of natural immunity or 2 doses of vaccine administration is uncertain (see 'Adults and adolescents' above). Serology is indicated in special situations, such as pre-pregnancy planning (see also 4.18 *Rubella*, 4.22 *Varicella* and 3.3.2 *Vaccination of women who are planning pregnancy, pregnant or breastfeeding, and preterm infants*). Serological tests to investigate immunity to measles are generally sensitive at detecting antibody produced by both prior natural infection and vaccination, although sensitivity varies by assay and the clinical setting (e.g. time since vaccination).[2] Interpretation of the results of serological testing may be enhanced by discussion with the laboratory that performed the test, ensuring that relevant clinical information is provided. An alternative to serological testing is presumptive administration of MMR vaccine dose(s). There is no known

increase in adverse events from vaccinating those with pre-existing immunity to one or more of the vaccine components (see 4.9.11 *Adverse events* below).

4.9.8 Pregnancy and breastfeeding

MMR-containing vaccines are contraindicated in pregnant women. Pregnancy should be avoided for 28 days after vaccination.[38]

MMR vaccines can be given to breastfeeding women. (See also 4.18 *Rubella*.)

MMRV vaccines are not recommended for use in persons aged ≥14 years.

There is no risk to pregnant women from contact with recently vaccinated persons. The vaccine virus is not transmitted from vaccinated persons to susceptible contacts.[1]

See also 4.18 *Rubella*, 4.22 *Varicella* and 3.3 *Groups with special vaccination requirements*, Table 3.3.1 *Recommendations for vaccination in pregnancy* for more information.

4.9.9 Contraindications

Anaphylaxis to vaccine components

MMR and MMRV vaccines are contraindicated in persons who have had:

- anaphylaxis following a previous dose of any MMR-containing vaccine
- anaphylaxis following any vaccine component.

Persons who are immunocompromised

Measles-, mumps- and rubella-containing vaccines contain live attenuated vaccine viruses and are contraindicated in persons who are immunocompromised. Thus, MMR-containing vaccines are contraindicated in the following groups:

- Persons immunocompromised due to HIV/AIDS. MMR vaccination of asymptomatic HIV-infected persons >12 months of age with an age-specific $CD4^+$ count of ≥15% may be considered[39-42] (see 'HIV-infected persons' in 3.3.3 *Vaccination of immunocompromised persons*). Since studies have not been performed using combination MMRV vaccines in asymptomatic HIV-infected persons or persons with an age-specific $CD4^+$ count of ≥15%, it is recommended that only MMR vaccine (and monovalent VV, see 4.22 *Varicella*) be considered for use in this setting.[41,43-45]
- Persons with other medical conditions associated with significant immunocompromise (see 3.3.3 *Vaccination of immunocompromised persons*).
- Persons receiving high-dose systemic immunosuppressive therapy, such as chemotherapy, radiation therapy or oral corticosteroids. MMR-containing vaccines are contraindicated in persons taking high-dose oral corticosteroids for more than 1 week (in children equivalent to >2 mg/kg per day prednisolone, and in adults >60 mg per day) (see 3.3.3 *Vaccination*

of immunocompromised persons). Those who have been receiving high-dose systemic steroids for more than 1 week may be vaccinated with live attenuated vaccines after corticosteroid therapy has been discontinued for at least 1 month[46] (see 4.9.10 *Precautions* below and 3.3.3 *Vaccination of immunocompromised persons*).

See also 3.3 *Groups with special vaccination requirements* and 4.22 *Varicella* for more information.

Pregnant women

See 4.9.8 *Pregnancy and breastfeeding* above.

4.9.10 Precautions

Persons with egg allergy

Children with egg allergy can be safely given MMR or MMRV vaccine.[1,47] Skin testing is not required prior to vaccine administration.[1] Although measles and mumps (but not rubella or varicella) vaccine viruses are grown in chick embryo tissue cultures, it is now recognised that measles- and mumps-containing vaccines contain negligible amounts of egg ovalbumin (see 4.9.13 *Variations from product information* below).

Vaccination with other live attenuated parenteral vaccines

If MMR or MMRV vaccine is not given simultaneously with other live attenuated parenteral vaccines (e.g. varicella, BCG, yellow fever), the vaccines should be given at least 4 weeks apart.

Vaccination after immunoglobulin or blood product administration

Administration of MMR or MMRV vaccine should be delayed after administration of immunoglobulin-containing products. After receipt of immunoglobulin-containing blood products, the expected immune response to measles, mumps, rubella and varicella vaccination may be impaired.[25,35,48] MMR-containing vaccines should not be given for between 3 and 11 months following the administration of immunoglobulin-containing blood products. The interval between receipt of the blood product and vaccination depends on the amount of immunoglobulin in each product, and is indicated in 3.3 *Groups with special vaccination requirements*, Table 3.3.6 *Recommended intervals between either immunoglobulins or blood products and MMR, MMRV or varicella vaccination*.[35] For further information, see 3.3.4 *Vaccination of recent recipients of normal human immunoglobulin and other blood products*.

Recent blood transfusion with washed red blood cells is *not* a contraindication to MMR or MMRV vaccines.

MMR vaccine may be administered concomitantly with, or at any time in relation to, anti-D immunoglobulin, but at a separate injection site. Anti-D immunoglobulin does not interfere with the antibody response to vaccine.

Immunoglobulin or blood product administration after vaccination

Immunoglobulin-containing products should not be administered for 3 weeks following vaccination with measles-containing vaccines, unless the benefits exceed those of vaccination. If immunoglobulin-containing products are administered within this interval, the vaccinated person should either be revaccinated later at the appropriate time following the product (as indicated in Table 3.3.6), or be tested for immunity 6 months later and then revaccinated if seronegative.

Rh (D) immunoglobulin (anti-D) may be given at the same time in different sites with separate syringes or at any time in relation to MMR vaccine, as it does not interfere with the antibody response to the vaccine.

HIV-infected persons

MMR vaccine can be given to asymptomatic HIV-infected persons >12 months of age with an age-specific $CD4^+$ count of ≥15%[49] (see 3.3 *Groups with special vaccination requirements*, Table 3.3.4 *Categories of immunocompromise in HIV-infected persons, based on age-specific $CD4^+$ counts and percentage of total lymphocytes*). This is because the risk posed by measles infection is considered to be greater than the likelihood of adverse events from vaccination.[46] MMR vaccine is contraindicated in immunocompromised HIV-infected persons (see 4.9.9 *Contraindications* above).

As there are no data available on the safety, immunogenicity or efficacy of MMRV vaccines in HIV-infected children, MMRV vaccine should not be administered as a substitute for MMR vaccine when vaccinating these children.[25,48]

Persons receiving immunosuppressive therapy

MMR-containing vaccines may be given to persons on low-dose systemic corticosteroid therapy (e.g. children on doses of ≤2 mg/kg per day for less than 1 week, and those on lower doses of 1 mg/kg per day or alternate-day regimens for longer periods). Persons receiving high-dose corticosteroids can receive MMR-containing vaccines after corticosteroid therapy has been discontinued for at least 1 month (see 4.9.9 *Contraindications* above).[46] Some experts suggest withholding lower doses of steroids 2 to 3 weeks prior to vaccination with live viral vaccines, if this is possible.[46,48] (See also 3.3.3 *Vaccination of immunocompromised persons*.)

Household contacts of persons who are immunocompromised

Household contacts of persons who are immunocompromised, should ensure that they are age-appropriately vaccinated against, or are immune to, measles, as well as mumps, rubella and varicella. MMR-containing vaccines can be safely administered to household contacts, as measles, mumps and rubella vaccine viruses are not transmissible from vaccinated persons to others.[25] If using MMRV vaccine, see 4.22 *Varicella* for information regarding varicella vaccine virus transmission.

Persons receiving long-term aspirin or salicylate therapy

There is no need to avoid salicylates before or after MMR or MMRV vaccination. Persons receiving long-term salicylate therapy (aspirin) can be vaccinated with MMRV, if indicated, as the benefit is likely to outweigh any possible risk of Reye syndrome occurring after vaccination with a varicella-containing vaccine (see 4.22 *Varicella*).

Persons with a history of thrombocytopenia

Thrombocytopenia is a rare adverse event following MMR vaccination (see also 4.9.11 *Adverse events* below).[1,50,51] In children with a past history of an episode(s) of idiopathic thrombocytopenia purpura (ITP), the risk of vaccine-associated thrombocytopenia occurring following a dose of MMR vaccine has been uncertain.[25,51] However, a recent systematic review concluded that MMR vaccination, either as a 1st or 2nd dose, did not lead to a recurrence of ITP.[52]

Personal or close family history of seizures or convulsions

Children with a personal or close family history of seizures or convulsions should be given MMR or MMRV vaccine, provided the parents/carers understand that there may be a febrile response 5 to 12 days after vaccination.[25] Advice should be given regarding reducing fever with paracetamol and other measures. Due to an increased risk of fever and febrile convulsions in 1st dose recipients of MMRV vaccine, MMRV vaccines are only recommended for use as the 2nd dose of MMR-containing vaccine (see 4.9.7 *Recommendations* above and 4.9.11 *Adverse events* below).

Tuberculin skin testing following MMR vaccination

Measles virus inhibits the response to tuberculin and tuberculin-positive persons may become tuberculin-negative for up to a month after measles infection.[25,53] As such, tuberculin skin testing (Mantoux test) may be unreliable for at least 4 weeks after the administration of measles-containing vaccines. There are no studies on the effect of MMR or MMRV vaccination on the results of interferon-gamma release assays (IGRAs).[54]

4.9.11 Adverse events

If using MMRV vaccine, additional adverse events relating to the varicella vaccine component are outlined in 4.22 *Varicella*.

Adverse events following administration of MMR-containing vaccines are generally mild and well tolerated.[2] Adverse events are much less common after the 2nd dose of MMR or MMRV vaccine than after the 1st dose.

Fever (with malaise and/or a rash, which is non-infectious) may occur after MMR vaccination, most commonly between 7 to 10 days (range 5 to 12 days) after vaccination and lasting about 2 to 3 days. This coincides with the period of peak measles vaccine virus replication. High fever (>39.4°C) occurs in approximately 5 to 15% of MMR vaccine recipients, and rash occurs in

approximately 5%.[2,25] There is also an increased risk for febrile seizures in the same time period of approximately 1 case per 3000 doses.[25]

It is recommended that vaccine recipients or their parents/carers be advised about possible symptoms, and given advice for reducing fever, including the use of paracetamol for fever in the period 5 to 12 days after vaccination.

Higher rates of fever were observed in clinical trials of both MMRV vaccines, particularly following dose 1, when compared with giving MMR vaccine and monovalent VV at the same time but at separate sites.[28-31] Two post-marketing studies in the United States identified an approximately 2-fold increased risk of fever and febrile convulsions in 1st dose recipients of MMRV vaccine, who were predominantly 12–23 months of age, in the period 7 to 10 days[55] (or 5 to 12 days)[56] after vaccination, compared with recipients of separate MMR and VV vaccines. MMRV vaccination resulted in 1 additional febrile seizure for every 2300 doses compared to separate MMR and VV vaccination.[55] An increase in fever or febrile convulsions has not been identified after the 2nd dose of MMRV vaccine in the United States, although most 2nd dose recipients were aged 4–6 years, an age at which the incidence of febrile convulsions is low.[57] These post-marketing studies were in children who received ProQuad; however, it is anticipated that this side effect profile would be similar in Priorix-tetra recipients.

A varicelliform rash may occur after MMRV vaccination (see 4.22.11 *Adverse events* in 4.22 *Varicella*). The appearance of a rash after monovalent varicella vaccine occurs in less than 5% of vaccine recipients (usually within 5 to 26 days), and similar rates are observed with the use of MMRV vaccine.[58]

Anaphylaxis following the administration of MMR vaccine is very rare (less than 1 in 1 million doses distributed).[25] Although no cases of anaphylaxis were reported in MMRV vaccine clinical trials, the incidence is likely to be similar to that occurring with use of MMR vaccine. Anaphylaxis after vaccination is likely due to anaphylactic sensitivity to gelatin or neomycin, not egg allergy (see 4.9.10 *Precautions* above).

Thrombocytopenia (usually self-limiting) has been very rarely associated with the rubella or measles component of MMR vaccine, occurring in 3 to 5 per 100 000 doses of MMR vaccine administered.[1,25,50,51] This is considerably less frequent than after natural measles, mumps and rubella infections.[51] Any association with MMRV vaccine is expected to be similar.

It is uncertain whether encephalopathy occurs after measles vaccination. If it does, it is at least 1000 times less frequent than as a complication from natural infection.[2,25]

Other rare adverse events attributed to MMR vaccine include transient lymphadenopathy and arthralgia (see 4.18 *Rubella*). Parotitis has been reported rarely (see 4.11 *Mumps*).[25]

Autism, autistic spectrum disorder and inflammatory bowel disease are not associated with the MMR vaccine. There has been no credible scientific evidence to support this claim and most proponents of the link have retracted this claim.[59,60] There is now a substantial body of evidence to refute it[61-64] (see Appendix 4 *Commonly asked questions about vaccination*).

4.9.12 Public health management of measles

Measles is a notifiable disease in all states and territories in Australia. The public health management of measles is described in *Measles: national guidelines for public health units*[37] (www.health.gov.au/cdnasongs) and is given urgent public health priority. Refer to the national guidelines for current case definitions, testing and post-exposure prophylaxis of contacts.

Further instructions about the public health management of measles can also be obtained from state/territory public health authorities (see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*).

MMR vaccine (and MMRV in some instances) is recommended for post-exposure prophylaxis within 72 hours of a non-immune individual being exposed to measles. See Table 4.9.2 for detailed information. Administration of normal human immunoglobulin (NHIG), rather than MMR or MMRV, is recommended in some settings (see Part 5 *Passive immunisation* and Table 4.9.2).[37] Post-exposure prophylaxis should be given on the direction of public health authorities.

Children >12 months of age who have received 1 dose of measles-containing vaccine can be offered their 2nd dose early (if at least 4 weeks after the 1st dose has elapsed) if they are considered at risk of coming in contact with measles[37] (see 4.9.7 *Recommendations* above and Table 4.9.2). If varicella vaccination is also indicated, MMRV vaccine can be used, although MMRV vaccine is not routinely recommended as the 1st dose of MMR-containing vaccine in children aged <4 years (see 4.9.7 *Recommendations* above). If a child receives the 2nd dose of measles-containing vaccine early, they are considered to have completed their vaccination schedule and therefore do not require another dose at 18 months of age or beyond, provided that the 2 doses were given at ≥12 months of age and at least 4 weeks apart.

Table 4.9.2: Post-exposure prophylaxis ≤72 hours since exposed to measles for non-immune individuals (adapted from *Measles: national guidelines for public health units*)[37]

Age or immune status	Measles-mumps-rubella (MMR) vaccination history		
	0 doses MMR or unknown	1 dose MMR	2 doses MMR
Immunocompromised (any age)	Normal human immunoglobulin (NHIG) 0.5 mL/kg to maximum of 15 mL	NHIG 0.5 mL/kg to maximum of 15 mL	NHIG 0.5 mL/kg to maximum of 15 mL
Birth to 5 months	NHIG 0.2 mL/kg ***only*** if mother has had <2 doses of MMR and no history of past measles infection, otherwise *no* NHIG	Not applicable	Not applicable
6 to 8 months	NHIG 0.2 mL/kg	Not applicable	Not applicable
9 to 11 months	MMR now, then another dose at 12 months of age or 4 weeks later (whichever is later)*	Not applicable	Not applicable
12 months to <4 years	MMR*	MMR (or MMRV) (*unless* 1st dose was given <4 weeks ago)	Nil necessary
≥4 years and born during or since 1966	MMR if not pregnant* If pregnant, offer NHIG (0.2 mL/kg to a maximum of 15 mL) and inform obstetrician or GP	MMR if not pregnant If pregnant, offer NHIG (0.2 mL/kg to a maximum of 15 mL) and inform obstetrician or GP	Nil necessary

* A subsequent dose of MMR-containing vaccine (MMR or MMRV) should be provided at least 4 weeks after the 1st valid dose (a valid dose is one given at ≥12 months of age) to complete a 2-dose vaccine schedule (see 4.9.7 *Recommendations* above).

4.9.13 Variations from product information

The product information for MMR and MMRV vaccines recommends that women of child-bearing age should be advised not to become pregnant for 3 months after vaccination. The ATAGI instead recommends avoiding pregnancy for 28 days after vaccination.[38]

The product information for Priorix, M-M-R II, Priorix-tetra and ProQuad states that persons with a history of anaphylactic or anaphylactoid reactions to egg should not be vaccinated. The ATAGI recommends instead that either Priorix, M-M-R II, Priorix-tetra or ProQuad can be given in this situation.[25]

The product information for Priorix-tetra states that it should be given by SC injection. The ATAGI recommends that it may also be given by IM injection.

The product information for ProQuad states that this vaccine is indicated for vaccination in individuals 12 months through 12 years of age. The product information for Priorix-tetra states that this vaccine can be used in persons from 9 months of age. The ATAGI recommends instead that both MMRV vaccines can be given to persons up to 14 years of age. The ATAGI also recommends that MMRV vaccine should *not* be used routinely as the 1st dose of MMR-containing vaccine in children aged <4 years.

The product information for both MMRV vaccines states that salicylates should be avoided for 6 weeks after vaccination, as Reye syndrome has been reported following the use of salicylates during natural varicella infection. The ATAGI recommends instead that non-immune persons receiving long-term salicylate therapy can receive varicella-containing vaccine, as the benefit is likely to outweigh any possible risk of Reye syndrome occurring after vaccination.

References

A full reference list is available on the electronic *Handbook* or website www.immunise.health.gov.au

4.10 MENINGOCOCCAL DISEASE

4.10.1 Bacteriology

Meningococcal disease is caused by the bacterium *Neisseria meningitidis* (or meningococcus), a Gram-negative diplococcus. There are 13 known serogroups distinguished by differences in surface polysaccharides of the outer membrane capsule. Meningococcal serogroups are designated by letters of the alphabet. Globally, serogroups A, B, C, W_{135} and Y most commonly cause disease. Meningococci can be further classified by differences in their outer membrane proteins, which are referred to as serotypes and serosubtypes.[1] More recently, molecular typing has been used to further differentiate meningococci. There is no consistent relationship between serogroup or serotype/subtype and virulence.[2]

4.10.2 Clinical features

N. meningitidis can cause meningitis, septicaemia or a combination of the two. Other localised infections, including pneumonia, arthritis and conjunctivitis, may also occur but are uncommon. Septicaemia, with or without meningitis, can be particularly severe. The overall mortality risk for invasive disease is high (between 5 and 10%), despite appropriate antibiotic therapy.[2] Of those who survive, approximately 10 to 20% develop permanent sequelae, including limb deformity, skin scarring and neurologic deficits.[1] Prior invasive meningococcal disease does not induce protective immunity against the implicated serogroup of meningococci. Therefore, persons with a history of meningococcal disease should still be vaccinated if required.

N. meningitidis is carried and transmitted only by humans. There are no known animal reservoirs. Asymptomatic respiratory tract carriage of meningococci is present in about 10% of the population, and the prevalence may be higher when groups of people occupy small areas of living space.[3,4] Recent studies indicate that there may be a number of factors that contribute to the increased risk of contracting meningococcal disease, including exposure to smokers, recent illness, living in crowded conditions and multiple intimate kissing partners.[2-4] Persons with inherited disorders of phagocytosis associated with properdin deficiency or absence of the terminal components of complement, as well as persons with functional or anatomical asplenia, have an increased risk of meningococcal infection.[1]

The disease is transmitted via droplets and has an incubation period of between 1 and 10 days, but commonly 3 to 4 days.[4] The capacity of meningococcal disease to have a fulminant and rapidly fatal course in previously healthy (and usually young) persons causes it to be greatly feared. Intensive public health follow-up is required after each single case to trace contacts and to institute appropriate public health measures for them. As a result of all these factors, this disease can cause widespread community alarm and generate significant media interest.[4]

4.10.3 Epidemiology

Meningococci cause both sporadic and epidemic disease throughout the world. Serogroup A disease occurs predominantly in low-income countries, such as those in Africa and Asia, while serogroup B is the major cause of sporadic meningococcal disease in most developed countries, including Australia. Serogroup C meningococci have been occasionally associated with small clusters of meningococcal disease cases in schools, universities and nightclubs in Australia in the past.[5-7] Rarely, there are clusters of meningococcal disease cases associated with serogroup B.[8]

As in other temperate climates, meningococcal disease cases occurring in Australia tend to follow a seasonal trend, with a large proportion of cases reported during late winter and early spring. The overall notification rate for invasive meningococcal disease to the National Notifiable Diseases Surveillance System reached a peak of 3.5 per 100 000 in 2001, but declined to 1 case per 100 000 in 2010.[9,10] There have been considerable differences noted in the incidence of meningococcal disease between Australian states and territories in the past. Notifications include meningococcal disease cases that were diagnosed on clinical grounds alone, and those cases that were confirmed by laboratory methods such as culture, serology or nucleic acid testing of clinical material. In 2009, 259 cases were reported nationally, of which 194 were laboratory-confirmed.[9,10] The majority of laboratory-confirmed meningococcal cases were serogroup B (83%) and serogroup C (5.6%).[10] There has been a sustained decline in serogroup C meningococcal disease among the 1–19 years age group, as well as other age groups not targeted in the vaccine program, since the 2003 introduction of routine serogroup C vaccination and catch-up programs.[9-11] In other countries that introduced a meningococcal C vaccination program, this herd immunity effect has also resulted in a reduction in incidence in age groups not targeted by the program.[12-14]

Meningococcal disease can occur in any age group, but a large proportion of cases occur in those <5 years of age, with a secondary peak seen in the 15–24 years age group.[10] In Australia, meningococcal disease in the <5 years age group is due predominantly to infection with serogroup B meningococci; very few cases of serogroup C meningococcal disease are now seen in this age group.[10,11] In the 15–19 years age group, both serogroup B and C disease were seen before the introduction of the meningococcal C conjugate vaccine in 2003. In contrast to Australia, New Zealand experienced an epidemic of meningococcal disease that was almost exclusively associated with a particular strain of serogroup B (B:4:P1.7b,4).[15,16] A meningococcal outer membrane vesicle vaccine (MeNZB) was used exclusively in New Zealand, and the program ceased in 2008.[15,16] This vaccine was only known to be effective against the serotype and serosubtype of the New Zealand serogroup B strain and was not available in Australia.

4.10.4 Vaccines

There are different types of meningococcal vaccines:

- meningococcal C conjugate vaccines (MenCCV)
- *Haemophilus influenzae* type b–meningococcal C combination vaccine (Hib-MenCCV)
- quadrivalent meningococcal conjugate vaccines (4vMenCV)
- quadrivalent meningococcal polysaccharide vaccines (4vMenPV).

Conjugate vaccines

Meningococcal C conjugate vaccines (MenCCV)

- ***Meningitec*** – Pfizer Australia Pty Ltd (meningococcal serogroup C–CRM_{197} conjugate). Each 0.5 mL pre-filled syringe contains 10 µg *Neisseria meningitidis* serogroup C oligosaccharide conjugated to approximately 15 µg of non-toxic *Corynebacterium diphtheriae* CRM_{197} protein; aluminium phosphate.
- ***Menjugate Syringe*** – CSL Limited/Novartis Vaccines and Diagnostics Pty Ltd (meningococcal serogroup C–CRM_{197} conjugate). Lyophilised powder in a monodose vial with a pre-filled diluent syringe. Each 0.5 mL reconstituted dose contains 10 µg *N. meningitidis* serogroup C oligosaccharide conjugated to 12.5–25 µg of non-toxic *C. diphtheriae* CRM_{197} protein; 1.0 mg aluminium hydroxide.
- ***NeisVac-C*** – Baxter Healthcare (meningococcal serogroup C–tetanus toxoid conjugate). Each 0.5 mL pre-filled syringe contains 10 µg *N. meningitidis* serogroup C polysaccharide conjugated to 10–20 µg of tetanus toxoid; 0.5 mg aluminium as aluminium hydroxide.

Combination vaccine that contains meningococcal C

- ***Menitorix*** – GlaxoSmithKline (*Haemophilus influenzae* type b [PRP-T]-meningococcal serogroup C–tetanus toxoid conjugate). Lyophilised powder in a monodose vial with a pre-filled diluent syringe. Each 0.5 mL reconstituted dose contains 5 µg Hib capsular polysaccharide (PRP) conjugated to 12.5 µg tetanus toxoid, and 5 µg *N. meningitidis* serogroup C polysaccharide conjugated to 5 µg tetanus toxoid; traces of trometamol and sucrose.

Quadrivalent meningococcal conjugate vaccines (4vMenCV)

- ***Menactra*** – Sanofi Pasteur Pty Ltd (meningococcal serogroups A, C, W_{135}, Y–diphtheria toxoid conjugate). Each 0.5 mL monodose vial

contains 4 µg each of serogroups A, C, W_{135} and Y polysaccharides conjugated with a total of approximately 48 µg of a diphtheria toxoid protein.

- ***Menveo*** – CSL Limited/Novartis Vaccines and Diagnostics Pty Ltd (meningococcal serogroups A, C, W_{135}, Y–CRM_{197} conjugate). Lyophilised powder containing serogroup A (MenA) in a monodose vial with a pre-filled syringe or vial containing serogroups C, W_{135} and Y (MenCWY) in saline suspension. Each 0.5 mL reconstituted dose contains 10 µg of serogroup A and 5 µg each of serogroups C, W_{135} and Y oligosaccharides individually conjugated with up to 33.3 µg of non-toxic *C. diphtheriae* CRM_{197} protein; sucrose.

All conjugate vaccines induce immunity within 10 to 14 days of administration.

MenCCVs confer protection *only* against serogroup C disease. 4vMenCVs will provide protection against four serogroups of meningococci: serogroups A, C, W_{135} and Y. Neither MenCCV nor 4vMenCV will provide protection against serogroup B meningococcal disease.

MenCCVs have been used in an infant schedule in many countries, including Australia.[11-13,17-19] The vaccine effectiveness following 1 dose of MenCCV has been estimated to range from 83 to 100%.[13,17] There has been a sustained decline in serogroup C meningococcal disease, which has also been observed in age groups not targeted in vaccination programs, both in Australia and overseas.[11,14] Duration of immunity is still uncertain. However, current serogroup C meningococcal disease epidemiology in Australia suggests ongoing protection in those groups previously vaccinated.[11]

Hib-MenCCV can be administered where a booster dose of *H. influenzae* type b and primary vaccination for meningococcal serogroup C is required. The immunogenicity and safety of Hib-MenCCV as a booster dose has been demonstrated in clinical trials and in the United Kingdom, where this vaccine is now administered as part of the infant schedule.[20-25]

Several clinical trials have demonstrated the immunogenicity of 4vMenCV, with human serum bactericidal assay titres of ≥1:4 reported in adolescents and young adults.[26-28] There have been a number of studies examining 4vMenCV in children.[29-31] All studies indicated that 4vMenCVs were safe and immunogenic in both infants and children.[29-33] Menveo has demonstrated superiority to Menactra in serum bactericidal assays to serogroups A, W_{135} and Y (and variably also to serogroup C); however, the clinical relevance of this is currently unknown.[27,34-36]

Polysaccharide vaccines

Quadrivalent meningococcal polysaccharide vaccines (4vMenPV)

- ***Mencevax ACWY*** – GlaxoSmithKline (meningococcal serogroups A, C, W_{135} and Y polysaccharides). Lyophilised pellet in a monodose vial with separate saline diluent. Each 0.5 mL reconstituted dose contains 50 µg of each meningococcal serogroup polysaccharide; 12.6 mg sucrose; 0.1 mg trometamol.
- ***Menomune*** – Sanofi Pasteur Pty Ltd (meningococcal serogroups A, C, W_{135} and Y polysaccharides). Lyophilised powder in a monodose vial with separate saline diluent. Each 0.5 mL reconstituted dose contains 50 µg of each meningococcal serogroup polysaccharide; 2.5–5 mg lactose.

4vMenPV provides protection against serogroups A, C, W_{135} and Y. These vaccines induce antibodies in 10 to 14 days in 90% of recipients >2 years of age. Immunity decreases markedly during the first 3 years following a single dose of vaccine, particularly in infants and young children. However, clinical protection persists for at least 3 years in school-aged children and adults.

The duration of immunity is further complicated by the induction of immunological hyporesponsiveness to the serogroup C component following repeated vaccination with 4vMenPV, as revaccination results in a reduced antibody response compared with the primary immunisation.[37] This phenomenon has been noted in both children and adults.[38-40] The demonstration of subsequent hyporesponsiveness has led to the concern that vaccinating persons at low risk may reduce the effectiveness of revaccination in a subsequent high-risk situation, although this has not been clinically demonstrated. This hyporesponsiveness can be overcome with meningococcal conjugate vaccines,[38] although additional doses of a conjugate vaccine may be required in young children. There is little response to the serogroup C component of the 4vMenPV before 18 months of age and little response to serogroup A before 3 months of age.[41]

4.10.5 Transport, storage and handling

Transport according to *National vaccine storage guidelines: Strive for 5*.[42] Store at +2°C to +8°C. Do not freeze. Protect from light.

Conjugate vaccines

Menjugate Syringe *must be reconstituted* by adding the entire contents of the diluent syringe to the vial and shaking until the powder is completely dissolved. Reconstituted vaccine should be used immediately.

The product information for NeisVac-C states that this vaccine can be stored at +25°C for a period of up to 9 months. *Refer to product information for further vaccine storage details.*

Menitorix *must be reconstituted* by adding the entire contents of the diluent syringe to the vial and shaking until the powder is completely dissolved. Reconstituted vaccine should be used as soon as practicable. If storage is necessary, hold at +2°C to +8°C for not more than 24 hours.

Menveo *must be reconstituted* by adding the entire contents of the liquid MenCWY syringe/vial to the lyophilised MenA vial and shaking until the powder is completely dissolved. Reconstituted vaccine should be used as soon as practicable. If storage is necessary, hold at +2°C to +8°C for not more than 24 hours.

Polysaccharide vaccines

Mencevax ACWY *must be reconstituted* by adding the entire contents of the diluent container to the vial and shaking until the powder is completely dissolved. Reconstituted vaccine should be used as soon as practicable. If storage is necessary, hold at +2°C to +8°C for not more than 8 hours.

Menomune *must be reconstituted* by adding the entire contents of the diluent container to the vial and shaking until the powder is completely dissolved. Reconstituted vaccine must be used within 24 hours.

4.10.6 Dosage and administration

Conjugate vaccines

The dose of all meningococcal conjugate vaccines (MenCCV, Hib-MenCCV, 4vMenCV) is 0.5 mL to be given by IM injection. Do not mix with other vaccines in the same syringe.

MenCCVs are registered for use in infants from 6 weeks of age. Hib-MenCCV is registered for use in infants from 6 weeks of age, and can be administered as the primary dose of serogroup C meningococcal vaccine and the booster dose of Hib vaccine.

Both 4vMenCVs may be given from 9 months of age (see 4.10.12 *Variations from product information* below).

Either MenCCV or Hib-MenCCV may be administered simultaneously with other vaccines in the NIP schedule (see 4.10.12 *Variations from product information* below).

Polysaccharide vaccines

The dose of both 4vMenPVs is 0.5 mL, to be given by SC injection.

4vMenPVs are registered for use in children ≥2 years of age, adolescents and adults.

4vMenPV may also be co-administered with other vaccines.

Interchangeability of meningococcal vaccines

Experience from the use of conjugate Hib vaccines suggests that the different brands of conjugate meningococcal vaccines are interchangeable.

There are limited data available on the length of time that should elapse before administration of 4vMenCV after giving MenCCV. The ATAGI recommends a minimum period of 8 weeks before 4vMenCV is given.

There are limited data available on the length of time that should elapse before administration of either MenCCV or 4vMenCV after giving 4vMenPV. A minimum period of 6 months is recommended before conjugate vaccine is given.[37,39,40]

4.10.7 Recommendations

Previous meningococcal disease, regardless of the serogroup, is *not* a contraindication to the administration of any meningococcal vaccine.

Meningococcal C conjugate-containing vaccines

Children aged 12 months

It is recommended that a single dose of MenCCV or Hib-MenCCV be given to all children at the age of 12 months.

Hib-MenCCV is administered as a single dose at 12 months of age where a booster dose of Hib and the primary dose of serogroup C meningococcal vaccine are required.

Vaccination before 12 months of age is not recommended, except in infants with inherited defects of properdin or complement, or functional or anatomical asplenia (see 'Persons at high risk for meningococcal disease' below).[43,44] Infants, other than those described in the circumstances below, who receive dose(s) of vaccine at <12 months of age should be given a further dose at 12 months of age or a minimum of 8 weeks after the last dose, whichever is later. However, it is not necessary to recall older children who received 3 doses of MenCCV before 12 months of age, as there has been no evidence to date of vaccine failure in infants vaccinated according to a 2, 4, 6 months schedule.

Persons at high risk for meningococcal disease

MenCCV is recommended for persons in the following situations:

- Close (household or household-like) contacts of meningococcal disease cases due to serogroup C, who are ≥6 weeks of age and who have not previously been vaccinated. A single dose of MenCCV is recommended under these circumstances, and in other instances where required for the control of disease outbreaks caused by serogroup C meningococci (refer to *Guidelines for the early clinical and public health management of meningococcal disease in Australia*).[2]

- Infants from 6 weeks to 12 months of age who have medical conditions that put them at high risk of meningococcal disease, such as functional or anatomical asplenia[43] or inherited defects of properdin or complement, persons receiving treatment with eculizumab (a monoclonal antibody directed against complement component C5),[45] or those post haematopoietic stem cell transplant (HSCT), are recommended to receive up to 2 doses of MenCCV vaccine prior to 12 months of age. (See also 3.3 *Groups with special vaccination requirements*.)

  Infants with these conditions who are 6 weeks to <6 months of age require 2 doses of MenCCV, given at least 8 weeks apart, followed by a dose of 4vMenCV at 12 months of age. Those who are 6 to 11 months of age, and have not previously received MenCCV, require 1 dose of MenCCV, followed by a dose of 4vMenCV at 12 months of age or 8 weeks after the 1st dose, whichever is later.

  Infants who received a dose of MenCCV, rather than 4vMenCV, at 12 months of age, should be vaccinated with 2 subsequent doses of 4vMenCV (see 'Quadrivalent meningococcal conjugate and polysaccharide vaccines' below and 3.3 *Groups with special vaccination requirements*).

Booster doses

Currently there are no indications for booster doses following either MenCCV or Hib-MenCCV. Studies assessing whether there is a need for booster doses are being conducted.

Quadrivalent meningococcal conjugate and polysaccharide vaccines

Routine vaccination with 4vMenCV or 4vMenPV is not recommended.[46] Where not otherwise contraindicated, a single dose of 4vMenCV should be administered in preference to 4vMenPV. A single dose of 4vMenCV, unless otherwise stated, is recommended for persons in the following situations:

- Laboratory personnel who frequently handle *N. meningitidis*.[2]
- Travellers (aged ≥9 months) who intend visiting parts of the world where epidemics of group A, W_{135} or Y disease are frequent (a current list of those countries is available from the World Health Organization at either www.who.int/ith or www.who.int/disease-outbreak-news).
- Close (household or household-like) contacts, aged ≥9 months of age,[47] of cases of serogroup A, W_{135} or Y meningococcal disease, or in outbreaks caused by these serogroups. Use 4vMenCV in preference to 4vMenPV in these circumstances, unless the latter is the only vaccine available.[2]
- Pilgrims attending the annual Hajj in Saudi Arabia. Saudi Arabian authorities require a valid certificate of vaccination as a condition to enter the country. Requirements are published in the World Health Organization *Weekly Epidemiological Record* annually. Follow links under publications at www.who.int/ith.

- Children (aged ≥9 months) and adults with high-risk medical conditions, such as functional or anatomical asplenia[43,44] or complement component disorders (C5-C9, properdin, factor D or factor H), persons receiving treatment with eculizumab (a monoclonal antibody directed against complement component C5),[45] or those post HSCT. In persons with these risk factors, a 2-dose primary schedule of 4vMenCV is recommended, with doses given approximately 8 weeks apart.[48] Give 4vMenCV at least 8 weeks after any previous MenCCV doses. In young children who have received 1 or more doses of MenCCV prior to 12 months of age, the 1st dose of 4vMenCV is recommended at 12 months of age. The 2nd 4vMenCV dose should be provided by 18 months of age. (See also 3.3 *Groups with special vaccination requirements* and Table 3.3.5 *Recommendations for vaccination in persons with functional or anatomical asplenia*.) For persons who have previously received a dose of 4vMenPV, a booster dose of 4vMenCV, 3 years after the last dose of 4vMenPV, is recommended (see 'Booster doses or revaccination' below).

Where 4vMenCV is contraindicated, a single dose of 4vMenPV can be given to persons aged ≥2 years, unless otherwise indicated.

Booster doses or revaccination

Although the duration of protection following 4vMenCV remains unknown, persons with medical conditions that place them at high risk of meningococcal disease (as described above) who have completed a 2-dose primary schedule of 4vMenCV, should receive 4vMenCV at 5-yearly intervals thereafter, until further data becomes available.[36,49,50] This includes high-risk infants who have received MenCCV in infancy, followed by 2 doses of 4vMenCV in the 2nd year of life. (See also 3.3 *Groups with special vaccination requirements* and Table 3.3.5 *Recommendations for vaccination in persons with functional or anatomical asplenia*.)

Persons aged ≥9 months with a medical condition that places them at high risk of meningococcal disease, and who have previously received 4vMenPV, should receive a booster dose of 4vMenCV, 3 years after their last dose of 4vMenPV. Thereafter, administer 4vMenCV every 5 years.

In persons with other risks for meningococcal disease, such as laboratory personnel or those travelling to endemic or hyperendemic regions, a dose of 4vMenCV should be administered every 5 years if the risk of meningococcal exposure is ongoing.

For those aged ≥2 years with underlying risk factors, but in whom 4vMenCV is contraindicated, ongoing boosting with 4vMenPV is recommended at 5-yearly intervals unless otherwise indicated.

4.10.8 Pregnancy and breastfeeding

Meningococcal vaccines are not routinely recommended for pregnant or breastfeeding women,[1,51,52] but can be given where clinically indicated (see 4.10.7 *Recommendations* above).

Refer to 3.3 *Groups with special vaccination requirements*, Table 3.3.1 *Recommendations for vaccination in pregnancy* for more information.

4.10.9 Contraindications

The only absolute contraindications to meningococcal vaccines are:

- anaphylaxis following a previous dose of any meningococcal vaccine
- anaphylaxis following any vaccine component.

Previous meningococcal disease, regardless of the serogroup, is *not* a contraindication to administration of any meningococcal vaccine.

4.10.10 Adverse events

Common adverse events caused by meningococcal conjugate vaccines are pain, redness and swelling at the site of injection, fever, irritability, drowsiness, decreased appetite and headaches.[13,21,23-26,29] There are some age-related differences in the type of adverse events following vaccination, with systemic adverse events tending to decrease with increasing age, and local adverse events tending to increase with increasing age. Headache, anorexia, fever and chills were more likely to be reported in the adolescent and adult age groups following administration of 4vMenCV.[26,29] Among recipients of 4vMenCV, rash and nausea were common. However, serious general adverse events are rare.[26,29]

The United States Vaccine Adverse Event Reporting System (VAERS) previously reported a series of cases of Guillain-Barré syndrome (GBS) temporally associated with the introduction of the 4vMenCV, Menactra.[53,54] The likelihood of coincidentally experiencing GBS after administration of 4vMenCV is expected to be greater among persons with a history of GBS than among persons with no history of GBS. Recent safety studies, during which over 2 million doses of Menactra were administered, found there was no risk of GBS after Menactra in the general population, and extrapolated these data to conclude that persons with a history of GBS are not at higher risk than they are after other vaccines that have no association with GBS.[55,56] It is, therefore, recommended that 4vMenCV can be administered to persons with previous GBS in whom vaccination is indicated.

Local adverse events after 4vMenPV include erythema, induration, tenderness, pain and local axillary lymphadenopathy. However, these reactions are usually mild and infrequent. Fever and chills occur in approximately 2% of young children, and may persist for 48 hours or longer, but significant general adverse events are rare.

4.10.11 Public health management of meningococcal disease

Meningococcal disease is notifiable in all states and territories in Australia.

Further instructions about the public health management of meningococcal disease, including management of cases of meningococcal disease and their contacts, should be obtained from state/territory public health authorities (see

Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*).

If a diagnosis of meningococcal disease is suspected, the patient should be immediately given parenteral (usually IM) penicillin and transferred to hospital.

A potential outbreak of meningococcal disease in an institutional or community setting is a public health emergency needing a rapid response from clinicians and public health practitioners. The decision to control an outbreak with a vaccination program should be made by the appropriate Public Health Unit, following the *Guidelines for the early clinical and public health management of meningococcal disease in Australia*.[2]

4.10.12 Variations from product information

The product information for meningococcal C conjugate vaccines states that, under the age of 12 months, either 2 (NeisVac-C) or 3 (Meningitec and Menjugate Syringe) doses of vaccine are required. The ATAGI recommends instead that meningococcal C vaccination is routinely not recommended before 12 months of age (unless specifically indicated).

The product information for Meningitec states that an allergic reaction following a previous dose is a contraindication to further doses. The ATAGI recommends instead that the only contraindication is a history of anaphylaxis to a previous dose or to any of the vaccine components.

The product information for NeisVac-C states that the vaccine should not be administered with pneumococcal conjugate vaccine, hepatitis B vaccine or PRP-OMP *Haemophilus influenzae* type b vaccine unless 'medically important'. The ATAGI recommends instead that the vaccine may be administered simultaneously with other vaccines in the NIP. There have been publications citing the co-administration of MenCCV with other combination vaccines and it was found to be immunogenic and safe.[57,58]

The product information for Menactra states that a previous episode of Guillain-Barré syndrome is a contraindication to vaccination with Menactra. The ATAGI recommends instead that either of the available 4vMenCVs can be administered.

The product information for Menactra states that this vaccine is indicated for use in persons aged 2–55 years. The ATAGI recommends instead that Menactra can be given to persons aged ≥9 months of age.

The product information for Menveo states that this vaccine is indicated for use in persons ≥11 years of age. The ATAGI recommends instead that Menveo can be given to persons aged ≥9 months of age.

The product information for all meningococcal vaccines (MenCCV, 4vMenCV and 4vMenPV) states that there are no data on the use of these vaccines in lactating women. The ATAGI recommends that breastfeeding women can be vaccinated.

The product information for both 4vMenCVs states that vaccine should be administered as a single dose. The ATAGI recommends that these vaccines can be given in a 2-dose primary schedule to children (aged ≥9 months) and adults with high-risk medical conditions.

The product information for both 4vMenCVs states that the need for, or timing of, booster doses has not yet been determined. The ATAGI recommends that, until more data become available, individuals with underlying risk factors, including functional or anatomical asplenia, should continue to receive 4vMenCV at 5-yearly intervals.

References

A full reference list is available on the electronic *Handbook* or website www.immunise.health.gov.au

4.11 MUMPS

4.11.1 Virology

Mumps is a paramyxovirus, genus *Rubulavirus*, with a single-stranded RNA genome. It is rapidly inactivated by heat, formalin, ether, chloroform and light.[1]

4.11.2 Clinical features

Mumps is an acute viral illness with an incubation period of 12 to 25 days.[2] Transmission is via respiratory secretions, including aerosol transmission, or by direct contact with saliva or possibly urine.[2] Asymptomatic infection occurs in one-third of cases.[3] Symptomatic disease ranges from mild upper respiratory symptoms to widespread systemic involvement.[3] A high proportion of mumps infections involve non-specific symptoms including fever, headache, malaise, myalgia and anorexia.[4] The characteristic bilateral, or occasionally unilateral, parotid swelling occurs in 60 to 70% of clinical cases.[4,5] Maximum infectiousness occurs between 2 days before onset of illness and 4 days afterwards, but patients may be infectious from 7 days before parotid swelling to 9 days after.[2] Meningeal symptoms and signs appear in approximately 10% of cases, but permanent neurologic sequelae are rare.[2] Mumps encephalitis has been estimated to occur in 1–2 per 10 000 cases, with a case-fatality rate of around 1.0%.[6] Deafness is relatively common in mumps meningoencephalitis, although permanent nerve deafness is rare (1 in 20 000 infections). Orchitis (usually unilateral) has been reported in up to 15 to 30% of clinical mumps cases in post-pubertal males, but subsequent sterility is rare.[6] Symptomatic involvement of other glands and organs has been observed less frequently (pancreatitis, oophoritis, hepatitis, myocarditis, thyroiditis, mastitis).[1,4]

Mumps infection during the first trimester of pregnancy may result in spontaneous abortion.[3,4] Maternal infection is not associated with an increased risk of congenital malformation.[3,4]

4.11.3 Epidemiology

Mumps is reported worldwide. Prior to universal vaccination, mumps was primarily a disease of childhood with the peak incidence in the 5–9 years age group. However, since 2000, peak rates have been reported in older adolescents and young adults, especially the 20–34 years age group.[7-10] Between 2002 and 2004, mumps notifications were the lowest recorded in Australia, averaging 0.4 per 100 000.[11] In 2005, notifications increased to 1.2 per 100 000, peaking at 2.7 per 100 000 in 2007, but have since declined to less than 1 per 100 000 since 2009.[10,11] There have also been recent outbreaks of mumps in the United States and Europe, where the peak rates of disease have been in the 18–24 years age group.[12-15]

Similar to measles, persons born in the late 1960s to mid-1980s (especially the 1978–1982 birth cohort) are recognised to be at a greater risk of mumps. Many missed being vaccinated or acquiring mumps infection as infants (when vaccine coverage was low and disease incidence was decreasing), and may also have missed catch-up vaccinations during their school years as part of either the Measles Control Campaign (which only targeted primary-school-aged children) or the Young Adult Measles Control Campaign (which did not result in high coverage).[16,17] During outbreaks, mumps attack rates are lowest in persons who have received 2 doses of mumps-containing vaccines, as this provides optimal long-term protection.[5,13] In Australia, over the 11-year period from 1996 to 2006, mumps was reported as the underlying cause of 5 deaths, all in adults aged over 80 years.[7-10]

4.11.4 Vaccines

Monovalent mumps vaccine is not available in Australia. Mumps vaccination is provided using either measles-mumps-rubella (MMR) or measles-mumps-rubella-varicella (MMRV) vaccines. Two quadrivalent combination vaccines containing live attenuated measles, mumps, rubella and varicella viruses (MMRV) are registered in Australia.

Clinical trials of MMR vaccine indicate 95% mumps seroconversion after a single dose and up to 100% after a 2nd dose.[4] However, outbreak investigations and post-marketing studies have reported 1-dose vaccine effectiveness to be between 60 and 90%.[13,18] A Cochrane review reported 1-dose vaccine effectiveness to be between 69% and 81% for the vaccine containing the Jeryl Lynn mumps strain and between 70% and 75% for the vaccine containing the Urabe strain.[19] While protection is greater in 2-dose vaccine recipients, recent outbreaks have reported mumps in 2-dose vaccine recipients, particularly young adults who received their vaccines more than 10 years previously.[14,15,20,21]

Combination MMRV vaccines have been shown, in clinical trials, to produce similar rates of seroconversion to all four vaccine components compared with MMR vaccine and monovalent varicella vaccines administered concomitantly at separate injection sites.[22-25]

See further information on MMR and MMRV vaccines in 4.9 *Measles* and 4.22 *Varicella*.

Trivalent measles–mumps–rubella (MMR) vaccines

- ***M-M-R II*** – CSL Limited/Merck & Co Inc (live attenuated measles virus [Enders' attenuated Edmonston strain], mumps virus [Jeryl Lynn B level strain] and rubella virus [Wistar RA 27/3 strain]). Lyophilised pellet in a monodose vial with separate diluent. Each 0.5 mL reconstituted dose contains ≥1000 tissue culture infectious dose 50% ($TCID_{50}$) of Enders' attenuated Edmonston measles virus, ≥12 500 $TCID_{50}$ of the Jeryl Lynn B level mumps virus, and ≥1000 $TCID_{50}$ of the Wistar RA 27/3 rubella virus; sorbitol; sucrose; hydrolysed gelatin; human albumin; fetal bovine serum; neomycin.
- ***Priorix*** – GlaxoSmithKline (live attenuated measles virus [Schwarz strain], mumps virus [RIT 4385 strain, derived from the Jeryl Lynn strain] and rubella virus [Wistar RA 27/3 strain]). Lyophilised pellet in a monodose vial with a pre-filled diluent syringe. Each 0.5 mL reconstituted dose contains $\geq 10^{3.0}$ cell culture infectious dose 50% ($CCID_{50}$) of the Schwarz measles virus, $\geq 10^{3.7}$ $CCID_{50}$ of the RIT 4385 mumps virus, and $\geq 10^{3.0}$ $CCID_{50}$ of the Wistar RA 27/3 rubella virus; lactose; neomycin; sorbitol; mannitol.

Quadrivalent measles-mumps-rubella-varicella (MMRV) vaccines

- ***Priorix-tetra*** – GlaxoSmithKline (live attenuated measles virus [Schwarz strain], mumps virus [RIT 4385 strain, derived from the Jeryl Lynn strain], rubella virus [Wistar RA 27/3 strain] and varicella-zoster virus [Oka strain]). Lyophilised pellet in a monodose vial with a pre-filled diluent syringe. Each 0.5 mL reconstituted dose contains $\geq 10^{3.0}$ $CCID_{50}$ of the Schwarz measles virus, $\geq 10^{4.4}$ $CCID_{50}$ of the RIT 4385 mumps virus, $\geq 10^{3.0}$ $CCID_{50}$ of the Wistar RA 27/3 rubella virus, and $\geq 10^{3.3}$ plaque-forming units (PFU) of Oka varicella-zoster virus; lactose; neomycin; sorbitol; mannitol.
- ***ProQuad*** – CSL Limited/Merck & Co Inc (live attenuated measles virus [Enders' attenuated Edmonston strain], mumps virus [Jeryl Lynn B level strain], rubella virus [Wistar RA 27/3 strain] and varicella-zoster virus [Oka/Merck strain]). Lyophilised powder in a monodose vial with a pre-filled diluent syringe. Each 0.5 mL reconstituted dose contains $\geq 10^{3.0}$ $TCID_{50}$ of Enders' attenuated Edmonston measles virus, $\geq 10^{4.3}$ $TCID_{50}$ of the Jeryl Lynn B level mumps virus, $\geq 10^{3.0}$ $TCID_{50}$ of the Wistar RA 27/3 rubella virus, and $\geq 10^{3.99}$ PFU of Oka/Merck varicella virus; sucrose; hydrolysed gelatin; urea; sorbitol; monosodium L-glutamate; human albumin; neomycin; residual components of MRC-5 cells; bovine serum albumin.

4.11.5 Transport, storage and handling

Transport according to *National vaccine storage guidelines: Strive for 5*.[26] Store at +2°C to +8°C. Do not freeze. Protect from light.

Both MMR and MMRV vaccines *must be reconstituted* by adding the entire contents of the diluent container to the vial containing the pellet and shaking until the pellet is completely dissolved.

Reconstituted Priorix (MMR), M-M-R II (MMR) and Priorix-tetra (MMRV) vaccines should be used as soon as practicable. If storage is necessary, hold at +2°C to +8°C for not more than 8 hours.

Reconstituted ProQuad (MMRV) vaccine must be used within 30 minutes.

4.11.6 Dosage and administration

The dose of Priorix (MMR) vaccine for both children and adults is 0.5 mL to be given by either SC or IM injection.

The dose of M-M-R II (MMR) vaccine for both children and adults is 0.5 mL to be given by SC injection.

For children <14 years of age, the dose of MMRV vaccine is 0.5 mL to be given by SC injection. Priorix-tetra may also be given by IM injection.[27]

MMRV vaccines are not recommended for use in persons aged ≥14 years.

When 2 doses of MMR-containing vaccine are required, the minimum interval between doses is 4 weeks.

Co-administration with other vaccines

MMR or MMRV vaccines can be given at the same time as other live attenuated parenteral vaccines (e.g. varicella, BCG, yellow fever) or other inactivated vaccines (including DTPa, hepatitis B, Hib, IPV, MenCCV, hepatitis A and pneumococcal conjugate vaccine),[28] using separate syringes and injection sites. If MMR or MMRV vaccine is not given simultaneously with other live attenuated parenteral vaccines, they should be given at least 4 weeks apart.

If MMR vaccine is given at the same time as monovalent varicella vaccine (VV), they should be given using separate syringes and injection sites. MMR vaccine and monovalent VV should *not* be mixed together prior to injection.

Separate administration of measles, mumps or rubella vaccine is not available as an alternative to MMR vaccine, although a monovalent varicella vaccine is available (see 4.22 *Varicella*).

Interchangeability of MMR-containing vaccines

In general, the two brands of MMR vaccine can be considered interchangeable, that is, the 2nd MMR dose does not have to be of the same brand as the 1st. The same principle applies to the two available MMRV vaccines,[28] although they are not routinely recommended in a 2-dose schedule.

4.11.7 Recommendations

Infants aged <12 months

MMR-containing vaccines are not routinely recommended for infants <12 months of age. However, MMR vaccine can be given to children from as early as 9 months of age in high-risk circumstances (see 4.9 *Measles*).

If MMR vaccine is given at <12 months of age, there is still a need for 2 vaccine doses to be administered at ≥12 months of age (see 4.9 *Measles*).

Children

Two doses of mumps-containing vaccine are recommended for all children. The 1st dose should be given at 12 months of age as MMR vaccine. MMRV vaccines are *not* recommended for use as the 1st dose of MMR-containing vaccine in children <4 years of age, due to a small but increased risk of fever and febrile seizures when given as the 1st MMR-containing vaccine dose in this age group (see Table 4.9.1 in 4.9 *Measles* and Table 4.22.1 in 4.22 *Varicella*). (See also 4.9.11 *Adverse events* in 4.9 *Measles* and 4.22.11 *Adverse events* in 4.22 *Varicella*.)

The 2nd dose of mumps-containing vaccine is recommended to be given routinely at 18 months of age as MMRV vaccine. This is to commence from July 2013 once MMRV vaccine(s) are available under the NIP (see Table 4.9.1 in 4.9 *Measles* and Table 4.22.1 in 4.22 *Varicella*). The recommended age for administration of the 2nd dose of mumps-containing vaccine will be moved down from 4 years of age, to provide earlier 2-dose protection against measles, mumps and rubella, and to improve vaccine uptake (see 4.11.3 *Epidemiology* above).

If MMRV vaccine is inadvertently administered as dose 1 of MMR-containing vaccine, the dose does not need to be repeated (providing it was given at ≥12 months of age); however, parents/carers should be advised regarding the small but increased risk of fever and febrile seizures (compared with that expected following MMR vaccine).

Adults and adolescents

Two doses of mumps-containing vaccine are recommended for all non-immune adolescents and adults (see 4.9 *Measles*). All persons born during or since 1966 who are ≥18 months of age (or, until catch-up following the move of the 2nd NIP dose of measles-containing vaccine to 18 months of age is completed, are ≥4 years of age) should have documented evidence of 2 doses of MMR-containing vaccine (administered at least 4 weeks apart with both doses administered at ≥12 months of age) or have serological evidence of protection for measles, mumps and rubella.

It is recommended that all adolescents and young adults have their vaccination records reviewed to ensure they have received 2 doses of MMR vaccine (see 4.11.3 *Epidemiology* above).

MMRV vaccines are not recommended for use in persons ≥14 years of age, due to a lack of data on safety and immunogenicity/efficacy in this age group. If a dose of MMRV vaccine is inadvertently given to an older person, this dose does not need to be repeated.

For further information on the recommendations for MMR and MMRV vaccines, see 4.9 *Measles* and 4.22 *Varicella*.

Serological testing for immunity to mumps

Serological testing for immunity to mumps (and measles, rubella and varicella) is not recommended before or after routine administration of the 2-dose childhood schedule of these vaccines.

However, serological testing for mumps (and measles and rubella) can be performed in cases where a history of natural immunity or 2 doses of vaccine administration is uncertain (see 'Adults and adolescents' above). Serology is indicated in special situations, such as pre-pregnancy planning (see also 4.9 *Measles*, 4.18 *Rubella* and 4.22 *Varicella*). Serological tests to investigate immunity to mumps are generally sensitive at detecting antibody produced by both prior natural infection and vaccination, although sensitivity varies by assay and the clinical setting (e.g. time since vaccination).[4] Interpretation of the results of serological testing may be enhanced by discussion with the laboratory that performed the test, ensuring that relevant clinical information is provided. An alternative to serological testing is presumptive administration of MMR vaccine dose(s). There is no known increase in adverse events from vaccinating those with pre-existing immunity to one or more of the vaccine components (see 4.11.11 *Adverse events* below).

4.11.8 Pregnancy and breastfeeding

MMR-containing vaccines are contraindicated in pregnant women. Pregnancy should be avoided for 28 days after vaccination.[29]

MMR vaccines can be given to breastfeeding women. (See also 4.18 *Rubella*.)

MMRV vaccines are not recommended for use in persons aged ≥14 years.

See also 4.9 *Measles*, 4.18 *Rubella*, 4.22 *Varicella* and 3.3 *Groups with special vaccination requirements*, Table 3.3.1 *Recommendations for vaccination in pregnancy* for more information.

4.11.9 Contraindications

For information on contraindications to MMR and MMRV vaccines, see 4.9 *Measles* and 4.22 *Varicella*.

4.11.10 Precautions

For additional precautions related to MMR and MMRV vaccines, see 4.9 *Measles* and 4.22 *Varicella*.

Vaccination with other live attenuated parenteral vaccines

If MMR or MMRV vaccine is not given simultaneously with other live attenuated parenteral vaccines (e.g. varicella, BCG, yellow fever), the vaccines should be given at least 4 weeks apart.

4.11.11 Adverse events

Adverse events following administration of MMR-containing vaccines are generally mild and well tolerated.[4] Adverse events are much less common after the 2nd dose of MMR or MMRV vaccine than after the 1st dose.

The most common adverse events following mumps vaccination are fever and parotitis.[4] Parotitis occurs most commonly from 10 to 14 days after vaccination. The incidence varies by vaccine strain; in studies of the Jeryl Lynn vaccine strain, parotid and/or submandibular swelling occurred in 0.5 to 1.6% of recipients.[4,30,31]

An increased risk of aseptic meningitis has been observed after vaccination with the Urabe strain of mumps vaccine in some countries.[4] However, the Urabe strain is *not* used in Australia. MMR and MMRV vaccines available in Australia contain a Jeryl Lynn-derived strain of mumps, which is not associated with an increased risk of aseptic meningitis.[32,33]

For further information on the adverse events associated with MMR and MMRV vaccines, see 4.9 *Measles* and 4.22 *Varicella*.

4.11.12 Public health management of mumps

Mumps is a notifiable disease in all states and territories in Australia.

Further instructions about the public health management of mumps, including management of cases of mumps and their contacts, should be obtained from state/territory public health authorities (see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*).

Mumps-containing vaccine does not provide protection if given after an individual has been exposed to mumps.[1,34] However, if the exposure did not result in infection, the vaccine would induce protection against subsequent infection. Normal human immunoglobulin (NHIG) has been shown *not* to be of value in post-exposure prophylaxis for mumps.[1,34]

4.11.13 Variations from product information

For information on MMR and MMRV vaccines, see 4.9 *Measles* and 4.22 *Varicella*.

References

A full reference list is available on the electronic *Handbook* or website www.immunise.health.gov.au

4.12 PERTUSSIS

4.12.1 Bacteriology

Pertussis (whooping cough) is caused by *Bordetella pertussis*, a fastidious, Gram-negative, pleomorphic bacillus. There are other organisms (such as *Bordetella parapertussis*, *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*) that can cause a pertussis-like syndrome.[1]

4.12.2 Clinical features

Pertussis is a respiratory infection with an incubation period of 7 to 20 days. In unvaccinated persons, *B. pertussis* is highly infectious, spreading by aerosols to 90% of susceptible household contacts.[2] Natural infection does not provide long-term protection and repeat infection can occur.[2] The characteristic paroxysmal cough with inspiratory whoop seen in unvaccinated children is less common in individuals who have varying degrees of immunity acquired from vaccination or infection.[3] It has been estimated that *B. pertussis* accounts for up to 7% of cough illnesses per year in adults and, each year, more than 25% of adults experience a coughing illness of at least 5 days duration.[4] Even in adults, pertussis can be associated with significant morbidity, with cough persisting for up to 3 months, and other significant symptoms, such as sleep disturbance or, rarely, rib fracture.[5] Identification of pertussis is limited by patient and physician awareness and, in some cases, the limited sensitivity of diagnostic tests; it is generally believed to be significantly under-diagnosed (see 4.12.11 *Public health management of pertussis* below).

Death due to pertussis is rare in people aged 10–70 years. However, the case-fatality rate in unvaccinated infants <6 months of age is estimated to be 0.8%.[6,7] The most common cause of death in persons with pertussis infection is pertussis pneumonia, sometimes complicated by seizures and hypoxic encephalopathy.[3]

4.12.3 Epidemiology

Despite a long-standing immunisation program, pertussis remains highly prevalent in Australia and the least well controlled of all vaccine-preventable diseases. Epidemics occur every 3 to 4 years. In unvaccinated populations, these outbreaks can be very large. In vaccinated populations, outbreaks are smaller, with greatly reduced mortality and morbidity, and may continue to occur every 3 to 4 years or be more widely spaced.[8] The maximal risk of infection and severe morbidity is before infants are old enough to have received at least 2 vaccine doses.[9] In recent years, among highly immunised communities, many cases of pertussis have occurred in adults and adolescents due to waning immunity.[8,10] These persons are a significant reservoir of infection. Evidence from several studies of infant pertussis cases indicates that family members, particularly parents, are the source of infection in more than 50% of cases where a primary case can be identified, and the presumed source in a higher proportion.[11-14] There have also been case reports documenting nosocomial infection in young infants

acquired from healthcare workers.[15-18] Pertussis hospitalisation rates for persons aged ≥60 years are higher than for other adults.[19]

Between 2000 and 2010, multiple epidemics of pertussis occurred in Australia; however, the timing and frequency of these varied by geographical location. More than 139 000 cases were reported over this 11-year period, with the highest annual incidence of notifications (156 cases per 100 000 population) reported in 2010.[20]

There have been a number of changes introduced to the NIP schedule over time in an attempt to improve control of pertussis. Introduction of a 5th dose of diphtheria, tetanus and whole-cell pertussis vaccine (DTPw) for 4–5-year-old children in August 1994 was followed by a decrease in notifications consistent with a vaccine effect; first among children aged 5 and 6 years, then by those in the 7–9 years age group.[8,21] Subsequently, the average age of pertussis notifications continued to increase. By 2005, the proportion of notifications in adults >20 years of age had reached 83%,[8] compared with 40% in the early 1990s.

Acellular pertussis vaccine (DTPa) replaced DTPw for booster doses in 1997, and for all doses from 1999. In 2003, the DTPa booster dose at 18 months of age was removed from the NIP, moving the 1st booster dose to 4 years of age. The removal of the 18-month booster dose from the schedule was based on evidence from an Italian longitudinal study of DTPa trial participants. The study found that a primary DTPa course at 2, 4 and 6 months of age provided 76 to 80% protection from prolonged cough disease and this was maintained until 6 years of age.[22]

In 2009–2010, in contrast to previous epidemics, the highest notification rates in Australia were in children <10 years of age; the proportion of notifications in adults >20 years of age decreased to 57%. The greatest increase in notification rate occurred in 3-year-old children. Although increased and more sensitive diagnostic testing using polymerase chain reaction (PCR) has contributed to this rise, vaccine effectiveness among 3-year olds has been estimated at around 60%,[23] consistent with waning of immunity following the primary DTPa course. In contrast to notifications, hospitalisation and death rates from pertussis in the most recent epidemic periods have not increased substantially.[24] A high proportion of hospitalisations, and almost all deaths, attributed to pertussis occur in infants too young to have received more than 1 dose of pertussis-containing vaccine.[19,25]

The prevention of severe pertussis morbidity and deaths, particularly in infants <3 months of age, is a major goal in Australia and similar countries. Two vaccination strategies have been considered to achieve this – indirect protection from immunisation of close adult contacts of newborn infants, known as the 'cocoon' strategy[26] (see 'Persons in contact with infants and others at increased risk from pertussis' in 4.12.7 *Recommendations* below) and direct protection from immunisation of the mother during the last trimester of pregnancy[27] (see 4.12.8

Pregnancy and breastfeeding below). Data to evaluate the effectiveness of indirect protection to infants from the cocoon approach are lacking.[28] However, this approach is expected to reduce infection risk to infants from family members, known to be an important source of pertussis infection,[13,14] especially for the youngest infants.[11,12]

4.12.4 Vaccines

Pertussis vaccine is available in Australia only in combination with diphtheria, tetanus and other antigens.

The acronym DTPa, using capital letters, signifies child formulations of diphtheria, tetanus and acellular pertussis-containing vaccines. The acronym dTpa is used for formulations that contain substantially lesser amounts of diphtheria toxoid and pertussis antigens than child (DTPa-containing) formulations; dTpa vaccines are usually used in adolescents and adults.

Acellular pertussis-containing vaccines have been used for both primary and booster vaccination of children in Australia since 1999. Whole-cell pertussis-containing vaccines were used exclusively before 1997. Between 1997 and 1999 acellular vaccines were used for booster doses. There are a number of acellular pertussis-containing vaccines that contain three or more purified components of *B. pertussis*. In the 3-component vaccines, these components are pertussis toxin (PT), filamentous haemagglutinin (FHA) and pertactin (PRN). In the 5-component vaccines, fimbrial (FIM) antigens are also included.

Pertussis vaccines provide good protection against severe and typical pertussis, but substantially less against milder coughing illness.[29,30] Vaccine efficacy of DTPa vaccines with three or more antigens has been reported as 71 to 78% for preventing milder symptoms of pertussis and 84% for preventing typical disease.[30] Epidemiological data suggest that receipt of the 1st dose of the primary DTPa course significantly reduces the incidence of severe pertussis disease in young infants, as measured by hospitalisation rates.[31-33] Data on the duration of immunity following DTPa vaccine indicate that waning occurs 5 to 6 years after the last dose of vaccine.[2,34] However, these studies could not control for levels of circulating pertussis in the population, which may boost the level of immunity and lead to over-estimation of the duration of protection against symptomatic disease.[29,30]

Reduced antigen content formulation, dTpa, vaccines are immunogenic.[35-38] A randomised trial in adults reported a point estimate of 92% efficacy against culture/nucleic acid test-positive disease within 2.5 years of vaccination with a 3-component monovalent pertussis vaccine.[4] Data on the duration of immunity to pertussis following a single booster dose of dTpa are limited. Long-term follow-up of adults vaccinated with dTpa has shown a rapid decline in levels of pertussis antibodies within the first 2 years after vaccination, with a continued steady decline out to 10 years after vaccination, although antibody levels remained above baseline.[39] A similar long-term follow-up of adolescents

demonstrated a more rapid decline, with pertussis antibody levels decreasing to or approaching pre-vaccination levels after 10 years.[40] The rate of decline in clinical protection is unknown, but some protection against clinical disease is likely to persist for up to 10 years. Recent studies have indicated that dTpa vaccine is immunogenic in the elderly.[38]

Vaccines containing DTPa are available in various combinations with inactivated poliomyelitis, hepatitis B and *Haemophilus influenzae* type b vaccines.

Formulations for children aged <10 years

- ***Infanrix hexa*** – GlaxoSmithKline (DTPa-hepB-IPV-Hib; diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus-*Haemophilus influenzae* type b). The vaccine consists of *both* a 0.5 mL pre-filled syringe containing ≥30 IU diphtheria toxoid, ≥40 IU tetanus toxoid, 25 µg pertussis toxoid (PT), 25 µg filamentous haemagglutinin (FHA), 8 µg pertactin (PRN), 10 µg recombinant HBsAg, 40 D-antigen units inactivated poliovirus type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett), adsorbed onto aluminium hydroxide/phosphate; traces of formaldehyde, polysorbate 80, polysorbate 20, polymyxin and neomycin; *and* a vial containing a lyophilised pellet of 10 µg purified Hib capsular polysaccharide (PRP) conjugated to 20–40 µg tetanus toxoid. May contain yeast proteins.
- ***Infanrix IPV*** – GlaxoSmithKline (DTPa-IPV; diphtheria-tetanus-acellular pertussis-inactivated poliovirus). Each 0.5 mL pre-filled syringe contains ≥30 IU diphtheria toxoid, ≥40 IU tetanus toxoid, 25 µg PT, 25 µg FHA, 8 µg PRN, 40 D-antigen units inactivated poliovirus type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett), adsorbed onto aluminium hydroxide; traces of formaldehyde, polysorbate 80, polymyxin and neomycin.
- ***Pediacel*** – Sanofi Pasteur Pty Ltd (DTPa-IPV-Hib; diphtheria-tetanus-acellular pertussis-inactivated poliovirus-*Haemophilus influenzae* type b). Each 0.5 mL monodose vial contains ≥30 IU diphtheria toxoid, ≥40 IU tetanus toxoid, 20 µg PT, 20 µg FHA, 3 µg PRN, 5 µg pertussis fimbriae (FIM) 2+3, 40 D-antigen units inactivated poliovirus type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett), 10 µg Hib capsular polysaccharide conjugated to 20 µg tetanus protein; 1.5 mg aluminium phosphate; ≤50 ng bovine serum albumin; phenoxyethanol as preservative; traces of

formaldehyde, glutaraldehyde, polysorbate 80, polymyxin, neomycin and streptomycin.

- ***Quadracel*** – Sanofi Pasteur Pty Ltd (DTPa-IPV; diphtheria-tetanus-acellular pertussis-inactivated poliovirus). Each 0.5 mL monodose vial contains ≥30 IU diphtheria toxoid, ≥40 IU tetanus toxoid, 20 µg PT, 20 µg FHA, 3 µg PRN, 5 µg FIM 2+3, 40 D-antigen units inactivated poliovirus type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett); 1.5 mg aluminium phosphate; ≤50 ng bovine serum albumin; phenoxyethanol as preservative; traces of formaldehyde, glutaraldehyde, polysorbate 80, polymyxin and neomycin.
- ***Tripacel*** – Sanofi Pasteur Pty Ltd (DTPa; diphtheria-tetanus-acellular pertussis). Each 0.5 mL monodose vial contains ≥30 IU diphtheria toxoid, ≥40 IU tetanus toxoid, 10 µg PT, 5 µg FHA, 3 µg PRN, 5 µg FIM 2+3; 1.5 mg aluminium phosphate; 3.4 mg phenoxyethanol.

Reduced antigen formulations for adults, adolescents and children aged ≥10 years

- ***Adacel*** – Sanofi Pasteur Pty Ltd (dTpa; diphtheria-tetanus-acellular pertussis). Each 0.5 mL monodose vial contains ≥2 IU diphtheria toxoid, ≥20 IU tetanus toxoid, 2.5 µg PT, 5 µg FHA, 3 µg PRN, 5 µg FIM 2+3; 0.33 mg aluminium as aluminium phosphate; phenoxyethanol as preservative; traces of formaldehyde and glutaraldehyde.
- ***Adacel Polio*** – Sanofi Pasteur Pty Ltd (dTpa-IPV; diphtheria-tetanus-acellular pertussis-inactivated poliovirus). Each 0.5 mL monodose vial or pre-filled syringe contains ≥2 IU diphtheria toxoid, ≥20 IU tetanus toxoid, 2.5 µg PT, 5 µg FHA, 3 µg PRN, 5 µg FIM 2+3, 40 D-antigen units inactivated poliovirus type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett); 0.33 mg aluminium as aluminium phosphate; phenoxyethanol as preservative; traces of formaldehyde, glutaraldehyde, polysorbate 80, polymyxin, neomycin and streptomycin.
- ***Boostrix*** – GlaxoSmithKline (dTpa; diphtheria-tetanus-acellular pertussis). Each 0.5 mL monodose vial or pre-filled syringe contains ≥2 IU diphtheria toxoid, ≥20 IU tetanus toxoid, 8 µg PT, 8 µg FHA, 2.5 µg PRN, adsorbed onto 0.5 mg aluminium as aluminium hydroxide/phosphate; traces of formaldehyde, polysorbate 80 and glycine.

- ***Boostrix-IPV*** – GlaxoSmithKline (dTpa-IPV; diphtheria-tetanus-acellular pertussis-inactivated poliovirus). Each 0.5 mL pre-filled syringe contains ≥2 IU diphtheria toxoid, ≥20 IU tetanus toxoid, 8 µg PT, 8 µg FHA, 2.5 µg PRN, 40 D-antigen units inactivated poliovirus type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett), adsorbed onto 0.5 mg aluminium as aluminium hydroxide/phosphate; traces of formaldehyde, polysorbate 80, polymyxin and neomycin.

4.12.5 Transport, storage and handling

Transport according to *National vaccine storage guidelines: Strive for 5*.[41] Store at +2°C to +8°C. Do not freeze. Protect from light.

Infanrix hexa *must be reconstituted* by adding the entire contents of the syringe to the vial and shaking until the pellet is completely dissolved. Reconstituted vaccine should be used as soon as practicable. If storage is necessary, hold at room temperature for not more than 8 hours.

4.12.6 Dosage and administration

The dose of all pertussis-containing vaccines is 0.5 mL to be given by IM injection.

Do not mix DTPa- or dTpa-containing vaccines with any other vaccine in the same syringe, unless specifically registered for use in this way.

4.12.7 Recommendations

Infants and children

Pertussis-containing vaccine is recommended in a 3-dose primary schedule for infants at 2, 4 and 6 months of age. Due to the high morbidity and occasional mortality associated with pertussis in the first few months of life, the 1st dose can be given as early as 6 weeks of age (see Table 2.1.5 *Minimum acceptable age for the 1st dose of scheduled vaccines in infants in special circumstances*). Giving a 1st dose at 6 weeks of age rather than 2 months of age is estimated to prevent an additional 8% of infant pertussis cases. The next scheduled doses should still be given at 4 months and 6 months of age.[31,42]

A booster dose of pertussis-containing vaccine, usually provided as DTPa-IPV, is recommended at 4 years of age, but can be given as early as 3.5 years of age. This booster dose is essential as waning of pertussis immunity occurs following receipt of the primary schedule.[2,34] For this booster dose, all brands of DTPa-containing vaccines are considered interchangeable.

Where required, DTPa-containing vaccines can be given for catch-up for either the primary doses or booster dose in children aged <10 years (see 2.1.5 *Catch-up*).

In addition, all household contacts (children and adults) of infants should be age-appropriately immunised to minimise the risk of severe disease occurring in young infants prior to completion of the primary course (see 'Adolescents' and 'Adults' below).

Parents who wish to minimise the likelihood of their child developing pertussis in the 2nd and 3rd years of life (prior to when the booster dose is due at 4 years of age) should be advised that an additional dose of pertussis-containing vaccine can be given in the 2nd year of life (e.g. at 18 months of age). This should also be considered when the child's mother received a dTpa vaccine during pregnancy, because of the potential for lesser antibody responses following the 3rd infant pertussis dose at 6 months of age (see 4.12.8 *Pregnancy and breastfeeding* below). It should be noted that a dose at this age is associated with an increased likelihood of a local adverse event, including extensive limb swelling, in a small percentage of children (see 4.12.10 *Adverse events* below).[43] DTPa (without other antigens) is currently unavailable in Australia; if an additional dose of a pertussis-containing vaccine is given in the 2nd year of life, any brand of DTPa-IPV may be used. Under these circumstances, the next dose of a DTPa-containing vaccine should not be given until 4 years of age. The additional dose in the 2nd year of life is not included on the NIP schedule.

Older children and adolescents

A 2nd booster dose is recommended for adolescents between 10 and 17 years of age, using the reduced antigen content dTpa. The optimal age for administering this dose is 11–13 years, due to waning antibody response following the 1st booster dose recommended at 4 years of age. This 2nd booster dose of pertussis-containing vaccine is essential for maintaining immunity to pertussis (and diphtheria and tetanus) into adulthood.[44]

For details on the management of children and adolescents who require catch-up vaccination for pertussis, see 2.1.5 *Catch-up*.

Adults

Vaccination with dTpa is recommended for any adult who wishes to reduce the likelihood of becoming ill with pertussis. Vaccination is particularly important if the adult meets the criteria of a special risk group (see 'Persons in contact with infants and others at increased risk from pertussis' below).

dTpa vaccine should be used in place of dT at the age routinely recommended for a tetanus and diphtheria booster (50 years). There is currently insufficient evidence to recommend routine 10-yearly booster doses of dTpa vaccine for all adults (who do not meet the criteria of a special risk group below). However, due to the increased morbidity associated with pertussis in the elderly,[19] adults aged ≥65 years should be offered a single dTpa booster if they have not received one

in the previous 10 years.[19,45] Adults of all ages who require a booster dose of dT vaccine should be encouraged to do so with dTpa vaccine, particularly if they have not received a dTpa dose previously (see 4.19 *Tetanus* and 4.2 *Diphtheria*).[46]

Travellers should receive a booster dose of dT (or dTpa if not given previously) if more than 10 years have elapsed since the last dose of dT-containing vaccine. For persons undertaking high-risk travel, consider giving a booster dose of either dTpa or dT (as appropriate) if more than 5 years have elapsed since the last dose of a dT-containing vaccine (see 4.19 *Tetanus* and 4.2 *Diphtheria*).

For those adults requiring additional protection from polio (see 4.14 *Poliomyelitis*), dTpa-IPV can be used.

For additional information on adults with no history of a primary course of dT or pertussis-containing vaccine requiring catch-up, see 4.19 *Tetanus* and 2.1.5 *Catch-up*.

Persons in contact with infants and others at increased risk from pertussis

There is significant morbidity associated with pertussis infection in infants <6 months of age, particularly those <3 months of age,[19] and the source of infection in infants is often a household contact[11-14] (see also 4.12.3 *Epidemiology* above). Pertussis vaccination of the close contacts of young infants (the cocoon strategy) is likely to reduce the risk of pertussis occurring in the infant and is recommended for the following groups.

Women who are planning pregnancy, pregnant or post-partum

dTpa vaccine is recommended as a single dose, given either during pre-pregnancy planning, or as soon as possible after delivery of the infant (preferably before hospital discharge). Alternatively, dTpa can be given to women during the third trimester of pregnancy (see 4.12.3 *Epidemiology* above and 4.12.8 *Pregnancy and breastfeeding* below). If 5 years or more have elapsed between a previous dose and the expected date of delivery for a subsequent pregnancy, a booster dose of dTpa (either in the third trimester or early post-partum) is recommended. The rationale for this, particularly pertaining to maternal vaccination during the third trimester, is that the level of maternal pertussis antibodies is thought to be the most important factor in infant protection, and after 5 years maternal antibodies may have declined[39,40] to a level such that direct and/or indirect protection to the infant is reduced. While it is possible that additional benefit could accrue from a booster dose at a shorter interval, or with each pregnancy, there is insufficient information to judge the likely risks and benefits of these alternatives.

Other adult household contacts and carers of infants <6 months of age

Adult household contacts and carers (e.g. fathers, grandparents) of infants <6 months of age should ideally receive a dTpa vaccine at least 2 weeks before beginning close contact with the infant. A booster dose of dTpa is recommended if 10 years have elapsed since a previous dose.[39,40]

Healthcare workers

All healthcare workers should receive dTpa vaccine because of the significant risk of nosocomial transmission of pertussis to vulnerable patients.[15-18] (See also 3.3 *Groups with special vaccination requirements,* Table 3.3.7 *Recommended vaccinations for persons at increased risk of certain occupationally acquired vaccine-preventable diseases*.) A booster dose of dTpa is recommended if 10 years have elapsed since a previous dose.[39,40] Vaccinated healthcare workers who develop symptoms compatible with pertussis should still be investigated for pertussis. There have been cases of nosocomial transmission of pertussis to infants from healthcare workers who have previously received dTpa vaccine.[17]

Staff working in early childhood education and care

Adults working with infants and young children aged <4 years should receive dTpa (see 3.3 *Groups with special vaccination requirements*, Table 3.3.7 *Recommended vaccinations for persons at increased risk of certain occupationally acquired vaccine-preventable diseases*). A booster dose of dTpa is recommended if 10 years have elapsed since a previous dose.[39,40]

Interval between dTpa and other tetanus/diphtheria-containing vaccines

A single dose of dTpa can be administered at any time after a dose of a vaccine containing tetanus and diphtheria toxoids. Studies indicate that the adverse reactions to a single dose of dTpa are similar whether administered shortly after (18 months), or at a longer interval after, a previous dose of a vaccine containing tetanus/diphtheria toxoids.[47-50] Where a tetanus- and diphtheria-containing vaccine has been given less than 18 months previously, the benefits of protection against pertussis gained from using dTpa, where recommended, are likely to outweigh the risk of an adverse event.[51]

Persons with a history of pertussis infection

Administration of pertussis vaccine in children, adolescents or adults who have had laboratory-confirmed pertussis infection is safe and is necessary, as natural immunity does not confer life-long protection. In particular, incompletely vaccinated infants <6 months of age who develop pertussis may not mount an adequate immune response following infection and should receive all routinely scheduled pertussis-containing vaccines.

4.12.8 Pregnancy and breastfeeding

dTpa vaccine can be given to pregnant or breastfeeding women.

Although there is not sufficient evidence to prefer maternal vaccination with dTpa during the third trimester of pregnancy to post-partum or pre-conception vaccination, it is an acceptable alternative option. Repeat vaccination of pregnant women (or women immediately post-partum) is recommended if there is an interval of 5 years between a previous dose and the expected delivery date[52]

(see 'Women who are planning pregnancy, pregnant or post-partum' in 4.12.7 *Recommendations* above).

Recently, it has been recommended in the United States, the United Kingdom and New Zealand that dTpa vaccine administered in the last trimester of pregnancy be preferred to post-partum maternal immunisation, for various reasons, including difficulties in implementation of the latter strategy, theoretical reasons why vaccination during pregnancy might be more effective, and the favourable safety profile of maternal vaccination.[53] Theoretical reasons for effectiveness are: 1) that administration of dTpa during the third trimester of pregnancy results in high maternal pertussis antibody levels and transplacental transfer of antibodies to the infant;[54,55] and 2) that the levels of pertussis antibodies measured in cord blood in such infants are similar to those observed in infants at 12 months of age following a 3-dose DTPa course.[56] This is likely to provide protection against pertussis in the 1st month of an infant's life, prior to commencement of the primary DTPa schedule. In addition, a woman vaccinated with dTpa during pregnancy will herself be protected against pertussis during the third trimester and will be less likely to transmit pertussis to the infant after delivery. Although specific safety data are limited, dTpa is an inactivated vaccine and there is evidence for the safety of this and other inactivated vaccines, such as tetanus and influenza, in pregnancy.[53,57] Safety of dTpa vaccines in pregnancy was not studied specifically during pre-market evaluations, but review of the available data from pregnancy registries, small studies and the United States Vaccine Adverse Event Reporting System did not indicate a higher frequency or unusual pattern of adverse events in pregnant women who received dTpa.[53]

A potential disadvantage of giving dTpa in the third trimester of pregnancy is that maternal pertussis antibodies may interfere with an infant's immune response following the primary 3-dose DTPa course at 2, 4 and 6 months of age,[53] a phenomenon referred to as 'blunting'.[27,53,58] However, because correlates of protection are not fully understood, the clinical importance of this is uncertain. Although severe morbidity and mortality from pertussis is rare after 6 months of age, it is possible that a reduced immune response to the infant's primary course of DTPa-containing vaccine could result in less protection against pertussis in the 2nd year of life. This provides the rationale for provision of an additional booster dose of a pertussis-containing vaccine (DTPa) in the 2nd year of life to children born to mothers who received dTpa during pregnancy (see 'Infants and children' in 4.12.7 *Recommendations* above).

Refer to 3.3 *Groups with special vaccination requirements*, Table 3.3.1 *Recommendations for vaccination in pregnancy* for more information.

4.12.9 Contraindications

The only absolute contraindications to acellular pertussis-containing vaccines are:

- anaphylaxis following a previous dose of any acellular pertussis-containing vaccine
- anaphylaxis following any vaccine component.

4.12.10 Adverse events

Acellular pertussis vaccines are associated with a much lower incidence of fever (approximately 20%) and local adverse events (approximately 10%) than whole-cell pertussis vaccines (approximately 45% and 40%, respectively), which are no longer used in Australia.[29,30,59] The reduced antigen content dTpa vaccines are safe and well tolerated in adults.[35,60,61] The incidence of fever is low, and comparable in vaccinated and placebo trial participants.[35,60,61] Booster doses of dTpa within 10 years are also safe and well tolerated in adults. Limb swelling reactions from booster doses are rare.[39,40,52]

Extensive limb swelling, defined as swelling and/or redness involving at least half the circumference of the limb and the joints both above and below the injection site, is a recognised adverse event that occurs rarely following booster doses of DTPa. Such reactions commence within 48 hours of vaccination, last for 1 to 7 days and resolve completely without sequelae.[43] The pathogenesis of extensive limb swelling is poorly understood. In an analysis of 4th and 5th dose follow-up studies that examined 12 different DTPa vaccines, 2% of 1015 children who received consecutive doses of the same DTPa vaccine reported entire thigh swelling, which resolved completely.[43] A history of extensive limb swelling after a booster dose of DTPa is not a contraindication to reduced antigen formulations of dTpa at 11–13 years of age (or older).[62] Parents of children about to receive the booster dose of a DTPa-containing vaccine (at 4 years of age) should be informed of the small but well-defined risk of this adverse event which, even when extensive, is usually not associated with significant pain or limitation of movement.

Febrile convulsions are very infrequently reported following DTPa-containing vaccines, within 48 hours of vaccination. The risk is even lower in infants who complete their primary course at 6 months of age, as febrile convulsions are uncommon in children <6 months of age. Children who experience a febrile convulsion after a dose of DTPa-containing vaccine have a slightly greater risk of a further febrile convulsion following a subsequent dose of a DTPa-containing vaccine. This risk can be minimised by appropriate measures to prevent fever, so vaccination is still recommended.

Hypotonic-hyporesponsive episodes (HHE), defined as an episode of pallor, limpness and unresponsiveness, occur rarely following DTPa vaccine, 1 to 48 hours after vaccination. Shallow respiration and cyanosis may also occur in

an HHE. An HHE may last from a few minutes to 36 hours. In Australia during 2009, 3.2 cases of HHE were reported per 100 000 doses of DTPa-containing vaccine given to children <1 year of age.[63] Follow-up of children with HHE shows no long-term neurological or other sequelae and they can receive further doses of DTPa-containing vaccines.[64] Children who have an HHE following DTPa-containing vaccines should receive further doses as recommended. Supervision may be required under some circumstances; advice can be obtained from clinics specialising in the management of adverse events following immunisation (see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*).

Pertussis-containing vaccines do not cause infantile spasms or epilepsy. Infants and children known to have active or progressive neurological disease can be safely vaccinated with DTPa-containing vaccines. A large Canadian study found no evidence of encephalopathy following acellular pertussis vaccines.[65] For infants and children with stable neurological disease (including cerebral palsy), or a family history of idiopathic epilepsy or other familial neurological disorder, the risk of adverse events following DTPa-containing vaccines is the same as for other infants of the same age.

Sudden infant death syndrome (SIDS) is not associated with either DTPa or any pertussis-containing vaccine.[66] Some studies suggest a decreased risk of SIDS in children who have been vaccinated.[67-69]

Brachial neuritis (inflammation of a nerve in the arm, causing weakness or numbness) has been described following the administration of tetanus toxoid-containing vaccines, with an estimated excess risk of approximately 0.5–1 in 100 000 doses in adults.[70,71]

4.12.11 Public health management of pertussis

Pertussis (both suspected and confirmed) is a notifiable disease in all states and territories in Australia. Detailed information regarding case definitions and the management of pertussis cases and contacts can be found in the national guidelines for control of pertussis[72] (www.health.gov.au/cdnasongs).

Further instructions about the public health management of pertussis can also be obtained from state/territory public health authorities (see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*).

Suspected cases of pertussis should be investigated, regardless of vaccination status, as immunisation is not 100% effective and immunity wanes over time. The diagnosis of pertussis can be confirmed by either culture or nucleic acid testing of a per-nasal swab or nasopharyngeal aspirate specimen, or by serology. The appropriate diagnostic test depends on the age, vaccination history and duration of symptoms. PCR is usually the diagnostic method of choice, particularly if pertussis is suspected in someone who has received a pertussis-containing vaccine within the previous 5 years.[73]

To reduce the risk of transmission of *B. pertussis*, persons with pertussis infection should commence appropriate antibiotic therapy on clinical suspicion, if within 21 days of the onset of coryza. Antibiotic treatment does not shorten the course of the illness, but reduces infectivity if provided early in the illness. Detailed information regarding appropriate macrolide antibiotics and dosing can be found in the national guidelines for control of pertussis.[72,74]

Management of contacts of cases

Vaccination

Since a primary vaccination course requires three or more injections to protect against pertussis, infant vaccination cannot be effectively used to protect unimmunised infants. Vaccination has not been shown to have a role in controlling outbreaks at any age, even in closed settings. However, unvaccinated or partially vaccinated contacts, up to their 10th birthday, should be offered DTPa-containing vaccines, and older contacts should be offered dTpa (see 2.1.5 *Catch-up*).

Passive immunisation with normal human immunoglobulin is not effective in the prevention of pertussis.

Chemoprophylaxis

The benefit of chemoprophylaxis in preventing the secondary transmission of pertussis is limited due to multiple factors, including delayed clinical presentation, delayed diagnosis and imperfect compliance.[75] The use of chemoprophylaxis for prevention of secondary cases should be limited to close contacts of cases in the household setting who are vulnerable to severe complications of pertussis, or who, in settings such as early childhood education and care or healthcare facilities, may transmit pertussis to vulnerable contacts. Further recommendations regarding chemoprophylaxis of close contacts can be found in the national guidelines for control of pertussis.[72]

4.12.12 Variations from product information

The product information for Infanrix hexa states that this vaccine is indicated for primary immunisation of infants from the age of 6 weeks. The ATAGI recommends that this vaccine may also be used for catch-up of the primary schedule in children <10 years of age.

The product information for Infanrix IPV states that this vaccine is indicated for use in a 3-dose primary schedule for immunisation of infants from the age of 6 weeks and as a single booster dose for children ≤6 years of age who have previously been vaccinated against diphtheria, tetanus, pertussis and poliomyelitis. In addition, the ATAGI recommends that this product may also be used for catch-up of the primary schedule or as a booster in children <10 years of age.

The product information for Quadracel states that this vaccine is indicated for use in a 3-dose primary schedule from the age of 2 months to 12 months and may also be used as a booster dose for children from 15 months to 6 years of age who have previously been vaccinated against diphtheria, tetanus, pertussis and poliomyelitis. The ATAGI recommends that, when appropriate, this product may also be used for either catch-up of the primary schedule or as a booster dose in children aged <10 years. The ATAGI also recommends that the primary schedule may be commenced at 6 weeks of age, if required.

The product information for Tripacel states that this vaccine is indicated for use in a 3-dose primary schedule from the age of 2 months to 12 months and may also be used as a booster dose for children from 15 months to 8 years of age who have previously been vaccinated against diphtheria, tetanus and pertussis. The ATAGI recommends that, when appropriate, this product may also be used for either catch-up of the primary schedule or as a booster dose in children aged <10 years. The ATAGI also recommends that the primary schedule may be commenced at 6 weeks of age, if required.

The product information for Pediacel states that this vaccine is indicated for primary immunisation of infants from the age of 6 weeks and may also be used as a booster dose for children from 15 to 20 months of age who have previously been vaccinated against diphtheria, tetanus, pertussis, poliomyelitis and *Haemophilus influenzae* type b. The ATAGI recommends that, when appropriate, this product may also be used for either catch-up of the primary schedule or as a booster dose in children aged <10 years.

The product information for Adacel and Boostrix (reduced antigen content dTpa) states that these vaccines are indicated for booster doses only. The ATAGI recommends instead that, when a 3-dose primary course of diphtheria/tetanus toxoids is given to an adolescent/adult, dTpa should replace the 1st dose of dT, with 2 subsequent doses of dT. If dT is *not* available, dTpa can be used for all 3 primary doses, but this is *not* routinely recommended.

The product information for Adacel and Boostrix state that there is no recommendation regarding the timing and frequency of booster doses against pertussis in adults; however, the ATAGI recommends that pregnant or post-partum women can receive a booster dose every 5 years and that other adults in contact with infants and/or at increased risk from pertussis can receive a booster dose every 10 years.

The product information for Boostrix, Boostrix-IPV and Adacel states that dTpa-containing vaccine should not be given within 5 years of a tetanus toxoid-containing vaccine. The product information for Adacel Polio states that dTpa-containing vaccine should not be given within 3 years of a tetanus toxoid-containing vaccine. The ATAGI recommends instead that, if protection against pertussis is required, dTpa-containing vaccines can be administered at any time following receipt of a dT-containing vaccine.

The product information for Boostrix, Boostrix-IPV, Infanrix hexa and Infanrix IPV states that these vaccines are contraindicated in children with encephalopathy of unknown aetiology or with neurologic complications occurring within 7 days following a vaccine dose. The ATAGI recommends instead that the only contraindication is a history of anaphylaxis to a previous dose or to any of the vaccine components.

References

A full reference list is available on the electronic *Handbook* or website www.immunise.health.gov.au

4.13 PNEUMOCOCCAL DISEASE

4.13.1 Bacteriology

Streptococcus pneumoniae (pneumococcus) is a Gram-positive coccus. The polysaccharide capsule is the most important virulence factor of pneumococci.[1,2] Over 90 capsular antigenic types (serotypes) have been recognised, each of which elicits type-specific immunity in the host.[3,4] The natural reservoir of pneumococci is the mucosal surface of the upper respiratory tract of humans.[1,3] In a large majority of hosts, pneumococci are carried with no apparent symptoms. Different pneumococcal serotypes vary in their propensity to cause nasopharyngeal colonisation or disease. Worldwide, only a limited number of serotypes are responsible for most cases of invasive pneumococcal disease (IPD) but the predominant serotypes vary by age group and geographic area.[5,6] Antibiotic resistance in pneumococci is an increasing challenge; in 2006, 11% of Australian IPD isolates were non-susceptible to penicillin and 3% were non-susceptible to ceftriaxone/cefotaxime.[7]

4.13.2 Clinical features

Person-to-person transmission of *S. pneumoniae* occurs via contact with respiratory droplets of colonised persons. Almost all pneumococcal disease probably begins with the establishment of nasopharyngeal colonisation. From the nasopharynx, pneumococci may spread locally into adjacent sites to cause sinusitis, otitis media or pneumonia. Pneumococci may enter the bloodstream, and also localise in the meninges, causing meningitis, or at other sites including bones, joints and soft tissues.[1-3,5] For disease surveillance purposes, detection of *S. pneumoniae* in a normally sterile site, such as blood, cerebrospinal fluid or pleural fluid, by culture or nucleic acid testing, is classified as IPD. The major clinical categories of IPD are meningitis, bacteraemic pneumonia, and bacteraemia without focus. In adults, pneumonia with bacteraemia is the most common manifestation of IPD. Although more difficult to measure for non-bacteraemic cases, it is estimated that pneumococci account for over one-third of all community-acquired pneumonia and up to half of hospitalised pneumonia in adults.[2,8] In children, the most common manifestation is bacteraemia without focus, accounting for approximately 70% of IPD, followed by pneumonia with bacteraemia. Meningitis, although least common, is the most severe category of IPD and has an estimated case-fatality rate of about 30%.[1,2] Acute otitis media (AOM) is the most common non-invasive manifestation of pneumococcal disease in children. *S. pneumoniae* is detected in 28 to 55% of middle ear aspirates from children with AOM.[2,5,9]

Immunocompromised persons who are unable to mount an adequate immune response to pneumococcal capsular antigens, including those with asplenia, have the highest risk of IPD.[1,2,4] Household crowding, exposure to cigarette smoke, childcare attendance, excessive alcohol consumption and certain non-immunocompromising chronic medical conditions are also associated with

greater risk and/or severity of IPD.[1,2,10,11] Indigenous populations in developed countries, including Aboriginal and Torres Strait Islander people in Australia, have a disproportionately high burden of IPD.[1,12,13]

4.13.3 Epidemiology

The highest incidence of IPD is seen at the extremes of age, in young children and the elderly.[5,7] In Australia, vaccination with 7-valent pneumococcal conjugate vaccine (7vPCV) was first funded under the NIP from mid-2001, to 5 years of age for Indigenous children living in Central Australia and children with specified predisposing medical conditions, and to 2 years of age for non-Indigenous children living in Central Australia and Indigenous children in the rest of the country. One dose of the 23-valent pneumococcal polysaccharide vaccine (23vPPV) at 18–24 months of age, as a booster following a primary 7vPCV schedule, was also funded for Indigenous children without predisposing medical conditions living in jurisdictions with the highest incidence of IPD (the Northern Territory, Queensland, South Australia and Western Australia). From January 2005, NIP-funded 7vPCV was extended to all infants nationally, together with catch-up vaccination for all children aged <2 years. High vaccination uptake of over 90% has been maintained since the inception of universal infant pneumococcal vaccination.

The introduction of 7vPCV led to a dramatic reduction in the overall incidence of IPD in Australia, which was greatest in the primary target group of children <2 years of age and for IPD caused by the seven vaccine serotypes. Among non-Indigenous children <2 years of age, the overall notification rate of IPD declined by 75%, from 78 per 100 000 in the pre-vaccination period (2002–2004) to 19.5 per 100 000 in the post-vaccination period (2007); IPD due to 7vPCV serotypes decreased by 97%, from 60.9 to 2.1 per 100 000, respectively.[14,15] There was also a marked reduction in pneumonia hospitalisations, presumed to be attributable to 7vPCV vaccination, in children <2 and 2–4 years of age (of 38% and 28%, respectively).[16] Reductions in IPD were also observed in age groups not targeted for vaccination ('herd immunity' effect); the incidence of IPD due to 7vPCV serotypes declined by between 50 and 60% in various age groups >5 years of age.[14]

Although 7vPCV use resulted in a marked reduction in rates of IPD due to vaccine serotypes, IPD among Indigenous children remains disproportionately higher than in non-Indigenous children, due to significantly higher rates of IPD caused by non-7vPCV serotypes.[7,15,17] (See also 3.1 *Vaccination for Aboriginal and Torres Strait Islander people*.)

Serotype distribution of pneumococcal disease is more diverse in adults than in children, and more diverse in Aboriginal and Torres Strait Islanders than in other Australians. Prior to universal infant vaccination, 85% of IPD in children aged <2 years was caused by the seven vaccine serotypes;[18] however, the proportion differed substantially between Indigenous children (46%) and

non-Indigenous children (88%).[19,20] Since the implementation of the universal 7vPCV program, increased rates of IPD caused by certain serotypes not contained in 7vPCV (replacement disease) have been observed in Australia and several other countries. This is particularly so among non-Indigenous children aged <2 years, in whom 44% of IPD in 2007 was due to serotype 19A.[15] In 2009 and 2010, two extended-valency pneumococcal conjugate vaccines (the 10-valent [10vPCV] and the 13-valent [13vPCV], respectively) became available in Australia. In the Northern Territory, 10vPCV replaced 7vPCV from October 2009. In other jurisdictions, 13vPCV (which includes serotype 19A) replaced 7vPCV under the NIP for infants in July 2011, and in the Northern Territory replaced 10vPCV from September 2011.

Vaccination using 23vPPV was introduced in 1999 for all Indigenous adults aged ≥50 years and younger Indigenous adults with risk factors. Since January 2005, 23vPPV has also been funded under the NIP for non-Indigenous adults aged ≥65 years. Persons aged <65 years with a condition(s) associated with an increased risk of IPD can access 23vPPV through the Pharmaceutical Benefits Scheme. Most IPD isolates in adults belong to serotypes contained in 23vPPV.[7,21] In non-Indigenous adults, the prevalence of risk factors among those with IPD increases with age. In contrast, among Indigenous adults, there is a high prevalence of risk factors in IPD cases of all ages.[21] Overall, among adults aged ≥65 years, the incidence of IPD was 29% lower in 2006–2007 than in 2002–2004. This was mostly due to a 53% decrease in the incidence of serotypes included in 7vPCV, despite increases in IPD caused by serotypes both included in (46%) and not included in (57%) 23vPPV.[14]

The impact of 23vPPV on rates of IPD in Indigenous adults has varied in different geographical areas and, at a national level, disparities remain in disease rates between Indigenous and non-Indigenous adults. As is the case for influenza and pneumonia, rates of IPD are highest in older Indigenous adults (see 3.1 *Vaccination for Aboriginal and Torres Strait Islander people*).

4.13.4 Vaccines

There are two different types of pneumococcal vaccines – pneumococcal conjugate vaccine (PCV) and pneumococcal polysaccharide vaccine (PPV). Among the pneumococcal conjugate vaccines, formulations vary in the number of pneumococcal serotypes included and the conjugating proteins used. Pneumococcal conjugate vaccines are immunogenic in young infants and can induce an immune memory response. In contrast, 23vPPV is poorly immunogenic for most serotypes in children aged <2 years and does not induce immune memory; however, 23vPPV contains more serotypes.

Pneumococcal conjugate vaccines

- ***Synflorix*** – GlaxoSmithKline (10-valent pneumococcal conjugate vaccine; 10vPCV). Each 0.5 mL monodose vial or pre-filled syringe contains 1 µg of pneumococcal capsular polysaccharide of serotypes 1, 5, 6B, 7F, 9V, 14, 23F and 3 µg of serotype 4, conjugated to a total of 9–16 µg of non-typeable *H. influenzae* protein D, 3 µg of serotype 18C conjugated to 5–10 µg of tetanus toxoid carrier protein, and 3 µg of serotype 19F conjugated to 3–6 µg of diphtheria toxoid carrier protein, adsorbed onto 0.5 mg aluminium as aluminium phosphate.
- ***Prevenar 13*** – Pfizer Australia Pty Ltd (13-valent pneumococcal conjugate vaccine; 13vPCV). Each 0.5 mL monodose pre-filled syringe contains 2.2 µg each of pneumococcal capsular polysaccharide of serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 23F and 4.4 µg of serotype 6B, conjugated to non-toxic *Corynebacterium diphtheriae* CRM_{197} protein, adsorbed onto 0.565 mg aluminium phosphate; succinic acid; polysorbate 80.

7-valent pneumococcal conjugate vaccine (7vPCV)

A 7vPCV with the mutant non-toxic diphtheria CRM_{197} protein as the conjugating protein (Prevenar) became available in Australia in 2001. Efficacy data on the 7vPCV from a pivotal trial in the United States found greater than 95% protective efficacy against IPD caused by the serotypes contained in the vaccine.[22] A Cochrane review of clinical trials estimated an efficacy of 80% against vaccine-type IPD for PCVs (most, but not all, of which used CRM_{197} as the conjugating protein) in children <2 years of age.[23] Based on the included studies, the effectiveness against IPD of any serotype among these children was 58%,[23] noting that the proportion of IPD due to vaccine serotypes varies among different populations. Effectiveness against X-ray confirmed pneumonia (using World Health Organization [WHO] criteria) was lower, at 27%.

A 3-dose primary vaccination schedule for 7vPCV consisting of doses at 2, 4 and 6 months of age without a booster in the 2nd year of life was recommended in Australia from 2001 (except for persons at increased risk of IPD). This recommendation was initially based on data suggesting similar efficacy against type-specific IPD with either 3 or 4 doses.[22] Subsequent Australian data have shown similar degrees of direct and indirect reduction in IPD and pneumonia hospitalisations as those seen in countries with alternate schedules.[24-27]

7vPCV is no longer available, having been replaced in 2011 by 13vPCV made by the same manufacturer.

10-valent pneumococcal conjugate vaccine (10vPCV)

10vPCV has been registered for use in Australia since 2009 and is included under the NIP. The protein D of non-typeable *H. influenzae* (NTHi) is one of the main conjugating proteins in this vaccine. This vaccine was used for all children aged <2 years in the Northern Territory from October 2009 to September 2011, after which 13vPCV has been used. (See also 3.1 *Vaccination for Aboriginal and Torres Strait Islander people*.)

Clinical trials on 10vPCV with efficacy outcomes are not yet published; registration of 10vPCV in Australia was based on immunogenicity data.[28-32] A clinical study of a prototype 11-valent pneumococcal vaccine (containing the 10 serotypes in 10vPCV plus serotype 3), also conjugated to NTHi protein D, showed significant protective efficacy of approximately 58% against acute otitis media caused by vaccine serotypes (as well as protective efficacy of approximately 36% against AOM caused by *H. influenzae*).[33] 10vPCV has been shown to produce robust antibody responses to all 10 serotypes contained in the vaccine after a 4th (booster) dose in the 2nd year of life, but lesser antibody responses after 3 primary doses given in infancy.[31,32] Although 10vPCV does not contain specific antigens for serotypes 6A or 19A, there were also measurable levels of antibody against these cross-reacting serotypes in functional antibody assays.[31,32]

13-valent pneumococcal conjugate vaccine (13vPCV)

13vPCV has been registered in Australia since 2010, and used in the NIP since July 2011. A single supplementary dose of 13vPCV for children aged 12–35 months who completed primary vaccination with 7vPCV was available under the NIP for 12 months from October 2011.

Registration of 13vPCV was based on immunogenicity studies showing non-inferiority for the 7vPCV serotypes and comparable antibody response to the additional serotypes.[34-39] This includes serotype 19A, for which high levels of functional antibody have been demonstrated. Early data from 13vPCV use in England and Wales in 2011 have shown an impact against IPD caused by the additional serotypes contained in the vaccine.[40]

Based on the substantial impact of the 7vPCV program on serotype-specific IPD, the similar composition of 13vPCV and 7vPCV, and immunogenicity data, a 2, 4, 6 month schedule without a booster is also recommended for 13vPCV (except for those with a medical condition(s) associated with an increased risk of IPD or Indigenous children living in high-incidence regions). The comparative effectiveness of this schedule will continue to be monitored.

13vPCV has also been registered since October 2011 for use in adults aged ≥50 years, based on immunogenicity data showing equivalent or better antibody responses than those provided by 23vPPV for the shared vaccine serotypes. There are currently no data on clinical outcomes for 13vPCV, but a study examining its efficacy against pneumonia in adults is underway.[41] In the absence of evidence

of superior effectiveness against IPD or non-IPD pneumonia, the relative benefit of 13vPCV over 23vPPV for adults is uncertain, since the serotype coverage of 13vPCV is more limited. It is also uncertain whether the level of reduction in IPD due to the additional serotypes contained in 13vPCV among adults (herd immunity effect) will be similar to that seen following widespread use of 7vPCV in children.

Pneumococcal polysaccharide vaccine

- ***Pneumovax 23*** – CSL Limited/Merck & Co Inc (23-valent pneumococcal polysaccharide vaccine; 23vPPV). Each 0.5 mL monodose vial contains 25 µg each of pneumococcal capsular polysaccharide of serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F and 33F; 0.25% phenol.

23vPPV contains polysaccharides derived from the 23 most frequent or most virulent capsular types of *S. pneumoniae* isolated from sterile fluids in the United States in the 1970s/early 1980s, with worldwide serotype distribution and potential cross-reactive serotypes also taken into consideration.[42] These serotypes are responsible for most IPD cases in adults in Australia. 23vPPV induces significant immune responses in immunocompetent adults, including the elderly, with no substantial differences in immune response between older and younger subjects, but poor responses in the immunocompromised.[43] In children <2 years of age, the antibody response is limited to a small number of serotypes without previous 7vPCV vaccination.[44]

The latest published Cochrane review in 2008 found an estimated overall protective efficacy of 74% for pneumococcal polysaccharide vaccines against IPD, based on randomised controlled trials (RCTs). The review also found a vaccine effectiveness of 52% against IPD in older adults or adults with conditions associated with an increased risk of IPD, based on observational studies, but lower efficacy against all-cause pneumonia, based on RCTs (29%).[45] Evidence from more recent controlled trials and observational studies using 23vPPV in the elderly population is similar.[46-52] Recent data from England and Wales reported 23vPPV vaccine effectiveness of 48% against IPD within 2 years of vaccination for adults aged ≥65 years, but effectiveness waned and became insignificant beyond 5 years. In the subset of adults aged 65–74 years with no risk factors, 23vPPV effectiveness was higher (65% within 2 years) and was maintained for longer.[53] In Victoria, 23vPPV vaccine effectiveness was estimated to be 71% for adults aged >65 years.[54]

There are no studies on the effectiveness of revaccination with 23vPPV for disease endpoints, although significant and sustained antibody responses after revaccination are seen in adults, including the elderly.[55-59] Evidence of

lesser antibody responses to 2nd or subsequent doses of 23vPPV in adults is variable,[55-58,60] and, even if present, its correlation with clinical effectiveness is unknown.

4.13.5 Transport, storage and handling

Transport according to *National vaccine storage guidelines: Strive for 5*.[61] Store at +2°C to +8°C. Do not freeze.

10vPCV should be protected from light.

4.13.6 Dosage and administration

The dose of pneumococcal conjugate vaccines (10vPCV, 13vPCV) is 0.5 mL, to be given by IM injection, in the opposite limb to other injectable vaccines, if possible.

The dose of pneumococcal polysaccharide vaccine (23vPPV) is 0.5 mL, to be given by either IM or SC injection, in the opposite limb to other injectable vaccines, if possible. The IM route is preferred, as a 3-fold greater rate of injection site reactions is found following administration of 23vPPV by the SC route.[62] However, a vaccine dose administered subcutaneously does not need to be repeated.

10vPCV (Synflorix) is registered for use in infants and children aged 6 weeks up to 5 years.

13vPCV (Prevenar 13) is registered for use in infants and children aged 6 weeks up to 17 years and adults aged ≥50 years.

23vPPV (Pneumovax 23) is registered for use in children aged ≥2 years and in adults.

Co-administration with other vaccines

10vPCV may be concurrently administered with other vaccines routinely used in the infant schedule.

13vPCV may be concurrently administered with other vaccines in the infant schedule, including inactivated trivalent influenza vaccine. However, parents/carers of infants or children who are recommended to receive both influenza vaccine and 13vPCV should be advised of the increased risk of fever following concomitant administration of these vaccines (see 4.13.10 *Precautions* below).

Simultaneous administration of Zostavax with pneumococcal polysaccharide vaccine is not routinely recommended; if possible, the two vaccines should be given at least 4 weeks apart. However, inadvertent administration of Zostavax and pneumococcal polysaccharide vaccine at the same time or at an interval of less than 4 weeks does not require revaccination. One clinical trial showed reduced immunogenicity of Zostavax in subjects who received both vaccines concomitantly, compared with those who received Zostavax alone; the immunogenicity of 23vPPV was not affected by concurrent administration.[63]

However, an observational study from the United States suggests this may not impact on Zostavax effectiveness.[64-66] (See also 4.24 *Zoster*.)

Interchangeability of 10vPCV and 13vPCV

There are no available specific data on the interchangeability of 10vPCV and 13vPCV. Although completion of a primary course of pneumococcal conjugate vaccine with the same formulation is generally preferred, if vaccination with 10vPCV is commenced (e.g. in children born overseas), completion of the course with 13vPCV is acceptable.

4.13.7 Recommendations

Children aged <2 years

All children are recommended to receive a complete course of pneumococcal conjugate vaccination. The total number of doses recommended depends on the vaccine type used, on whether the child has a medical condition(s) associated with an increased risk of IPD (see List 4.13.1), on the child's Indigenous status and on whether the child is living in a jurisdiction with a high incidence of IPD (the Northern Territory, Queensland, South Australia or Western Australia).

If 10vPCV is used for primary vaccination in infants, a total of 4 doses are recommended, regardless of the child's Indigenous status or place of residence, or whether the child has any underlying medical condition(s) associated with an increased risk of IPD. The recommended schedule is 3 primary doses, at 2, 4 and 6 months of age, followed by 1 booster dose at between 12 and 18 months of age (at least 6 months after the 3rd primary dose) (a '3+1' schedule).

If 13vPCV is used for primary vaccination in infants, the total recommended schedule for most children is 3 primary doses, at 2, 4 and 6 months of age (a '3+0' schedule); however, additional doses are required for some children, as summarised in Table 4.13.1. A booster dose of 13vPCV is recommended for young Indigenous children living in the four jurisdictions specified above. In these children, the risk of IPD is comparable to the risk of IPD in children with certain medical conditions (see List 4.13.1).

The 1st dose of pneumococcal conjugate vaccine can be given as early as 6 weeks of age. If the 1st dose is given at 6 weeks of age, the next scheduled doses should still be given at 4 months and 6 months of age.

Table 4.13.1: Recommendations for pneumococcal vaccination for children aged <5 years

	Recommended age for pneumococcal vaccine doses					
	2 months*	4 months	6 months	12 months	12–18 months	4–5 years
Children without any medical conditions associated with an increased risk of invasive pneumococcal disease (IPD)						
If 10vPCV is used for the primary course:						
All children	10vPCV	10vPCV	10vPCV	–	10vPCV	–
If 13vPCV is used for the primary course:						
Non-Indigenous children and Indigenous children in ACT, NSW, Tas or Vic	13vPCV	13vPCV	13vPCV	–	–	–
Indigenous children in NT, Qld, SA or WA	13vPCV	13vPCV	13vPCV	–	13vPCV†	–
Children with a medical condition(s) associated with an increased risk of IPD‡						
All children	13vPCV	13vPCV	13vPCV	13vPCV†§	–	23vPPV

* The 1st dose can be given as early as 6 weeks of age; the next scheduled doses should still be given at 4 months and 6 months of age.

† Only *one* booster dose of 13vPCV is required in the 2nd year of life, even if a child is both Indigenous, living in the Northern Territory, Queensland, South Australia or Western Australia, and also has one or more medical conditions associated with an increased risk of IPD.

‡ Refer to List 4.13.1, Categories A and B, for medical conditions associated with an increased risk of IPD in children.

§ The booster dose is due at 12 months of age, or later, depending on when the medical condition is diagnosed; see also 2.1.5 *Catch-up*, Table 2.1.11 *Catch-up schedule for 13vPCV (Prevenar 13) and 23vPPV (Pneumovax 23) in children with a medical condition(s) associated with an increased risk of IPD, presenting at age <2 years*.

For children aged 7–23 months who have not completed a full course of pneumococcal conjugate vaccines, the timing and number of further doses for 'catch-up' vaccination depends on age and previous doses administered. For recommendations, see the following three tables in 2.1.5 *Catch-up*:

- Table 2.1.9 *Catch-up schedule for 13vPCV (Prevenar 13) for non-Indigenous children, and Indigenous children residing in the Australian Capital Territory, New South Wales, Tasmania and Victoria, who do not have any medical condition(s) associated with an increased risk of invasive pneumococcal disease (IPD), aged <5 years*
- Table 2.1.10 *Catch-up schedule for 13vPCV (Prevenar 13) for Indigenous children residing in the Northern Territory, Queensland, South Australia or Western Australia ONLY, who do not have any medical condition(s) associated with an increased risk of invasive pneumococcal disease (IPD), aged <5 years*

- Table 2.1.11 *Catch-up schedule for 13vPCV (Prevenar 13) and 23vPPV (Pneumovax 23) in children with a medical condition(s) associated with an increased risk of IPD, presenting at age <2 years* (for children aged 7–23 months with a medical condition(s) associated with an increased risk of IPD who have not completed a full course of pneumococcal conjugate vaccines).

If catch-up is required in a child who has commenced vaccination with 10vPCV, subsequent doses should be with 13vPCV. If 13vPCV is not available, 10vPCV may be used, and catch-up vaccination should be provided according to the rules in Table 2.1.10.

List 4.13.1: Conditions associated with an increased risk of invasive pneumococcal disease (IPD) in children and adults, by severity of risk*†

Category A: Conditions associated with the *highest* increased risk of IPD

- functional or anatomical asplenia, including:
  - » sickle cell disease or other haemoglobinopathies
  - » congenital or acquired asplenia (e.g. splenectomy), splenic dysfunction
- immunocompromising conditions, including:
  - » congenital or acquired immune deficiency, including symptomatic IgG subclass or isolated IgA deficiency (*Note*: children who require monthly immunoglobulin infusion are unlikely to benefit from vaccination)
  - » immunosuppressive therapy (including corticosteroid therapy ≥2 mg/kg per day of prednisolone or equivalent for more than 1 week) or radiation therapy, where there is sufficient immune reconstitution for vaccine response to be expected
  - » haematological and other malignancies
  - » solid organ transplant
  - » haematopoietic stem cell transplant (HSCT)‡
  - » HIV infection (including AIDS)
  - » chronic renal failure, or relapsing or persistent nephrotic syndrome
- proven or presumptive cerebrospinal fluid (CSF) leak
- cochlear implants
- intracranial shunts

Category B: Conditions associated with an increased risk of IPD

- chronic cardiac disease
  - » particularly cyanotic heart disease or cardiac failure in children
  - » excluding hypertension only (in adults)
- chronic lung disease, including:
  - » chronic lung disease in preterm infants
  - » cystic fibrosis
  - » severe asthma in adults (requiring frequent hospital visits and use of multiple medications)
- diabetes mellitus
- Down syndrome
- alcoholism
- chronic liver disease
- preterm birth at <28 weeks gestation§
- tobacco smoking¶

* See also 3.3.3 *Vaccination of immunocompromised persons* for more recommendations for immunocompromised persons, including more specific revaccination recommendations for haematopoietic stem cell transplant recipients.

† Recommendations for pneumococcal vaccination differ for those aged >5 years (but not for those aged <5 years) between categories in this table, i.e. depending on whether the person is in 'Category A: Conditions associated with the highest increased risk of IPD' or 'Category B: Conditions associated with an increased risk of IPD'. See also relevant sections below.

‡ HSCT recipients require 3 doses of 13vPCV post transplantation, followed by 23vPPV, irrespective of previous vaccine doses received (see Table 3.3.3 *Recommendations for revaccination following HSCT in children and adults, irrespective of previous immunisation history*).

§ All infants born at <28 weeks gestation should receive vaccines recommended for those up to age 5 years with a medical condition(s) associated with an increased risk of IPD, according to Table 4.13.1. Thereafter, they only require further pneumococcal vaccine doses if they have chronic lung disease, and/or other chronic medical conditions as specified above.

¶ Tobacco smoking is not a medical condition, but is associated with an increased risk of IPD.

Children aged 2–5 years

Children aged 2–5 years who *do not* have a medical condition associated with an increased risk of IPD are not routinely recommended to receive further pneumococcal vaccine doses. If they have not previously received any PCV doses, or had only 1 dose of a pneumococcal conjugate vaccine before 12 months of age, a single dose of 13vPCV is recommended (see 2.1.5 *Catch-up*, Table 2.1.9 *Catch-up schedule for 13vPCV (Prevenar 13) for non-Indigenous children, and*

Indigenous children residing in the Australian Capital Territory, New South Wales, Tasmania and Victoria, who do not have any medical condition(s) associated with an increased risk of IPD, aged <5 years and Table 2.1.10 *Catch-up schedule for 13vPCV (Prevenar 13) for Indigenous children residing in the Northern Territory, Queensland, South Australia or Western Australia ONLY, who do not have any medical condition(s) associated with an increased risk of IPD, aged <5 years*).

Children who have a medical condition(s) associated with an increased risk of IPD, as described in List 4.13.1 (Categories A and B), should receive a dose of 23vPPV at 4–5 years of age. Table 4.13.2 indicates which vaccines are recommended, depending on prior vaccination history. The need for additional doses of pneumococcal vaccine is based on the continuing higher susceptibility of these children to IPD at older ages, and extrapolation from data showing that boosting of immune responses to certain 7vPCV serotypes occurs when a dose of 23vPPV follows a prior 7vPCV dose(s).[63,67-70] Recommendations for children with a medical condition(s) associated with an increased risk of IPD (Categories A and B) are the same regardless of Indigenous status or jurisdiction of residence.

A minimum interval of 2 months between the last dose of 13vPCV and 23PPV is recommended, based on a small number of studies among children of different ages with underlying conditions, which have shown that 23vPPV is immunogenic if given approximately 2 months after a 7vPCV dose.[71-74]

Table 4.13.2: Recommendations for pneumococcal vaccination for children aged 2–5 years with a medical condition(s) associated with an increased risk of invasive pneumococcal disease (IPD) *(see List 4.13.1, Categories A and B)**

Vaccination history†		Recommendations	
Primary course of any pneumococcal conjugate vaccine	**Supplementary/ booster dose of 13vPCV (at age ≥12 months)**	**Number of further 13vPCV dose(s) required for children aged 2–5 years**	**Single 23vPPV dose required at age 4–5 years‡**
Completed	Received	0	Yes
Completed	Not received	1	Yes
Not completed	Not received	2§	Yes

* HSCT recipients require 3 doses of 13vPCV post transplantation, followed by 23vPPV, irrespective of previous vaccine doses received (see Table 3.3.3 *Recommendations for revaccination following HSCT in children and adults, irrespective of previous immunisation history*).

† See also 2.1.5 *Catch-up*, Table 2.1.11 *Catch-up schedule for 13vPCV (Prevenar 13) and 23vPPV (Pneumovax 23) in children with a medical condition(s) associated with an increased risk of IPD, presenting at age <2 years*. *Note*: this table primarily refers to 13vPCV, but could apply to use of 10vPCV if the former was not available.

‡ At least 2 months after the last dose of PCV, whichever is later.

§ Minimum interval between the 2 doses should be 2 months.

Children aged >5 years to <18 years

Pneumococcal vaccine is not recommended for children in this age group who do not have a medical condition(s) associated with an increased risk of IPD (see List 4.13.1). The exception is in older Indigenous children (aged >15 years) who have an increased risk of IPD, especially in the Northern Territory, where a dose of 23vPPV is provided to all Indigenous adolescents at approximately 15 years of age, based on the very high prevalence of conditions associated with an increased risk of IPD and incidence of IPD in this sub-population (see 'Adults aged ≥18 years' below and 3.1 *Vaccination for Aboriginal and Torres Strait Islander people*).

For children with a medical condition(s) associated with an increased risk of IPD, further pneumococcal vaccine doses are recommended, as discussed below, depending on the child's level of risk.

Those with the highest increased risk of IPD (List 4.13.1, Category A)

Children aged >5 to <18 years with a *pre-existing* chronic medical condition(s) associated with the highest increased risk of IPD (List 4.13.1, Category A), who were previously vaccinated according to the recommendations in Table 4.13.2, should receive another 23vPPV dose 5 years after their 1st 23vPPV dose, at approximately 10 years of age. Their next 23vPPV dose should be approximately 10 years later, at age 18–20 years. (See also 'Adults with a condition(s) associated with an increased risk of IPD' below.) If a child in this category has never received a dose of 13vPCV previously, 1 dose of 13vPCV should be administered, with the exception of HSCT recipients who should receive 3 doses of 13vPCV (see Table 3.3.3 *Recommendations for revaccination following HSCT in children and adults, irrespective of previous immunisation history*). This should then be followed by 23vPPV approximately 2 months later (if no prior 23vPPV dose has been received), or a minimum of 5 years after a prior 23vPPV dose (see above). The minimum interval between a previous 23vPPV dose and the single 13vPCV dose, if required, is 12 months.

Children in this age group with a *newly* identified medical condition(s) associated with the highest increased risk of IPD (List 4.13.1, Category A) are recommended to receive a dose of 23vPPV at diagnosis. If they have not previously received a dose of 13vPCV, they should receive one 13vPCV dose at diagnosis, followed by their 1st 23vPPV dose a minimum of 2 months later. A further dose of 23vPPV is recommended 5 years after the 1st 23vPPV dose (minimum 2 months after 13vPCV). Their next 23vPPV dose should be approximately 10 years later, or at age 18–20 years, whichever is later (see 'Adults with a condition(s) associated with an increased risk of IPD' below).

Those with an increased risk of IPD (List 4.13.1, Category B)

Children aged >5 to <18 years with a *pre-existing* medical condition(s) associated with an increased risk of IPD (List 4.13.1, Category B) who received a dose of 23vPPV at 4–5 years of age should receive a 2nd dose of 23vPPV approximately 10 years later, at 15–18 years of age. That dose should be counted as their 1st

adult 23vPPV dose. Based on current evidence, 13vPCV is not specifically recommended for children in this age and risk group, regardless of previous vaccination history.

For children in this age group with a *newly* identified medical condition(s) associated with an increased risk of IPD (List 4.13.1, Category B), a single dose of 23vPPV is recommended at the time of diagnosis. In the rare situation where a previous dose of 23vPPV has been given (e.g. in Indigenous children in some jurisdictions), this dose should be given at least 5 years after the previous 23vPPV dose. The next 23vPPV dose should be given approximately 5–10 years after the 1st 23vPPV dose and counted as their 1st adult 23vPPV dose (see 'Adults with a condition(s) associated with an increased risk of IPD' below).

Adults aged ≥18 years

The recommendations for use of 23vPPV in adults who do not have a condition(s) associated with an increased risk of IPD are summarised in Table 4.13.3. Recommendations for the use of 13vPCV and/or 23vPPV in adults with a condition(s) associated with an increased risk of IPD (List 4.13.1, Category A or B) are described in the text below.

The number of doses recommended depends on age, Indigenous status and the presence of a condition(s) associated with an increased risk of IPD. Up to 3 doses (i.e. 2 revaccinations) of 23vPPV in adulthood are recommended, depending on these factors. This is based on limited data on adverse events and effectiveness, as well as uncertainty regarding the clinical significance of blunting of antibody response (immune hyporesponsiveness) following revaccination with 23vPPV, especially with multiple revaccinations.

For adults, prior childhood doses of 23vPPV that may have been given at either 18–24 months and/or 4–5 years of age should not be counted; that is, they are not relevant to the recommendations given in Table 4.13.3. In the Northern Territory, a dose of 23vPPV is provided to all Indigenous adolescents at approximately 15 years of age, based on the very high prevalence of conditions associated with an increased risk of IPD and incidence of IPD in this population; this dose should be considered as a dose received in adulthood for the purpose of limiting the total lifetime number of 23vPPV doses to 3.

Although 13vPCV is registered for use in adults aged ≥50 years, there is currently insufficient evidence to recommend its use in preference to 23vPPV at the individual or population level for persons aged ≥18 years who do not have a condition(s) associated with an increased risk of IPD (see 4.13.4 *Vaccines* above). Updated recommendations on the use of 13vPCV in adults without an increased risk of IPD will be made when more data are available (see Immunise Australia website www.immunise.health.gov.au).

Non-Indigenous adults

A single dose of 23vPPV is recommended for adults at 65 years of age. For those aged >65 years who did not receive a dose at 65 years of age, a single catch-up dose of 23vPPV should be offered as soon as possible. Routine revaccination with 23vPPV for non-Indigenous adults without a condition(s) associated with an increased risk of IPD is not recommended (see Table 4.13.3).

Aboriginal and Torres Strait Islander (Indigenous) adults

A 1st dose of 23vPPV is recommended for all Indigenous adults reaching the age of 50 years (Table 4.13.3). This is based on the increased risk of IPD in Indigenous adults compared with non-Indigenous adults, and the high prevalence of conditions associated with an increased risk of IPD (including tobacco smoking) in Indigenous adults after 50 years of age, compared with younger ages. A 2nd dose of 23vPPV is recommended 5 years after the 1st dose. For those aged ≥50 years who have never received a dose of 23vPPV, a 1st dose should be offered as soon as possible, with a 2nd dose recommended 5 years after the 1st dose.

Indigenous adults aged <50 years with a condition(s) associated with an increased risk of IPD (List 4.13.1), should be vaccinated according to the recommendation for 'Adults with a condition(s) associated with an increased risk of IPD' below.

Table 4.13.3: Recommendations for pneumococcal vaccination using 23vPPV for adults who *do not* have a condition(s) associated with an increased risk of invasive pneumococcal disease (IPD)*

Non-Indigenous adults			
Current age (years)	**1st dose of 23vPPV**	**2nd dose of 23vPPV (1st revaccination)**	**3rd dose of 23vPPV (2nd revaccination)**
18 to <65 years	Not recommended	Not recommended	Not recommended
≥65 years	Give now	Not recommended	Not recommended
Indigenous adults			
Current age (years)	**1st dose of 23vPPV**	**2nd dose of 23vPPV (1st revaccination)**	**3rd dose of 23vPPV (2nd revaccination)**
18 to <50 years	Not recommended†	Not recommended	Not recommended
≥50 years	Give now†‡	5 years after 1st dose†‡	Not recommended

* See List 4.13.1 for conditions associated with an increased risk of IPD. Recommendations for those who have a condition(s) that places them at an increased risk of IPD are listed in the text below.

† In the Northern Territory, a dose of 23vPPV is provided to all Indigenous adolescents at approximately 15 years of age, based on the very high prevalence of conditions associated with an increased risk of IPD and incidence of IPD in this sub-population. This dose should be considered a dose received in adulthood for the purpose of limiting the total lifetime number of 23vPPV doses to 3.

‡ The minimum interval between any 2 doses of 23vPPV should be 5 years, and no more than 3 lifetime adult doses of 23vPPV are recommended.

Adults with a condition(s) associated with an increased risk of IPD (List 4.13.1)

Use of 13vPCV

Adults with a medical condition(s) associated with the highest increased risk of IPD in List 4.13.1, Category A (immunocompromising conditions, functional or anatomical asplenia, CSF leak, cochlear implant), are recommended to receive a single dose of 13vPCV,[75] with the exception of HSCT recipients who should receive 3 doses of 13vPCV (see Table 3.3.3 *Recommendations for revaccination following HSCT in children and adults, irrespective of previous immunisation history*). For those with a *newly diagnosed* (or newly recognised for the purposes of requiring vaccination) condition, the dose of 13vPCV should be given at the time of diagnosis and followed by 23vPPV doses. The 1st 23vPPV dose should be given a minimum of 2 months after 13vPCV (see 'Use of 23vPPV' below). For adults with a *pre-existing* condition listed in Category A, and who have received 1 or more prior doses of 23vPPV, the dose of 13vPCV should be given at least 12 months after the most recent dose of 23vPPV. (See also 'Persons with functional or anatomical asplenia' in 3.3.3 *Vaccination of immunocompromised persons*.)

Adults who have a condition listed in Category B in List 4.13.1 are not recommended to receive 13vPCV. 13vPCV is registered for use in children up to the age of 5 years only and in adults aged ≥50 years, and data in adults and in immunocompromised persons is limited. However, based on extrapolation from data on the 7vPCV,[76] providing a dose of 13vPCV to adults at the highest increased risk of IPD is likely to be beneficial.

Use of 23vPPV

All adults with a condition(s) associated with an increased risk of IPD (List 4.13.1, Categories A and B) are recommended to receive additional doses of 23vPPV (compared with those who do not have an increased risk).

In adults with a *pre-existing* condition (List 4.13.1, Categories A and B) the 1st adult dose of 23vPPV is recommended at approximately 18 years of age (see also 'Children aged >5 years to <18 years' above), or a minimum of 5 years after the most recent dose of 23vPPV, and is to be followed by up to 2 additional doses. For those *newly diagnosed*, or who have never received pneumococcal vaccination, a 1st dose of 23vPPV is recommended at identification of the risk condition if they are in Category B. If the adult has a condition(s) associated with the highest increased risk of IPD (listed in Category A), they should receive a single dose of 13vPCV at time of diagnosis (see above), followed by a 1st dose of 23vPPV a minimum of 2 months later.

A 2nd dose of 23vPPV is recommended for all at-risk adults in Categories A and B at approximately 5–10 years (minimum of 5 years) after the 1st dose of 23vPPV. A 3rd dose of 23vPPV is recommended at the age of 50 years for Indigenous adults and 65 years for non-Indigenous adults, or a minimum of 5 years after the 2nd dose, whichever is later.

For older adults with a *newly diagnosed* condition who have already received an age-based 1st dose of 23vPPV at age 65 years (non-Indigenous) or 50 years (Indigenous), a single revaccination dose of 23vPPV is recommended a minimum of 5 years after the previous dose of 23vPPV. For persons with a medical condition(s) associated with the highest increased risk of IPD (Category A), a 3rd dose of 23vPPV is recommended, a minimum of 5 years after the 2nd dose or at age 65 years, whichever is later.

If a younger adult (e.g. an Indigenous adult living in the Northern Territory) has received a dose of 23vPPV before identification of a risk condition in Category B, a 2nd dose of 23vPPV is recommended at diagnosis of the condition, or a minimum of 5 years after the 1st dose, whichever is later. A 3rd dose of 23vPPV is recommended at the age of 50 years for Indigenous adults and 65 years for non-Indigenous adults, or a minimum of 5 years after the 2nd dose, whichever is later.

In general, no more than three 23vPPV doses are recommended during a person's adult life.

4.13.8 Pregnancy and breastfeeding

23vPPV is not routinely recommended for pregnant or breastfeeding women. Although 23vPPV has been administered in pregnancy in the context of clinical trials[77] with no evidence of adverse effects, data are limited; deferral of vaccination with 23vPPV until after delivery is recommended unless there is an increased risk of IPD. Women of child-bearing age who have a condition(s) associated with an increased risk of IPD should be vaccinated before a planned pregnancy, or as soon as practicable after delivery (see 4.13.7 *Recommendations* above). 23vPPV may be given to breastfeeding women.

Data on use the use of 10vPCV and 13vPCV during pregnancy or lactation are not available. For adults with a condition(s) associated with an increased risk of IPD for whom a dose of 13vPCV is recommended, the dose should be deferred until after delivery and cessation of breastfeeding.

Refer to 3.3 *Groups with special vaccination requirements*, Table 3.3.1 *Recommendations for vaccination in pregnancy* for more information.

4.13.9 Contraindications

The only absolute contraindications to pneumococcal vaccines are:

- anaphylaxis following a previous dose of any pneumococcal vaccine
- anaphylaxis following any vaccine component.

4.13.10 Precautions

13-valent pneumococcal conjugate vaccine and inactivated influenza vaccines

One study in the United States has suggested that there is a slightly higher risk of febrile seizure associated with concurrent administration of 13vPCV and inactivated trivalent influenza vaccine than after receipt of either of the vaccines alone on separate days.[67] The increased likelihood of febrile seizures occurred within 1 day of vaccination in children aged 6–59 months who received 13vPCV concurrently with a 1st dose of inactivated trivalent influenza vaccine. The risk was estimated to be about 18 excess cases per 100 000 doses for those aged 6–59 months, with a peak of 45 per 100 000 doses for those aged 16 months. Given this relatively low increase in risk, providing 13vPCV and inactivated trivalent influenza vaccine concurrently to children aged 12–23 months is acceptable; however, immunisation service providers should advise parents regarding this, and provide the option of administering these two vaccines on separate days (with an interval of not less than 3 days). (See also 4.7 *Influenza*.) In the event that fever occurs following either vaccine, an interval may minimise the risk of increased adverse reactions.

4.13.11 Adverse events

10-valent pneumococcal conjugate vaccine

The safety profile of 10vPCV is similar to that of 7vPCV,[68] with no clinically relevant difference when co-administered with routine childhood vaccines.[69] In clinical trials, erythema, pain, or swelling of any degree at the injection site each occurred in approximately 30 to 50% of 10vPCV recipients. Erythema of >30 mm occurred in up to about 5% of 10vPCV recipients in the primary course. The frequency of local adverse events was higher after the booster dose. Irritability and drowsiness were reported in about 50% of 10vPCV recipients when co-administered with a DTPa-combination vaccine, but severe reactions occurred in fewer than 5%. When co-administered with DTPa-based combination vaccines, fever with temperature ≥38°C was reported in about 33% of 10vPCV recipients after primary or booster doses. Approximately 2 to 6% of 10vPCV recipients reported rectal temperature >39°C after primary vaccination and 1.5 to 3% after booster vaccination.[68]

13-valent pneumococcal conjugate vaccine

Pooled safety analysis from 13 clinical trials showed that the safety profile of 13vPCV in young children is similar to that of 7vPCV.[70,78] Pain/tenderness and erythema at the injection site occurred in about 50% of all 13vPCV recipients, and induration or swelling in about 33%. Pain interfering with movement occurred in about 8%. Moderate erythema and induration occurred more commonly after the toddler dose than after an infant dose, in about 13% of recipients. About 37% of 13vPCV childhood recipients reported fever, with about 5% reporting fever >39°C.[78] Fever occurred more frequently after the toddler dose than after the primary doses.[79] Other common systemic reactions included irritability, drowsiness/increased sleep and decreased appetite, reported in 70%, 60% and 39% of 13vPCV recipients, respectively.[78] Frequencies of each of these adverse events were comparable to those in 7vPCV recipients.[78]

Post-marketing surveillance in the United States has suggested the possibility of a higher risk of febrile seizure within a day of vaccination among those who received concurrent administration of 13vPCV and inactivated trivalent influenza vaccine in 2010–2011, compared with those who received either vaccine alone, especially in children aged 12–23 months (see 4.13.10 *Precautions* above).[67]

There is only limited information available on the safety of 13vPCV use in adults, from a study in which adults aged ≥65 years received 13vPCV with or without concurrent vaccination with the trivalent seasonal influenza vaccine.[80] Pain, redness and/or swelling at the 13vPCV injection site were very common, occurring in 47% in both groups. The common systemic reactions that were reported significantly more often among 13vPCV than placebo recipients, both concurrently receiving the trivalent influenza vaccine, were chills, rash and new muscle pain. Overall, there were no significant differences in adverse event

frequencies between those with or without prior 23vPPV doses. Recipients of concurrent administration of inactivated trivalent seasonal influenza vaccine with 13vPCV reported a higher frequency of systemic but not local reactions.[80]

23-valent pneumococcal polysaccharide vaccine

The proportion of vaccine recipients reporting local and systemic reactions after a primary or a repeat dose of pneumococcal polysaccharide vaccines varies among different study populations, and possibly with age.[55,57,81] About 50% or more of 23vPPV recipients will experience some soreness after the 1st dose, and swelling and redness are also very common, occurring in approximately 20% of recipients. Moderate or severe local adverse events that limit arm movement are also quite common, occurring in up to 5% of 1st dose recipients. Systemic reactions like myalgia, fatigue and chills are also very common. Fever ≥37.5°C occurs in up to 10% of 23vPPV recipients, but high fever is uncommon.[55,57,81]

Larger and more recent studies indicate that both local and systemic adverse events occur more commonly after a repeat dose of 23vPPV than after the 1st dose in adults, particularly more severe local adverse events, which may occur in up to approximately 20% of revaccinated subjects.[55,57,81] These findings effectively supersede the inconsistent findings from some smaller studies, which were limited by subject numbers and methodology.[82-86] Nevertheless, the local adverse events were mostly non-serious and self-limiting. In these studies, the repeat doses were given at least 5 years after the previous dose. Another study, which used hospitalisations coded as cellulitis or abscess of the upper limb within 3 days of pneumococcal vaccination as a proxy measure for very severe local adverse events, showed that these adverse events were significantly more likely when a repeat dose was given within 5 years of the 1st dose.[87] As severe local reactions are also associated with higher antibody levels,[57,62,81,88] this is the likely driver of the relationship with shorter intervals between the repeat and the primary dose and suggests that such local reactions are associated with more robust immunity.

4.13.12 Variations from product information

The product information for Prevenar 13 recommends 4 doses of 13vPCV for vaccination commencing at 6 weeks of age, with further doses at 4, 6 and 12–15 months of age; 3 doses for vaccination commencing between 7 and 11 months of age; and 2 doses for vaccination commencing between 12 and 23 months of age. The ATAGI recommends instead that 1 dose less than that stated in the product information be given to healthy children who are not at increased risk of IPD. The ATAGI recommends that the 1st dose be given at 2 months of age, and that this dose can be given as early as 6 weeks of age. The next scheduled doses should be given at 4 months and 6 months of age.

13vPCV is registered for use in children up to 17 years of age and adults aged ≥50 years. The ATAGI recommends a dose of 13vPCV for adults of any age who have a condition(s) associated with the highest risk of IPD (see List 4.13.1,

Category A). This is based on the likely benefit outweighing uncertainties and risks, and on immunogenicity and safety data in children.

The product information for Pneumovax 23 states that Pneumovax 23 and Zostavax should not be given concurrently. The ATAGI instead recommends that while concurrent administration of Zostavax with pneumococcal polysaccharide vaccine is not routinely recommended, and if possible the two vaccines should be given at least 4 weeks apart, inadvertent administration of Zostavax and pneumococcal polysaccharide vaccine at the same time or at an interval of less than 4 weeks does not require revaccination.

References

A full reference list is available on the electronic *Handbook* or website www.immunise.health.gov.au

4.14 POLIOMYELITIS

4.14.1 Virology

Polioviruses are classified as enteroviruses in the family Picornaviridae.[1] They have an RNA genome, and can inhabit the gastrointestinal tract transiently. There are three poliovirus serotypes, referred to as either type 1, type 2 or type 3. The virus enters through the mouth, multiplies in the pharynx and gut and is excreted in the stools for several weeks. The virus invades local lymphoid tissue, enters the bloodstream and may then infect and replicate in cells of the central nervous system.[2]

4.14.2 Clinical features

Poliomyelitis is an acute illness following gastrointestinal infection by one of the three types of poliovirus. Transmission is through faecal–oral and, occasionally, oral–oral spread.[3] The infection may be clinically inapparent. If symptoms occur, they may include headache, gastrointestinal disturbance, malaise and stiffness of the neck and back, with or without paralysis. Paralysis is classically asymmetrical. Paralytic polio is a complication of poliovirus aseptic meningitis, and may be spinal (79%), bulbar (2%) or bulbospinal (19%). The case-fatality rate in paralytic polio is 2 to 5% in children and 15 to 30% in adults. The case-fatality rate in bulbar polio is up to 75%. The infection rate in households with susceptible young children can reach 100%. The ratio of inapparent or asymptomatic infection to paralytic infection may be as high as 1000:1 in children and 75:1 in adults, depending on the poliovirus type and social and environmental conditions.[2]

The incubation period ranges from 3 to 21 days. Infected persons are most infectious from 7 to 10 days before to 7 to 10 days after the onset of symptoms. The oral vaccine virus may be shed in the faeces for 6 weeks or more,[2] and for up to several years in people who are immunocompromised. Oral vaccine strains shed for many years may mutate into potentially neurovirulent strains.[4-9]

4.14.3 Epidemiology

The incidence of poliomyelitis has been dramatically reduced worldwide with the World Health Organization (WHO) aiming to achieve cessation of all wild poliovirus transmission worldwide by 2013 through an intensified Global Polio Eradication Initiative. There have been imported poliomyelitis case reports in parts of Southeast Asia, eastern Europe and Africa.[10-12] Further information is available from the WHO Polio Eradication website (www.polioeradication.org). In 1994, the continents of North and South America were certified to be free of polio,[13] followed by the Western Pacific region (including Australia) in 2000[14] and the European region in 2002.[15] In countries where the disease incidence is low but transmission is still occurring, poliomyelitis cases are seen sporadically or as outbreaks among non-vaccinated persons. In 2012, polio had been

virtually eradicated in India, but there were still cases in Afghanistan, Nigeria and Pakistan.[16]

In Australia, the peak incidence of poliomyelitis was 39.1/100 000 in 1938. There has been a dramatic fall in incidence since 1952, but epidemics occurred in 1956 and 1961–62. The most recent laboratory-confirmed case of wild poliomyelitis in Australia occurred in 2007 in an overseas-born student who acquired the disease during a visit to Pakistan.[17] The last case of wild poliomyelitis prior to this was in 1977, due to an importation from Turkey, but two vaccine-associated cases were notified in 1986 and 1995.[18,19] Because of the rapid progress in global polio eradication and the diminished risk of wild virus-associated disease, inactivated poliomyelitis vaccine (IPV) is now used for all doses of polio vaccine in Australia.[3,20] The advantage of using IPV is that it cannot cause vaccine-associated paralytic poliomyelitis (VAPP).[21] Emergence of highly evolved vaccine-derived polioviruses (VDPV) in persons with primary immunodeficiency (iVDPV) with long-term excretion, and polio outbreaks due to circulating VDPV (cVDPV), particularly in areas with low vaccine coverage, are associated with oral poliomyelitis vaccine (OPV) administration.[22,23]

4.14.4 Vaccines

Inactivated poliomyelitis vaccine

- ***IPOL*** – Sanofi Pasteur Pty Ltd (IPV; inactivated poliovirus). Each 0.5 mL pre-filled syringe contains 40 D-antigen units inactivated poliovirus type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett); 2–3 µL phenoxyethanol; 2–20 µg formaldehyde; polysorbate 80; traces of neomycin, streptomycin, polymyxin B and bovine serum albumin.

Combination vaccines that contain IPV

Formulations for children aged <10 years

- ***Infanrix hexa*** – GlaxoSmithKline (DTPa-hepB-IPV-Hib; diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus-*Haemophilus influenzae* type b). The vaccine consists of *both* a 0.5 mL pre-filled syringe containing ≥30 IU diphtheria toxoid, ≥40 IU tetanus toxoid, 25 µg pertussis toxoid (PT), 25 µg filamentous haemagglutinin (FHA), 8 µg pertactin (PRN), 10 µg recombinant HBsAg, 40 D-antigen units inactivated poliovirus type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett), adsorbed onto aluminium hydroxide/phosphate; traces of formaldehyde, polysorbate 80, polysorbate 20, polymyxin and neomycin; *and* a vial containing a lyophilised pellet of 10 µg purified Hib capsular

polysaccharide (PRP) conjugated to 20–40 µg tetanus toxoid. May contain yeast proteins.

- ***Infanrix IPV*** – GlaxoSmithKline (DTPa-IPV; diphtheria-tetanus-acellular pertussis-inactivated poliovirus). Each 0.5 mL pre-filled syringe contains ≥30 IU diphtheria toxoid, ≥40 IU tetanus toxoid, 25 µg PT, 25 µg FHA, 8 µg PRN, 40 D-antigen units inactivated poliovirus type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett), adsorbed onto aluminium hydroxide; traces of formaldehyde, polysorbate 80, polymyxin and neomycin.
- ***Pediacel*** – Sanofi Pasteur Pty Ltd (DTPa-IPV-Hib; diphtheria-tetanus-acellular pertussis-inactivated poliovirus-*Haemophilus influenzae* type b). Each 0.5 mL monodose vial contains ≥30 IU diphtheria toxoid, ≥40 IU tetanus toxoid, 20 µg PT, 20 µg FHA, 3 µg PRN, 5 µg pertussis fimbriae (FIM) 2+3, 40 D-antigen units inactivated poliovirus type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett), 10 µg Hib capsular polysaccharide conjugated to 20 µg tetanus protein; 1.5 mg aluminium phosphate; ≤50 ng bovine serum albumin; phenoxyethanol as preservative; traces of formaldehyde, glutaraldehyde, polysorbate 80, polymyxin, neomycin and streptomycin.
- ***Quadracel*** – Sanofi Pasteur Pty Ltd (DTPa-IPV; diphtheria-tetanus-acellular pertussis-inactivated poliovirus). Each 0.5 mL monodose vial contains ≥30 IU diphtheria toxoid, ≥40 IU tetanus toxoid, 20 µg PT, 20 µg FHA, 3 µg PRN, 5 µg FIM 2+3, 40 D-antigen units inactivated poliovirus type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett); 1.5 mg aluminium phosphate; ≤50 ng bovine serum albumin; phenoxyethanol as preservative; traces of formaldehyde, glutaraldehyde, polysorbate 80, polymyxin and neomycin.

Reduced antigen formulations for adults, adolescents and children aged ≥10 years

- ***Adacel Polio*** – Sanofi Pasteur Pty Ltd (dTpa-IPV; diphtheria-tetanus-acellular pertussis-inactivated poliovirus). Each 0.5 mL monodose vial or pre-filled syringe contains ≥2 IU diphtheria toxoid, ≥20 IU tetanus toxoid, 2.5 µg PT, 5 µg FHA, 3 µg PRN, 5 µg FIM 2+3, 40 D-antigen units inactivated poliovirus type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett); 0.33 mg aluminium as aluminium phosphate; phenoxyethanol as preservative; traces of

formaldehyde, glutaraldehyde, polysorbate 80, polymyxin, neomycin and streptomycin.

- ***Boostrix-IPV*** – GlaxoSmithKline (dTpa-IPV; diphtheria-tetanus-acellular pertussis-inactivated poliovirus). Each 0.5 mL pre-filled syringe contains ≥2 IU diphtheria toxoid, ≥20 IU tetanus toxoid, 8 µg PT, 8 µg FHA, 2.5 µg PRN, 40 D-antigen units inactivated poliovirus type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett), adsorbed onto 0.5 mg aluminium as aluminium hydroxide/phosphate; traces of formaldehyde, polysorbate 80, polymyxin and neomycin.

IPV (IPOL) and IPV-containing combination vaccines contain polioviruses of types 1, 2 and 3 inactivated by formaldehyde. A course of 3 doses with an interval of 2 months between each dose produces long-lasting immunity (both mucosal and humoral) to all three poliovirus types. IPV produces considerably lower levels of intestinal immunity than OPV.

4.14.5 Transport, storage and handling

Transport according to *National vaccine storage guidelines: Strive for 5*.[24] Store at +2°C to +8°C. Do not freeze. Protect from light.

Infanrix hexa *must be reconstituted* by adding the entire contents of the syringe to the vial and shaking until the pellet is completely dissolved. Reconstituted vaccine should be used as soon as practicable. If storage is necessary, hold at room temperature for not more than 8 hours.

4.14.6 Dosage and administration

The dose of IPV (IPOL) is 0.5 mL, to be given by SC injection. If IPV (IPOL) is inadvertently given intramuscularly, there is no need to repeat the dose.

The dose of the IPV-containing combination vaccines is 0.5 mL, to be given by IM injection.

The primary course consists of 3 doses of vaccine. An interval of 2 months between doses is recommended, but the minimum interval can be as short as 1 month for catch-up in children or adults.

Interchangeability of oral and inactivated poliomyelitis vaccine

OPV is no longer in use in Australia. OPV and IPV are interchangeable. Children commenced on OPV should complete their polio vaccination schedule using IPV (IPOL) or IPV-containing vaccines.[25]

4.14.7 Recommendations

Primary vaccination of infants and children

IPV (IPOL) or IPV-containing vaccines are recommended for infants at 2, 4 and 6 months of age. The 1st dose of an IPV-containing vaccine can be given as early as 6 weeks of age. If the 1st dose is given at 6 weeks of age, the next scheduled doses should still be given at 4 months and 6 months of age. An open, randomised, multi-centre trial comparing the hexavalent and pentavalent IPV-containing vaccines found that infants receiving either vaccine at 2, 4 and 6 months of age had seroprotective levels of antibody to poliovirus types 1, 2 and 3.[26] Extra doses of IPV (IPOL) or IPV-containing vaccines are not needed for babies born prematurely.

Where only IPV vaccination is required, IPOL can be used for catch-up in children. If other antigens including poliomyelitis are required, Infanrix IPV or Infanrix hexa can be used for catch-up in children aged <10 years (see 2.1.5 *Catch-up*).

Booster doses for children

A booster dose of IPV (IPOL) or IPV-containing vaccine is recommended at 4 years of age. This is commonly provided as DTPa-IPV, which can be given as early as 3.5 years (see also 4.12 *Pertussis* and 4.19 *Tetanus*).

A completed poliomyelitis vaccination schedule for children is 3 primary doses and 1 booster dose of IPV (IPOL) or an IPV-containing vaccine.

Where a child received their 3rd primary dose of IPV or an IPV-containing vaccine after the age of 4 years, a booster dose is *not* required.

Primary vaccination of adults

A course of 3 doses of IPV (IPOL) or IPV-containing vaccines is recommended for the primary vaccination of adults. No adult should remain unvaccinated against poliomyelitis. For more information see 2.1.5 *Catch-up.*

Booster doses for adults

Booster doses for adults are not necessary unless an individual is at special risk, such as:

- travellers to areas or countries where poliomyelitis is epidemic or endemic;[25] see also WHO recommendations on vaccinations for travellers (www.who.int/ith/chapters/en/index.html)[27] and 3.2 *Vaccination for international travel*
- healthcare workers, including laboratory workers, in possible contact with poliomyelitis cases or poliomyelitis virus.

For those exposed to a continuing risk of infection, booster doses are desirable every 10 years. dTpa-IPV combination vaccines can be used where otherwise indicated.

4.14.8 Pregnancy and breastfeeding

IPV (IPOL) or IPV-containing vaccines are not routinely recommended for pregnant or breastfeeding women, but can be given where vaccination is considered necessary (see 4.14.7 *Recommendations* above).

Refer to 3.3 *Groups with special vaccination requirements*, Table 3.3.1 *Recommendations for vaccination in pregnancy* for more information.

4.14.9 Contraindications

The only absolute contraindications to IPV (IPOL) or IPV-containing vaccines are:

- anaphylaxis following a previous dose of any IPV-containing vaccine
- anaphylaxis following any vaccine component.

4.14.10 Adverse events

IPV (IPOL) or IPV-containing vaccines cause erythema (in 33% of vaccine recipients), pain (in 13%), and induration (in 1%) at the injection site. Other symptoms reported in young babies are fever, crying and decreased appetite (in 5 to 10%).

Repeat doses of IPV or IPV-containing vaccines have not been associated with increased adverse events and, where extra doses are required, are safe.

4.14.11 Public health management of poliomyelitis

Poliomyelitis is a notifiable disease in all states and territories in Australia.

Further instructions about the public health management of poliomyelitis, including management of cases of poliomyelitis and their contacts, should be obtained from state/territory public health authorities (see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*).

4.14.12 Variations from product information

The product information for Infanrix hexa states that this vaccine is indicated for primary immunisation of infants from the age of 6 weeks. The ATAGI recommends that this vaccine may also be used for catch-up of the primary schedule in children <10 years of age.

The product information for Infanrix IPV states that this vaccine is indicated for use in a 3-dose primary schedule for immunisation of infants from the age of 6 weeks and as a single booster dose for children ≤6 years of age who have previously been vaccinated against diphtheria, tetanus, pertussis and poliomyelitis. In addition, the ATAGI recommends that this product may also be used for catch-up of the primary schedule or as a booster in children <10 years of age.

The product information for Quadracel states that this vaccine is indicated for use in a 3-dose primary schedule from the age of 2 months to 12 months and may also be used as a booster dose for children from 15 months to 6 years of age who have previously been vaccinated against diphtheria, tetanus, pertussis and poliomyelitis. The ATAGI recommends that, when appropriate, this product may also be used for either catch-up of the primary schedule or as a booster dose in children aged <10 years. The ATAGI also recommends that the primary schedule may be commenced at 6 weeks of age, if required.

The product information for Pediacel states that this vaccine is indicated for primary immunisation of infants from the age of 6 weeks and may also be used as a booster dose for children from 15 to 20 months of age who have previously been vaccinated against diphtheria, tetanus, pertussis, poliomyelitis and *Haemophilus influenzae* type b. The ATAGI recommends that, when appropriate, this product may also be used for either catch-up of the primary schedule or as a booster dose in children aged <10 years.

The product information for Boostrix-IPV states that dTpa-containing vaccine should not be given within 5 years of a tetanus toxoid-containing vaccine. The product information for Adacel Polio states that dTpa-containing vaccine should not be given within 3 years of a tetanus toxoid-containing vaccine. The ATAGI recommends instead that, if protection against pertussis is required, dTpa-containing vaccines can be administered at any time following receipt of a dT-containing vaccine.

The product information for Boostrix-IPV and Infanrix IPV states that these vaccines are contraindicated in children with encephalopathy of unknown aetiology or with neurologic complications occurring within 7 days following a vaccine dose. The ATAGI recommends instead that the only contraindication is a history of anaphylaxis to a previous dose or to any of the vaccine components.

References

A full reference list is available on the electronic *Handbook* or website www.immunise.health.gov.au

4.15 Q FEVER

4.15.1 Bacteriology

Q fever is caused by *Coxiella burnetii*, an obligate intracellular bacterium.[1] The organism is inactivated at pasteurisation temperatures. It survives well in air, soil, water and dust, and may also be disseminated on fomites such as wool, hides, clothing, straw and packing materials.[2,3] *C. burnetii* has been weaponised and is considered a Category B biothreat agent.[4]

4.15.2 Clinical features

Q fever can be acute or chronic, and there is increasing recognition of long-term sequelae. Infection is asymptomatic in at least half of cases.[5,6]

Acute Q fever usually has an incubation period of 2 to 3½ weeks, depending on the inoculum size and other variables[7] (range from 4 days up to 6 weeks). Clinical symptoms vary by country, but, in Australia, the most common presentation is rapid onset of high fever, rigors, profuse sweats, extreme fatigue, muscle and joint pain, severe headache and photophobia.[5,6] As the attack progresses, there is usually evidence of hepatitis, occasionally with frank jaundice; a proportion of patients may have pneumonia, which is usually mild but can require mechanical ventilation. If untreated, the acute illness lasts 1 to 3 weeks and may be accompanied by substantial weight loss in more severe cases.[5,6] Infection often results in time off work, lasting a few days to several weeks.[8]

C. burnetii may cause chronic manifestations, the most commonly reported being subacute endocarditis. Less common presentations include granulomatous lesions in bone, joints, liver, lung, testis and soft tissues. Infection in early pregnancy, or even before conception, may recrudesce at term and cause fetal damage.[9-11]

Studies have also identified a late sequela to infection, post Q fever fatigue syndrome (QFS), which occurs in about 10 to 15% of patients who have previously had acute Q fever.[12-15] Research suggests that non-infective antigenic complexes of *C. burnetii* persist for many years after acute Q fever, and the maintenance of immune responses to these antigens might be the biological basis by which QFS occurs.[13,16-18]

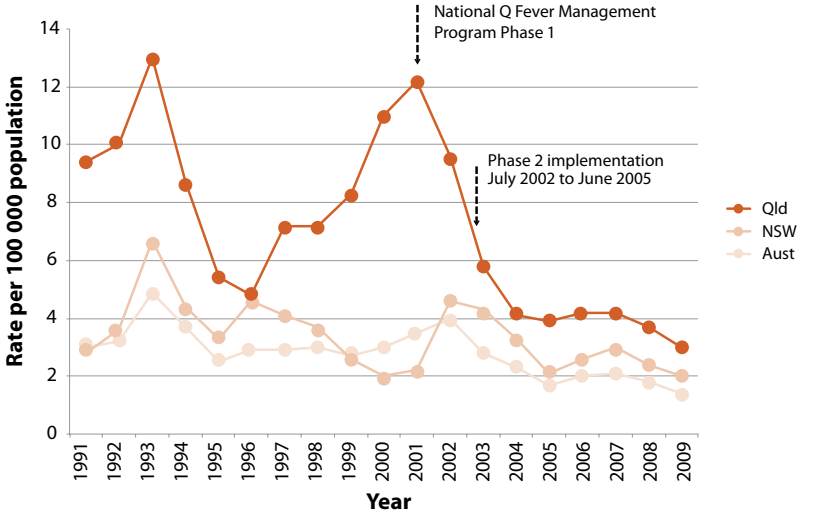
4.15.3 Epidemiology

C. burnetii infects both wild and domestic animals and their ticks, with cattle, sheep and goats being the main sources of human infection.[19-21] Companion animals such as cats and dogs may also be infected, as well as native Australian animals such as kangaroos, and introduced animals such as feral cats and camels.[19,21-23] The animals shed *C. burnetii* into the environment through their placental tissue or birth fluids, which contain exceptionally high numbers of *Coxiella* organisms, and also via their milk, urine and faeces. *C. burnetii* is highly infectious[24] and can survive in the environment. The organism is transmitted to

humans via the inhalation of infected aerosols or dust. Those most at risk include workers from the meat and livestock industries and shearers, with non-immune new employees or visitors being at highest risk of infection. Nevertheless, Q fever is not confined to occupationally exposed groups; there are numerous reports of sporadic cases or outbreaks in the general population in proximity to infected animals in stockyards, feedlots, processing plants or farms. Although most notifications occur among men from rural areas or with occupational exposure, a recent serosurvey from Queensland indicated a high rate of exposure among urban residents, including women and children.[25]

Use of Q fever vaccine in Australia can be considered in 4 periods: from 1991 to 1993, when vaccine was used in a limited number of abattoirs; from 1994 to 2000, when vaccination steadily increased to cover large abattoirs in most states;[26] from 2001 to 2006, during the period of the Australian Government sponsored National Q fever Management Program (NQFMP);[27] and the period since 2007 after the NQFMP finished, where the vaccination remains available on the private market. The NQFMP funded screening and vaccination of abattoir workers and shearers and then extended vaccination to farmers, their families and employees in the livestock-rearing industry. Following introduction of the program, the number of Q fever cases reported to the National Notifiable Diseases Surveillance System declined by over 50% (see Figure 4.15.1),[27] with the greatest reductions among young men aged 15–39 years, consistent with high documented vaccine uptake among abattoir workers.[26-28] As a result, other occupational groups as well as non-occupational animal exposures appear to be accounting for an increasing proportion of notifications.[8,29]

Figure 4.15.1: Q fever notifications for Australia, New South Wales and Queensland, 1991 to 2009[30]



4.15.4 Vaccine

- ***Q-Vax*** – CSL Limited (Q fever vaccine). Each 0.5 mL pre-filled syringe contains 25 µg purified killed suspension of *Coxiella burnetii*; thiomersal 0.01% w/v. Traces of formalin. May contain egg proteins.
- ***Q-Vax Skin Test*** – CSL Limited (Q fever skin test). Each 0.5 mL liquid vial when diluted to 15 mL with sodium chloride contains 16.7 ng of purified killed suspension of *C. burnetii* in each diluted 0.1 mL dose; thiomersal 0.01% w/v before dilution. Traces of formalin. May contain egg proteins.

The Q fever vaccine and skin test consist of a purified killed suspension of *C. burnetii*. It is prepared from the Phase I Henzerling strain of *C. burnetii*, grown in the yolk sacs of embryonated eggs. The organisms are extracted, inactivated with formalin, and freed from excess egg proteins by fractionation and ultracentrifugation. Thiomersal 0.01% w/v is added as a preservative.

Phase I whole-cell vaccines have been shown to be highly antigenic and protective against challenge, both in laboratory animals and in volunteer trials.[31] Serological response to the vaccine is chiefly IgM antibody to *C. burnetii* Phase I antigen. In subjects weakly seropositive before vaccination, the response is mainly IgG antibody to Phase I and Phase II antigens.[32] Lack of seroconversion is not a reliable marker of lack of vaccination.[31] Although the seroconversion rate may be low, long-term cell-mediated immunity develops[33] and estimates of vaccine efficacy have ranged from 83 to 100%, based on the results of open and placebo-controlled trials, and post-marketing studies.[34-38] It is important that vaccination status is reported for all notified cases and apparent vaccine failures are investigated.

It should be noted that vaccination during the incubation period of a natural attack of Q fever does not prevent the development of the disease.[31]

The Q fever vaccine and skin test are available for purchase in Australia through the private market. The Australian Government may fund the vaccine and skin test in emergency situations where there is a Q fever outbreak.

4.15.5 Transport, storage and handling

Transport the vaccine according to *National vaccine storage guidelines: Strive for 5*.[39] Store at +2°C to +8°C. Do not freeze or store in direct contact with ice packs. If vaccine has been exposed to temperatures less than 0°C, do not use it. Protect from light.

Diluted Q-Vax Skin Test should be freshly prepared, stored at +2°C to +8°C and used within 6 hours.

4.15.6 Dosage and administration

The dose of Q fever vaccine is 0.5 mL, to be given by SC injection, after ascertaining that serological and skin testing have been performed and that both tests are negative (see 'Pre-vaccination testing' below).

Q fever vaccination and skin testing training is undertaken via an educational video available online. Please contact the manufacturer for access details.

4.15.7 Recommendations

Children aged <15 years

Q fever vaccine is not recommended in children aged <15 years. There are no data on the safety or efficacy of Q fever vaccine in this age group.

Adolescents aged ≥15 years and adults

Q fever vaccine is recommended for those at risk of infection with *C. burnetii*. This includes abattoir workers, farmers, stockyard workers, shearers, animal transporters, and others exposed to cattle, camels, sheep, goats and kangaroos or their products (including products of conception). It also includes veterinarians, veterinary nurses, veterinary students, professional dog and cat breeders, agricultural college staff and students, wildlife and zoo workers (working with high-risk animals) and laboratory personnel handling veterinary specimens or working with the organism (see also 3.3.7 *Vaccination of persons at occupational risk*, Table 3.3.7 *Recommended vaccinations for persons at increased risk of certain occupationally acquired vaccine-preventable diseases*).

Workers at pig abattoirs do *not* require Q fever vaccination.

Pre-vaccination testing

- Before vaccination, persons with a negative history of previous infection with Q fever must have serum antibody estimations and skin tests to exclude those likely to have hypersensitivity reactions to the vaccine resulting from previous (possibly unrecognised) exposure to the organism.
- If the person has a positive history of previous infection with Q fever, or has already been vaccinated for Q fever, vaccination is *contraindicated* and therefore skin testing and serology are *not* required. (See also below.)
- It is essential to take a detailed history and to obtain documentation of previous Q fever vaccination or laboratory results confirming Q fever disease in all potential vaccinees. Some persons who have had verified Q fever disease in the past may show no response to serological or skin testing; however, they may still experience serious reactions to Q fever vaccine. Persons who have worked in the livestock or meat industries for some time should be questioned particularly carefully. The Australian Q Fever Register (www.qfever.org), established by Meat and Livestock Australia (MLA), has records of receipt of Q fever vaccination for some

individuals, which can be accessed by registered users. If there is any doubt about serological or skin test results, testing should be repeated 2 to 3 weeks later (see below for interpretation).

- Serological and skin test results should be taken into account, according to Table 4.15.1, before vaccination. Antibody studies were originally done by complement fixation (CF) tests at serum dilutions of 1 in 2.5, 5 and 10 against the Phase II antigen of *C. burnetii*. Although this is generally satisfactory, many testing laboratories now use enzyme immunoassay (EIA) or immunofluorescent antibody (IFA) to detect IgG antibody to *C. burnetii* as an indicator of past exposure. Subjects who are CF antibody positive at 1 in 2.5, IFA positive at 1 in 10 or more, or with a definite positive absorbance value in the EIA, should *not* be vaccinated.
- Skin testing and interpretation should only be carried out by experienced personnel. Details of immunisation service providers trained in the administration of Q fever skin testing can be obtained online from the Australian Q Fever Register (www.qfever.org). Skin testing is performed by diluting 0.5 mL of the Q-Vax Skin Test in 14.5 mL of sodium chloride (injection grade). Diluted Q-Vax Skin Test should be freshly prepared, stored at +2°C to +8°C and used within 6 hours. A 0.1 mL dose of the diluted Q-Vax Skin Test is injected intradermally into the volar surface of the forearm. Commercial isopropyl alcohol skin wipes should not be used. If the skin is not visibly clean, then methylated spirits may be used. Skin reactions are common 3 to 4 days after skin testing; however, these reactions generally resolve by day 7 when the skin test is read. A positive reaction is indicated by any induration at the site of injection after 7 days. Individuals giving such a reaction must *not* be vaccinated, because they may develop severe local reactions.
- The result of testing is considered 'indeterminate' when skin test induration is just palpable and the antibody test is either equivocal or negative, or when there is no skin induration and an equivocal antibody test (see Table 4.15.1).

  An indeterminate result, which occurs in only a small proportion of subjects, may be the consequence of past infection with Q fever. It may also merely indicate the presence in the subject of antibodies to antigens shared between *C. burnetii* and other bacteria. Australian Q fever vaccine providers have dealt with this finding in one of two ways:

  » Repeat the skin test and interpret as per the guidelines for initial testing. Collect serum 2 to 3 weeks later to look for a rise in titre of *C. burnetii* antibodies in the IFA test, using Phase I and Phase II antigens and immunoglobulin class analysis. A significant increase (defined as a 4-fold rise in titre of paired sera) indicates previous Q fever infection and vaccination is then contraindicated.

» Vaccinate the subject using SC injection of a 5 µg (0.1 mL) dose instead of a 25 µg (0.5 mL) dose of the vaccine. If there are no adverse events (e.g. severe local induration or severe systemic effects, perhaps accompanied by fever) 48 hours after the injection, a further 0.4 mL (20 µg) dose of the vaccine is given within the next 2 to 3 weeks, that is, before the development of cell-mediated immunity to the 1st dose.

Table 4.15.1: Interpretation and action for serological and skin test results (with modifications from *A guide to Q fever and Q fever vaccination* (CSL Biotherapies, 2009)[6])

Serology	Skin test	Interpretation/Action
Positive antibody test*	Any skin test result	Sensitised: do not vaccinate
Equivocal antibody test†	Positive‡ Borderline§ or Negative¶	Sensitised: do not vaccinate Indeterminate (see above)
Negative antibody test#	Positive Borderline Negative	Sensitised: do not vaccinate Indeterminate (see above) Non-immune: vaccinate

* Positive antibody test: CF antibody or IFA positive (according to criteria used by diagnosing laboratory [see above]; or definite positive EIA absorbance value (according to manufacturer's instructions)

† Equivocal antibody test: CF antibody or IFA equivocal (according to criteria used by diagnosing laboratory); or equivocal EIA absorbance value (according to manufacturer's instructions)

‡ Positive skin test: induration present

§ Borderline skin test: induration just palpable

¶ Negative skin test: no induration

Negative antibody test: CF antibody or IFA negative (according to criteria used by diagnosing laboratory); or definite negative EIA absorbance value (according to manufacturer's instructions)

Booster doses

Immunity produced by the vaccine appears to be long-lasting (in excess of 5 years). Until further information becomes available, revaccination or booster doses of the vaccine are *not* recommended because of the risk of accentuated local adverse events.

4.15.8 Pregnancy and breastfeeding

Q fever vaccine is not routinely recommended for pregnant or breastfeeding women.

Q fever vaccine contains inactivated products; inactivated bacterial vaccines are not considered to be harmful in pregnancy. However, safety of the vaccine in pregnancy has not been established. No information is available on the use of Q fever vaccine during breastfeeding.

Refer to 3.3 *Groups with special vaccination requirements*, Table 3.3.1 *Recommendations for vaccination in pregnancy* for more information.

4.15.9 Contraindications

Q fever vaccine is contraindicated in the following groups:

- persons with a history of laboratory-confirmed Q fever, or with medical documentation that supports a previous diagnosis of Q fever
- persons shown to be immune by either serological testing or sensitivity to the organism by skin testing
- persons who have been previously vaccinated against Q fever
- persons with known hypersensitivity to egg proteins or any component of the vaccine (Q-Vax may contain traces of egg protein and formalin).[40]

There is no information available on the accuracy of skin testing or the efficacy and safety of Q fever vaccine use in persons who are immunocompromised. In general, skin testing and Q fever vaccine should be avoided in such persons.

There are no data on the safety or efficacy of Q fever vaccine in children. Q fever vaccine is not recommended for use in those aged <15 years.

4.15.10 Precautions

Vaccination of subjects already immune to *C. burnetii* as a result of either previous infection or vaccination may result in severe local or systemic adverse events. It is important that persons with a negative history of previous infection with Q fever must have serum antibody estimations and skin tests performed prior to vaccination (see 'Pre-vaccination testing' above).

4.15.11 Adverse events

Non-immune subjects very commonly show local tenderness (48%) and erythema (33%) at the vaccination site. Local induration or oedema is uncommon, occurring in <1% of recipients. General symptoms occur commonly in about 10% of vaccine recipients and may include mild influenza-like symptoms, such as headache (9%), fever (up to 0.2%), chills and minor sweating.[6,40]

Erythematous skin reactions are common 3 to 4 days after skin testing; however, these reactions generally resolve by day 7 when the skin test is read.

There were also two patterns of more significant adverse events among the estimated more than 130 000 persons vaccinated between 1989 and 2004.[5,26] The first and familiar pattern is the intensified local reaction at the injection site, which may occur shortly after vaccination in individuals sensitised immunologically by previous infection or vaccination. Rarely, an abscess develops and requires excision and drainage. This acute reaction may be accompanied by short-term systemic symptoms resembling the post Q fever fatigue syndrome. However, not all those with positive pre-vaccination skin and/or serological tests develop severe reactions. The use of the pre-vaccination

skin test developed by the US National Institute of Health and the National Institute of Allergy and Infectious Diseases,[41] which was later combined with antibody testing in Australia, has largely eliminated reactions due to previous immune sensitisation. Despite this, the adverse experience from earlier American trials,[31] in which subjects were not pre-tested, were vaccinated repeatedly or were inoculated with vaccines of a different composition and larger bacterial mass, are still quoted in the general Q fever literature as representative of the broader experience with whole-cell Q fever vaccines.

The second, much less frequent, pattern has been reported in people who are skin and antibody test-negative at the time of vaccination and who do not have any immediate reaction. Some 1 to 8 months after vaccination, some vaccine recipients, predominantly women, have developed an indurated lesion at the inoculation site. At the time when the indurated lesion develops, the original skin test site often becomes positive, presumably indicating a late developing cellular immune response. These lesions are not fluctuant and do not progress to an abscess. Most gradually decline in size and resolve over some months without treatment. A few lesions have been biopsied or excised and have shown accumulations of macrophages and lymphocytes.[42,43]

4.15.12 Public health management of Q fever

Q fever is a notifiable disease in all states and territories in Australia.

Further instructions about the public health management of Q fever, including management of cases of Q fever, should be obtained from state/territory public health authorities (see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*).

4.15.13 Variations from product information

The product information for Q-Vax does not include the use of a reduced dose of vaccine in persons who have indeterminate results on either serological or skin testing. The ATAGI recommends instead that experienced Q fever vaccinators may elect to give reduced vaccine doses in subjects who have indeterminate results on either serological or skin testing.

References

A full reference list is available on the electronic *Handbook* or website www.immunise.health.gov.au

4.16 RABIES AND OTHER LYSSAVIRUSES (INCLUDING AUSTRALIAN BAT LYSSAVIRUS)

4.16.1 Virology

Lyssaviruses are single-stranded RNA viruses in the family Rhabdoviridae, genus *Lyssavirus*. There are 12 known species within the genus *Lyssavirus*, including the classical rabies virus and other closely related lyssaviruses such as the Australian bat lyssavirus (ABLV) and European bat lyssaviruses.[1]

4.16.2 Clinical features

Rabies is a zoonotic disease caused by human exposure to saliva or nerve tissue of an animal infected with rabies virus or other lyssaviruses. As the clinical disease caused by classical rabies virus and other lyssaviruses is indistinguishable, the term 'rabies' refers to disease caused by any of the known lyssavirus species.[2-5] Human exposure can occur via a scratch or bite that has broken the skin, or via direct contact with the mucosal surface of a person, such as nose, eye or mouth. Most human cases of rabies occur after animal bites – cases after animal scratches, the licking by animals of open wounds or contact of animal saliva with intact mucous membranes are very rare. Aerosol transmission has never been well documented in the natural environment.[6] There has been transmission of rabies virus reported following tissue transplantation from donors who died with undiagnosed rabies.[7] Transmission of rabies virus to humans through unpasteurised milk may be possible; however, rare reports of transmission via this route have not been confirmed.[8]

Once a person is infected, the incubation period of rabies is usually 3 to 8 weeks, but can range from as short as a week to, on rare occasions, several years. The risk of rabies is higher, and the incubation period shorter, after severe and multiple wounds proximate to the central nervous system (such as on the head and neck) and in richly innervated sites (such as the fingers).

Rabies is almost invariably fatal. Typically, in the prodromal phase of rabies, which lasts up to 10 days, the patient may experience non-specific symptoms such as anorexia, cough, fever, headache, myalgia, nausea, sore throat, tiredness and vomiting.[9] Paraesthesiae and/or fasciculations at or near the site of the wound may be present at this stage. Anxiety, agitation and apprehension may also occur. Most rabies patients present with the furious or encephalitic form.[10] In the encephalitic phase, objective signs of nervous system involvement include aerophobia, hydrophobia, bizarre behaviour, disorientation and hyperactivity. Signs of autonomic instability such as hypersalivation, hyperthermia and hyperventilation may occur.[10] The neurological status of the patient deteriorates over a period of up to 12 days, and the patient either dies abruptly from cardiac or respiratory arrest, or lapses into a coma.

4.16.3 Epidemiology

The epidemiology of rabies varies depending on the lyssavirus species and the animal host. Lyssaviruses have been found in all continents, except Antarctica.[11] Rabies that is due to the classical rabies virus and occurs in land dwelling (terrestrial) mammals is present throughout much of Africa, Asia, the Americas and Europe, where the virus is maintained in certain species of mammals, particularly dogs. In countries where rabies vaccination of domestic animals is widespread (North America and Europe), wild animals such as raccoons and foxes are important reservoirs. The continual maintenance of rabies in animal populations in these countries is referred to as enzootic rabies. Australia, New Zealand, Japan, Papua New Guinea and Pacific island nations are currently free of rabies in terrestrial mammals. However, a country's status can change at any time. For example, in 2008 on the island of Bali, Indonesia, rabies was reported in dogs, with cases later reported in humans.[12] Prior to this, Bali had been considered free of rabies, although rabies was known to occur in other areas of Indonesia.[13]

In some parts of the world, bats are important reservoirs of classical rabies as well as other lyssaviruses, with bat lyssaviruses found in areas that are considered free from terrestrial rabies. ABLV was first reported in bats in 1996; since then, two cases of fatal encephalitis caused by ABLV have been reported in Australians, one in 1996 and the other in 1998.[2,14] Both patients had been bitten by bats. Evidence of ABLV infection has since been identified in all four species of Australian fruit bats (flying foxes) and in several species of Australian insectivorous bats.[4,15-17] It should therefore be assumed that all Australian bats have the potential to be infected with ABLV. Different regions in Australia have reported higher risk of potential ABLV exposures.[18,19] ABLV has not been isolated from bats outside Australia. However, closely related lyssaviruses are found in bats in other countries. For example, European bat lyssavirus 1 and European bat lyssavirus 2 have been isolated in bats in some parts of Europe. Four human deaths from European bat lyssavirus variants have been reported in Europe, all with no record of prophylactic rabies immunisation.[3,5] As such, bats anywhere in the world should be considered a potential source of lyssaviruses and a potential risk for acquiring rabies, depending on the exposure.

Information on the global occurrence of rabies can be obtained from reputable international authorities.[11,20,21] In addition, advice on potential lyssavirus exposures and their management should be obtained by contacting the relevant Australian state/territory health authorities (see 4.16.12 P*ublic health management of lyssavirus infections* below).

4.16.4 Rabies vaccines

- ***Mérieux Inactivated Rabies Vaccine*** – Sanofi Pasteur Pty Ltd (human diploid cell vaccine [HDCV]). Lyophilised powder in a monodose vial with 1.0 mL distilled water as diluent. Each 1.0 mL reconstituted dose contains ≥2.5 IU inactivated rabies virus; 100–150 µg neomycin; ≤70 mg human serum albumin; trace of phenol red (indicator). May contain trace amounts of bovine gelatin and β-propiolactone.
- ***Rabipur Inactivated Rabies Virus Vaccine*** – CSL Limited/Novartis Vaccines and Diagnostics Pty Ltd (purified chick embryo cell vaccine [PCECV]). Lyophilised powder in a monodose vial with 1.0 mL distilled water as diluent. Each 1.0 mL reconstituted dose contains ≥2.5 IU inactivated rabies virus; trace amounts of neomycin, chlortetracycline, trometamol, β-propiolactone, monopotassium glutamate and amphotericin B. May contain trace amounts of bovine gelatin and egg protein.

There are two inactivated rabies cell culture-derived vaccines available in Australia.

The Mérieux vaccine is a lyophilised, stabilised suspension of inactivated Wistar rabies virus that has been cultured on human diploid cells and then inactivated by β-propiolactone. This human diploid cell vaccine (HDCV) is coloured off-white, but after reconstitution with the diluent it turns a pinkish colour due to the presence of phenol red. The vaccine does not contain a preservative.

Rabipur is a lyophilised, stabilised suspension of inactivated Flury LEP rabies virus that has been cultured on purified chick embryo cells and then inactivated by β-propiolactone. This purified chick embryo cell vaccine (PCECV) does not contain a preservative.

Rabies vaccine is effective and safe when used for pre-exposure prophylaxis (PreP) and post-exposure prophylaxis (PEP) for rabies virus.[22,23] Although data on the effectiveness of rabies vaccine as prophylaxis against other lyssaviruses are limited, the available animal data and clinical experience support its use.[19,24-29]

4.16.5 Rabies immunoglobulin

- ***Imogam Rabies Pasteurized*** – Sanofi Pasteur Pty Ltd (human rabies immunoglobulin [HRIG]). Each 1.0 mL contains IgG class human rabies antibodies with a minimum titre of 150 IU; 22.5 mg glycine; 1 mg sodium chloride. Supplied in 2 mL vials.

Human rabies immunoglobulin (HRIG) is prepared by cold ethanol fractionation from the plasma of hyperimmunised human donors.

4.16.6 Transport, storage and handling

Rabies vaccine

Transport according to *National vaccine storage guidelines: Strive for 5*.[30] Store at +2°C to +8°C. Do not freeze.

Both rabies vaccines *must be reconstituted* by adding the entire contents of the diluent container to the vial and shaking until the powder is completely dissolved. Reconstituted vaccine should be used immediately.

Human rabies immunoglobulin

Transport according to *National vaccine storage guidelines: Strive for 5*.[30] Store at +2°C to +8°C. Do not freeze. Protect from light.

HRIG should be used immediately once the vial is opened.

4.16.7 Dosage and administration

Rabies vaccine

The dose of rabies vaccine for use in PreP and PEP is 1.0 mL, to be given by IM injection and is the same for infants, children and adults.

HDCV can also be given by SC injection; however, if PCECV is inadvertently given via the SC route, the dose should be repeated.

Note: *Rabies vaccination administered via the intradermal (ID) route is not routinely used in Australia and is not recommended. The use of the ID route for rabies vaccination is the practitioner's own responsibility, as rabies vaccines are not registered for use via this route in Australia. ID administration is particularly not recommended for post-exposure prophylaxis. For detailed information on the restrictions that apply to the use of ID vaccination, if undertaken for PreP, see 'Pre-exposure prophylaxis administered via the intradermal route' below.*

Rabies vaccine should be given in the deltoid area, as rabies virus neutralising antibody (VNAb) titres may be reduced after administration in other sites. In particular, vaccine should never be given in the buttock, as failure of pre-exposure prophylaxis has been reported when given by this route.[31] In infants <12 months of age, administration into the anterolateral aspect of the thigh is recommended.

Pre-exposure prophylaxis (PreP)

The recommended schedule for pre-exposure prophylaxis (PreP) for rabies or other lyssavirus infection consists of a total of 3 doses of vaccine; the 1st dose of vaccine is given on day 0, and subsequent doses on days 7 and 21–28. Although the 3rd dose can be given as early as 21 days, there are no data to support the use

of an even more accelerated schedule for those with limited time before travel to a rabies-enzootic area.

Post-exposure prophylaxis (PEP)

In persons previously unvaccinated, the recommended schedule for post-exposure prophylaxis (PEP) for immunocompetent persons consists of 4 doses of vaccine. The 1st dose of vaccine is given as soon as practicable (day 0), and subsequent doses are given on days 3, 7 and 14; deviations of a few days from this schedule are probably unimportant.[22]

The recommended schedule for PEP for previously unvaccinated immunocompromised persons consists of 5 doses of vaccine. The 1st dose of vaccine is given as soon as practicable (day 0), and subsequent doses are given on days 3, 7, 14 and 28; deviations of a few days from this schedule are probably unimportant.

The recommended schedule for PEP for people who have been previously vaccinated against rabies consists of 2 doses of rabies vaccine on days 0 and 3 (noting caveats in Figures 4.16.1 and 4.16.2).

For more detailed information see 4.16.8 *Recommendations* below.

Human rabies immunoglobulin

When HRIG is indicated, the dose is 20 IU per kilogram of body mass and is the same for infants, children and adults. HRIG should be administered at the same time as the 1st dose (day 0) of rabies vaccine. Do not administer HRIG if 8 days or more have elapsed since the 1st dose of vaccine, as the HRIG may interfere with the immune response to the vaccine. For more detailed information see 4.16.8 *Recommendations* below.

HRIG should be *infiltrated in and around all wounds using as much of the calculated dose as possible*, and the remainder of HRIG administered intramuscularly at a site away from the rabies vaccine injection site. If the wounds are severe and the calculated volume of HRIG is inadequate for complete infiltration of all wounds (e.g. extensive dog bites in a young child), the HRIG should be diluted in saline to make up an adequate volume for the careful infiltration of all wounds.

Wounds to fingers and hands may be small, particularly following exposures to bats, and infiltration of HRIG into these wounds is likely to be both technically difficult and painful for the recipient.[32] However, due to the extensive nerve supply to these sites[9,10,33] it is important that as much of the calculated dose of HRIG as possible should be infiltrated into finger and hand wounds using either a 25 or 26 gauge needle. To avoid the development of a compartment syndrome, the HRIG should be infiltrated very gently, and should not cause the adjacent finger tissue to go frankly pale or white. It may be necessary to give a ring-block using a local anaesthetic.[32]

Interchangeability of rabies vaccines

The World Health Organization (WHO) does not recommend interchanging rabies cell culture-derived vaccines (CCV), but states that, in situations where it is unavoidable, a PreP or PEP course can be completed with an alternative rabies CCV, providing the vaccine is WHO-endorsed (also termed 'pre-qualified').[22] Various international vaccine advisory groups state that rabies CCV are interchangeable. This is supported by the similarities in tissue culture vaccine production methods as well as antibody responses and adverse reactions following vaccination. In one study that specifically assessed the interchangeability of HDCV and PCECV, 165 subjects were randomised to receive rabies PreP (days 0, 7 and 21–28) using either HDCV or PCECV.[34] One year following PreP, each group received 1 or 2 booster doses of PCECV. The booster dose resulted in an anamnestic response (geometric mean titre several orders of magnitude >0.5 IU/mL) in all subjects by day 7, independent of the vaccine that was used to deliver the primary course. It is expected that this response would be similar with other rabies CCV.

4.16.8 Recommendations

Measures to avoid potential rabies virus and other lyssavirus (including ABLV) exposures

Travellers to rabies-enzootic regions should be advised to avoid close contact with either wild or domestic animals; this is particularly important for children.[35-37] They should be advised about pre-travel (i.e. pre-exposure) rabies vaccination (or, if appropriate, booster doses), and on what to do should they be either bitten or scratched by an animal while abroad.[37-41] It is recommended that prior to travel, travellers be educated regarding first aid treatment for rabies exposures, irrespective of prior vaccination.

Recommendations to decrease the risk of exposure to rabies include:

- Do not allow young children to feed, pat or play with animals. The height of young children makes bites to the face and head more likely.
- Avoid contact with stray dogs or cats. Remain vigilant when walking, running or cycling.
- Do not carry food, and do not feed or pat monkeys, even in popular areas around temples or markets where travellers may be encouraged to interact with the monkeys. In particular, avoid focusing attention on monkeys carrying their young, as they may feel threatened and bite suddenly.

In addition, contact with bats should be avoided anywhere in the world, including Australia. Only appropriately vaccinated and trained persons should handle bats. If bats must be handled, safety precautions, such as wearing protective gloves and clothing, should be observed.

Pre-exposure prophylaxis for rabies virus and other lyssaviruses (including ABLV)

PreP with rabies vaccine is recommended for:

- persons liable to receive bites or scratches from bats (this includes bat handlers, veterinarians, wildlife officers and others who come into direct contact with bats) in any country, including Australia
- travellers and expatriates who will be spending time in rabies-enzootic areas; PreP should occur following a risk assessment that takes into consideration the likelihood of interaction with animals and access to emergency medical attention
- persons working with terrestrial animals in rabies-enzootic areas
- research laboratory personnel working with any live lyssaviruses.

Parents travelling with children to rabies-enzootic areas should consider PreP for younger children, as many children, if bitten by dogs, are often bitten on the face and hands because they are at an optimal height for such contact.

Serological testing to confirm seroconversion is only necessary in certain circumstances (see 'Serological testing following rabies vaccination' below).[22]

PreP simplifies the management of a subsequent exposure because fewer doses of vaccine are needed and because rabies immunoglobulin (RIG) is not required (see 'Post-exposure prophylaxis for rabies virus and other lyssavirus (including ABLV) exposures' below). This is particularly important as RIG (human or equine) is often difficult to obtain in many developing countries and its safety may not be guaranteed.

Pre-exposure prophylaxis administered via the intradermal route

Intradermal PreP is not recommended because, although initial antibody titres may be higher, titres at 14 days are lower and wane more rapidly after ID administration of rabies vaccine than after either IM or SC administration. There may also be a slow initial immune response following exposure to rabies virus in those given ID rabies vaccine.[42-44] For these reasons, *it is strongly recommended that the IM route (IM or SC if HDCV is used) be used for pre-exposure prophylaxis*. (See also 4.16.7 *Dosage and administration* above.)

However, if ID rabies PreP is considered (using a dose of 0.1 mL on days 0, 7 and 28) it is essential that:

- it is given by vaccine providers with not only expertise in, but also regular practice of, the ID technique
- it is not administered to anyone who is immunocompromised
- it is not administered to persons taking either chloroquine or other antimalarials structurally related to chloroquine (e.g. mefloquine), at either the time of, or within a month following, vaccination[45]
- any remaining vaccine is discarded at the end of the session during which the vial is opened (8 hours)

- the rabies VNAb level is checked 14 to 21 days following completion of the pre-exposure course of ID vaccine (see 'Serological testing following rabies vaccination' below)
- it is only used for PreP for classical rabies exposures (there are no data on the protection provided by ID rabies vaccination for the prevention of infection with other lyssaviruses, including ABLV).

Post-exposure prophylaxis for rabies virus and other lyssavirus (including ABLV) exposures

PEP for rabies virus and other lyssavirus exposures consists of prompt wound management, vaccine and HRIG administration. The appropriate combination of these components depends on the extent of the exposure, the animal source of the exposure, the person's immune status and their previous vaccination history. The different PEP pathways are described in more detail below and PEP management algorithms are outlined in Figures 4.16.1 and 4.16.2.

Types of potential rabies virus and other lyssavirus (including ABLV) exposures

Three different categories of lyssavirus exposure are outlined in Table 4.16.1, based on those already described by the WHO.[22] The appropriate PEP pathway following each of the different exposure categories varies depending on whether the source of exposure was a terrestrial animal or a bat. Different PEP management pathways following potential bat exposures compared with terrestrial animal exposures are required because the risk from wounds from bats is often difficult to determine due to the limited injury inflicted and there is evidence that superficial bat exposures are more likely to result in human infection.[31]

An algorithm detailing the appropriate PEP pathway following potential classical rabies virus exposure from a terrestrial animal is provided in Figure 4.16.1; an algorithm for use following potential lyssavirus exposure from a bat is provided in Figure 4.16.2.

Table 4.16.1: Lyssavirus exposure categories, to be used in conjunction with Figure 4.16.1 or 4.16.2 to determine appropriate post-exposure prophylaxis

Type of exposure	Description
Category I	Touching or feeding animals, licks on intact skin, as well as exposure to blood, urine or faeces or to an animal that has been dead for more than 4 hours
Category II	Nibbling of uncovered skin, minor scratches or abrasions without bleeding
Category III	Single or multiple transdermal bites or scratches, contamination of mucous membrane with saliva from licks, licks on broken skin

Source: Modified from WHO 2010[22]

The relevant state/territory health authority should be contacted about any potential exposure sustained from a terrestrial animal in a rabies-enzootic area, or any potential exposure sustained from a bat anywhere in the world[46] (see 4.16.12 *Public health management of lyssavirus infections* below). Dogs and monkeys are the usual exposures in Asia, Africa and Central and South America, but exposures to other terrestrial mammals and bats must also be assessed for potential classical rabies virus transmission. If a traveller presents >10 days after being bitten or scratched by either a domestic dog, cat or ferret in a rabies-enzootic country, and it can be reliably ascertained that the animal has remained healthy (>10 days after the exposure), PEP is not required. Otherwise, PEP appropriate for the category and source of exposure (see Figure 4.16.1 or 4.16.2) should be administered, even if there has been a considerable delay in reporting the incident.

The relevant state/territory veterinary or health authority should be contacted regarding any potential exposure to Australian bats (for ABLV) (see 4.16.12 *Public health management of lyssavirus infections* below). This includes situations where the category of the exposure is unsure, for example, for a person or child who has woken up with a bat present in a confined space but with no recollection of contact. If possible, and without placing others at risk of exposure, the bat should be kept and arrangements promptly made for testing the bat for ABLV. Following wound management (see below), the administration of HRIG and rabies vaccine can be withheld if the bat's ABLV status will be available within 48 hours of the exposure. If the result will not be available within 48 hours, the appropriate post-exposure prophylaxis should begin as soon as is practicable, following the bat exposure algorithm as outlined in Figure 4.16.2. Where a bat is tested at a reference laboratory and later found to be negative for ABLV, then PEP for the person exposed to that bat can be discontinued.

Wound management in post-exposure prophylaxis

One of the most vital steps following a potential rabies virus or other lyssavirus exposure is wound management. Immediate and thorough washing of all bite wounds and scratches with soap and water, and the application of a virucidal preparation such as povidone-iodine solution after the washing, are important measures in the prevention of rabies. Consideration should also be given to the possibility of tetanus and other wound infections, and appropriate measures taken. Primary suture of a bite from a potentially rabid animal should be avoided. Bites should be cleaned, debrided and infiltrated well with HRIG, when indicated (see Figure 4.16.1 or 4.16.2).

Post-exposure prophylaxis of persons who are previously unvaccinated

Vaccine

After performing wound management, rabies vaccine should be administered with or without HRIG (see 'Human rabies immunoglobulin' below), depending on the category and source of exposure, as outlined in Figure 4.16.1 or Figure 4.16.2, and described below.

Persons who have not previously received a complete rabies vaccine course, and are immunocompetent, should receive a total of 4 doses of rabies vaccine (see 4.16.7 *Dosage and administration* above). Although no clinical trial has assessed the efficacy of rabies vaccine, the rationale supporting the use of a 4-dose schedule in immunocompetent persons is based on 11 studies where the immunogenicity of either cell culture-derived vaccine was consistently >0.5 IU/mL by day 30 (after 4 doses) and, in a majority of participants, was >0.5 IU/mL by day 14 (after 3 doses). Antibody responses observed after the 4th and 5th doses were both several orders of magnitude larger than the WHO cut-off of 0.5 IU/mL and were similar in value. As the additional immune boosting following a 5th dose is minimal, a 5th dose is not required in immunocompetent persons.[47-57]

Persons who have not previously received a complete rabies vaccine course and who have either an immunocompromising illness, or are taking immunosuppressant medications, should receive a 5-dose vaccine schedule (see 4.16.7 *Dosage and administration* above).[58-60] The rabies VNAb titre should be measured 14 to 21 days after the 5th dose and a further dose given if the titre is reported as inadequate (i.e. <0.5 IU/mL). Serological testing should be repeated following the 6th dose, and, if titres remain <0.5 IU/mL, infectious disease specialist advice should be sought (see 'Serological testing following rabies vaccination' below).

Corticosteroids and immunosuppressive therapy can interfere with the development of active immunity and, therefore, if possible, should not be administered during the period of post-exposure prophylaxis.[61]

Human rabies immunoglobulin

The administration of a single dose of HRIG (see 4.16.7 *Dosage and administration* above), in addition to vaccination, in previously unvaccinated persons is only indicated in certain circumstances as outlined in Figure 4.16.1 or Figure 4.16.2, and as described below. HRIG is given to provide localised anti-rabies antibody protection while the person responds to the rabies vaccine. This should follow adequate wound care (see 'Wound management in post-exposure prophylaxis' above).

HRIG is *not* recommended in persons who:

- received the 1st dose (day 0) of vaccine more than 7 days prior to presenting for HRIG (i.e. 8 days or more have elapsed since the 1st dose of vaccine was given)
- have a documented history of previous completed recommended PreP or PEP (see 4.16.7 *Dosage and administration* above)
- have documented evidence of adequate VNAb titres (see 'Serological testing following rabies vaccination' below).

Such persons should receive rabies vaccine only (see 'Post-exposure prophylaxis of persons who have been previously vaccinated' below).

Although data are limited on the effectiveness of rabies vaccine and HRIG as PEP against infection with lyssaviruses other than classical rabies virus, the available animal data and clinical experience support their use.[19,24-29]

Post-exposure prophylaxis of persons who have been previously vaccinated

Wound management must still be carried out irrespective of prior rabies vaccination.

Persons who have evidence of a previous completed recommended PreP or PEP regimen, or who have a previously documented adequate VNAb titre, require a total of 2 doses of rabies vaccine (see Figure 4.16.1 or Figure 4.16.2). This includes immunocompromised individuals; however, VNAb levels should be checked after the 2nd dose to ensure they are adequate (see 'Serological testing following rabies vaccination' below).

Note: PreP or PEP vaccine administered via the ID route is not considered appropriate previous vaccination unless documentation of an adequate VNAb titre is available (see 'Serological testing following rabies vaccination' below).

HRIG is not required and should not be administered, as its use may suppress the level of anamnestic response and circulating VNAb.

In cases where a person's vaccination status is uncertain because the documentation of a full course of rabies vaccine is not available, the full PEP regimen should be administered.

Post-exposure prophylaxis commenced overseas

Australians travelling overseas who are exposed to a potentially rabid animal (including bats from any country) may be given PEP using vaccines and schedules not used in Australia. In very rare circumstances, if an older nerve tissue-derived rabies vaccine has been administered, any doses given should be disregarded (see Table 4.16.2). However, it is most likely that a person vaccinated overseas will have received a cell culture-derived vaccine (see 'Interchangeability of rabies vaccines' in 4.16.7 *Dosage and administration* above).[22,34] If a person has received a cell culture-derived vaccine abroad, it is recommended that the standard post-exposure prophylaxis regimen be continued in Australia with either HDCV or PCECV.

WHO-approved post-exposure rabies vaccination regimens include:

- Zagreb (2 doses on day 0, doses on days 7 and 21: annotated as 2-0-1-1)
- Essen (doses given on days 0, 3, 7, 14 and 28 (or 30): annotated as 1-1-1-1-1)
- Modified Essen (doses given on days 0, 3, 7 and 14: annotated as 1-1-1-1).

If the PEP was started overseas but HRIG or equine RIG was not given, and the person presents in Australia within 7 days of commencing PEP, HRIG should be given as soon as is practicable (and within 7 days of the 1st rabies vaccine dose).

If the person presents in Australia 8 days or more after commencing PEP, then HRIG should not be administered and the appropriate number of remaining doses of rabies vaccine administered.

For these and other scenarios that may arise, Table 4.16.2 outlines the most common PEP regimens that may be commenced overseas and the recommended schedule to complete PEP in Australia.

In the case of PEP commenced overseas, every traveller should be advised to request a PEP certificate from the vaccination centre and to obtain or record the following information (preferably in English):

- the contact details for the clinic attended (telephone and email address)
- the batch and source of RIG used (Note: equine RIG rather than human RIG may be used in some countries)
- the volume of RIG administered
- the type of cell culture vaccine used
- the vaccine batch number
- the number of vials used
- the route of vaccine administration
- the date of RIG and/or vaccine administration.

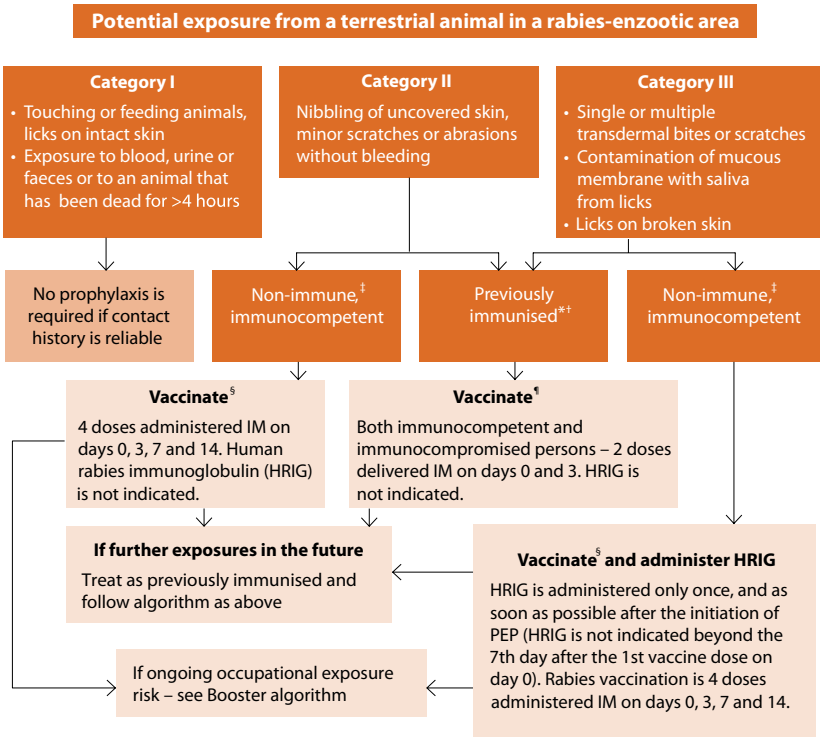
These details help inform decisions about PEP on return home.

Table 4.16.2: Post-exposure prophylaxis commenced overseas and recommended completion in Australia

Vaccine type/route administered overseas/ rabies immunoglobulin (RIG)	Rabies vaccine schedule in Australia	HRIG Category III terrestrial animal exposures and Category II and III bat exposures only*
Nerve tissue vaccine	Recommence schedule starting from day 0	Administer HRIG if no RIG already given Do *not* give HRIG if 8 days or more since 1st dose of vaccine (day 0)
Unsure/unknown/poor documentation	Recommence schedule starting from day 0	Administer HRIG if no RIG already given Do *not* give HRIG if 8 days or more since 1st dose of vaccine (day 0)
Well documented, RIG (equine or human) given, plus vaccine given either IM or ID	Align with nearest due dose and resume schedule administering vaccine IM (IM or SC if HDCV used)	*No* HRIG needed
2 vaccine doses given IM on day 0 *Irrespective of whether* RIG (equine or human) was administered at same time as the 1st doses of vaccine	Give a further 2 doses; the 1st dose on day 7 and the 2nd dose on day 14	Administer HRIG if no RIG already given Do *not* give HRIG if 8 days or more since 1st doses of vaccine (day 0)
Immunocompromised with vaccines administered ID	Irrespective of number of previous doses, administer a 5-dose schedule IM (IM or SC if HDCV used) and check serology (see 'Serological testing following rabies vaccination' below)	Administer HRIG if no RIG already given Do *not* give HRIG if 8 days or more since 1st dose of vaccine (day 0)

* See Table 4.16.1 *Lyssavirus exposure categories* and Figures 4.16.1 and 4.16.2 for further information of PEP pathways, including HRIG administration following either a terrestrial animal or bat exposure.

Figure 4.16.1: Post-exposure prophylaxis algorithm for potential exposure to classical rabies virus from a terrestrial animal overseas



* If in doubt, treat as non-immune.

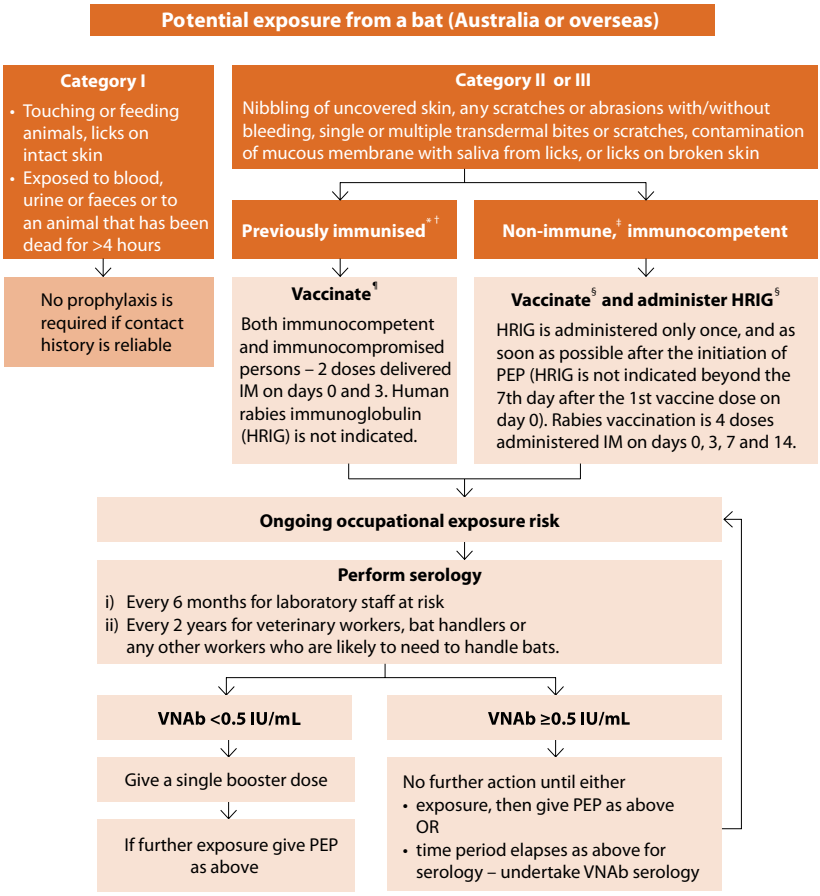
† Previously immunised – documentation of a completed recommended PreP or PEP rabies vaccine regimen. This is irrespective of the time period since the last dose was administered. This may either be a completed primary pre-exposure course or post-exposure course and includes those where subsequent boosting has occurred, or documented rabies antibody (VNAb) titres of ≥0.5 IU/mL.

‡ Non-immune – person who has never received pre- or post-exposure immunisation with rabies vaccine, has had incomplete/inadequate primary vaccination course.

§ Immunocompromised persons, not previously vaccinated, should receive 5 doses of vaccine on days 0, 3, 7, 14 and 28. Serology should be checked 14 to 21 days post dose 5 and a further dose offered if the result is <0.5 IU/mL. In immunocompromised persons, HRIG should be administered if a Category II or III exposure.

¶ Immunocompromised persons, previously immunised, should have serological testing 14 to 21 days after the 2nd dose to confirm acceptable VNAb levels. If the result is <0.5 IU/mL, expert advice should be sought regarding the total number of doses required for PEP.

Figure 4.16.2: Post-exposure prophylaxis algorithm for potential exposure to lyssaviruses from bats in Australia or overseas



* If in doubt, treat as non-immune.

† Previously immunised – documentation of a completed recommended PreP or PEP rabies vaccine regimen. This is irrespective of the time period since the last dose was administered. This may either be a completed primary pre-exposure course or post-exposure course and includes those where subsequent boosting has occurred, or documented rabies antibody (VNAb) titres of ≥0.5 IU/mL.

‡ Non-immune – person who has never received pre- or post-exposure immunisation with rabies vaccine or has had incomplete/inadequate primary vaccination course.

§ Immunocompromised persons, not previously vaccinated, should receive 5 doses of vaccine on days 0, 3, 7, 14 and 28. Serology should be checked 14 to 21 days post dose 5 and a further dose offered if the result is <0.5 IU/mL. In immunocompromised persons, HRIG should be administered if a Category II or III exposure.

¶ Immunocompromised persons, previously immunised, should have serological testing 14 to 21 days after the 2nd dose to confirm acceptable VNAb levels. If the result is <0.5 IU/mL, expert advice should be sought regarding the total number of doses required for PEP.

Booster doses

A recent WHO position paper applied a quality assessment of a moderate level of scientific evidence to support that cell culture-derived rabies vaccines induce long-term immunity of at least 10 years.[22]

The WHO states that booster doses are not required for persons who are travelling to, or living in, an area of high rabies risk and who have completed a primary course, either pre- or post-exposure, using either of the currently available cell culture-derived vaccines.[22]

Booster doses of rabies vaccine are recommended for immunised persons who have ongoing occupational exposure to lyssaviruses in Australia or overseas[62] (see Figure 4.16.3).

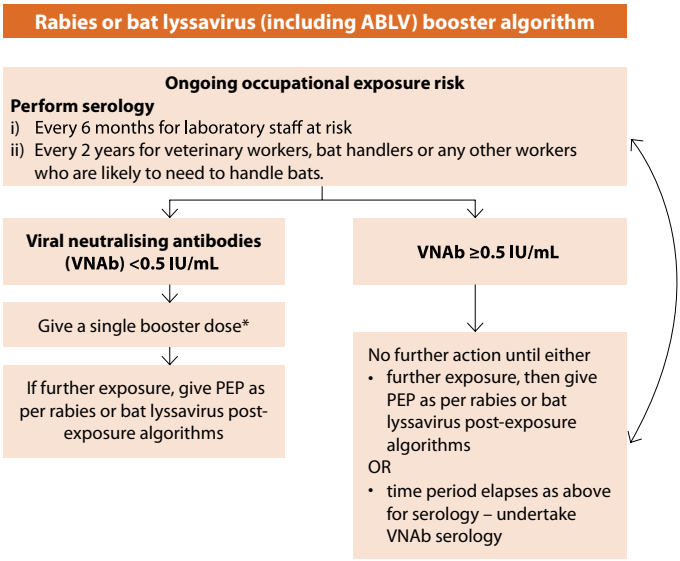
These include:

- Persons who work with live lyssaviruses in research laboratories who should have rabies neutralising antibody titres measured every 6 months. If the titre is reported as inadequate (<0.5 IU/mL), they should have a booster dose.
- Others with exposures to bats in Australia or overseas, and those who are likely to be exposed to potentially rabid terrestrial mammals overseas, who should have rabies antibody titres measured every 2 years. If the titre is reported as inadequate (<0.5 IU/mL), they should have a booster dose. Alternatively, a booster dose may be offered every 2 years without determining the antibody titre.

Points that should be considered as to whether a person should receive a booster dose of rabies vaccine because their antibody level falls below 0.5 IU/mL are:

- anticipated risk of exposure (i.e. routinely handling sick animals or rabies reservoir species in enzootic areas)
- length of time until the next antibody measurement
- individual health status (consider immunocompromising conditions or a history of poor vaccine response)
- timely access to vaccine and administration should a potential exposure occur.

Figure 4.16.3: Booster algorithm for persons at ongoing risk of exposure to either rabies or other lyssaviruses, including Australian bat lyssavirus (ABLV)



* Immunocompromised patients' serology should be checked 14 to 21 days post booster dose and a further dose offered if the result remains <0.5 IU/mL.

Serological testing following rabies vaccination

The WHO defines adequate immunity to rabies virus as the presence of a VNAb titre ≥0.5 IU/mL.[63]

Routine serological testing for rabies following PreP or PEP vaccination is not usually necessary. However, persons who are immunocompromised should have their VNAb titres determined 14 to 21 days after the 3rd dose of vaccine in a PreP schedule or after the 5th dose of vaccine in a PEP schedule; a further dose should be given if the titre is reported as inadequate (i.e. <0.5 IU/mL). Serological testing should then be repeated and, if titres remain <0.5 IU/mL, infectious disease specialist advice should be sought.[22]

If PreP was administered via the ID route, the rabies antibody level should be checked 14 to 21 days following completion of the pre-exposure course to ensure VNAb levels are adequate. If inadequate, expert advice should be sought.

Persons who are at risk of repeated exposure to rabies or other lyssaviruses, including ABLV, should have their VNAb titre determined every 6 months

to 2 years, depending on the risk of exposure, to assess the need for booster vaccination (see 'Booster doses' above).

4.16.9 Pregnancy and breastfeeding

Rabies vaccine and HRIG are recommended in pregnant or breastfeeding women following a potential exposure to rabies virus, ABLV or another bat lyssavirus[64,65] (see 4.16.8 *Recommendations* above and 3.3 *Groups with special vaccination requirements*, Table 3.3.1 *Recommendations for vaccination in pregnancy*).

4.16.10 Contraindications

There are no absolute contraindications to use of either rabies vaccine or HRIG as post-exposure prophylaxis in persons with a potential exposure to rabies or other lyssaviruses, including ABLV. This is because rabies disease is almost always lethal.

Persons with an anaphylactic sensitivity to eggs, or to egg proteins, should not receive PCECV. HDCV should be used instead.

See also 4.16.11 *Adverse events* below.

4.16.11 Adverse events

Cell culture-derived vaccines are generally well tolerated. In a large study, the following adverse events were reported after administration of HDCV to adults: sore arm (in 15 to 25% of vaccine recipients), headache (in 5 to 8%), malaise, nausea or both (in 2 to 5%), and allergic oedema (in 0.1%).[66] Similar adverse event profiles have been reported for the PCECV; these reactions occur at the same rates in children.[22,23,67-72]

Although anaphylactic reactions are rare (approximately 1 per 10 000 vaccinations) following administration of HDCV, approximately 6% of persons receiving booster doses may experience allergic reactions. The reactions typically occur 2 to 21 days after a booster dose, and are characterised by generalised urticaria, sometimes with arthralgia, arthritis, oedema, nausea, vomiting, fever and malaise.[66] These reactions are not life-threatening; they have been attributed to the presence of β-propiolactone-altered human albumin in the implicated vaccines.[66]

HRIG has an excellent safety profile and, in general, no chance of immediate hypersensitivity reactions as is more often the case with some equine sources of rabies immunoglobulin.[22]

Management of adverse events

Once initiated, rabies post-exposure prophylaxis should not be interrupted or discontinued because of local reactions or mild systemic reactions. Such reactions can usually be managed with simple analgesics.

Because rabies disease is almost always lethal, the recommended vaccination regimens, in particular the PEP regimen, should be continued even if a significant

allergic reaction occurs following a dose of rabies vaccine. Antihistamines can be administered in an attempt to ameliorate any subsequent reactions.

A patient's risk of developing either lyssavirus infection or rabies must be carefully considered before deciding to discontinue vaccination.

4.16.12 Public health management of lyssavirus infections

Classical rabies virus and ABLV virus infections in humans are notifiable diseases in all states and territories in Australia.

Other lyssavirus cases that do not meet the case definition for ABLV or rabies virus infection are also notifiable in all states and territories in Australia.

Detailed information regarding the management of disease from rabies and other lyssaviruses, including ABLV, can be found in the national guidelines for public health units[46] (www.health.gov.au/cdnasongs).

Both HRIG and rabies vaccine are available for PEP from the relevant state/territory health authorities (see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*).

4.16.13 Variations from product information

Neither of the product information sheets for the two vaccines available in Australia mentions that they can be used for both PreP and PEP for ABLV exposures. The ATAGI instead recommends that, where indicated, either of the available rabies vaccines can be used as PreP or PEP as per 4.16.8 *Recommendations* above.

The product information for HDCV recommends a routine 6th dose at 90 days in a PEP regimen. The ATAGI recommends instead that a 4-dose schedule be used for PEP in immunocompetent persons. Further doses should be offered to a person who is immunocompromised and who has an inadequate antibody level following the 5-dose PEP regimen.

The product information for HDCV also recommends a pre-exposure booster after a year. The ATAGI instead recommends boosters between 6 months and 2 years for persons at continuing occupational risk (see 'Booster doses' in 4.16.8 *Recommendations* above).

The product information for PCECV recommends a routine 5th dose at 28 days in a PEP regimen and the product information for HDCV recommends a routine 5th and 6th dose at days 30 and 90, respectively, in a PEP regimen. The ATAGI recommends instead that a 4-dose schedule with either cell culture-derived vaccine be used for PEP in immunocompetent persons. A 5th dose at day 28 should be offered to persons who are immunocompromised. Further doses should be offered to persons who are immunocompromised and have an inadequate antibody level following the 5th dose of PEP.

References

A full reference list is available on the electronic *Handbook* or website www.immunise.health.gov.au

4.17 ROTAVIRUS

4.17.1 Virology

Rotaviruses are non-enveloped RNA viruses that are classified according to the two surface proteins they contain: VP7, the 'G' glycoprotein, and VP4, the protease-cleaved 'P' protein. The G and P proteins are targets for the neutralising antibodies that contribute to protection against reinfection and disease.[1,2] The two gene segments that encode these proteins can segregate independently, and a binary typing system, consisting of both P and G types, has been developed. Rotavirus strains are most commonly referred to by their G serotype, with G1, G2, G3, G4 and G9 accounting for around 90% of serotypes, both globally and in Australia.[3,4] The most common P types found in combination with these G types are P1A[8] (found with all common G types except G2) and P1B[4], usually found in combination with G2.[5]

4.17.2 Clinical features

Rotavirus is the predominant agent of severe dehydrating gastroenteritis in infants and young children in both developed and developing countries.[1,2] The spectrum of rotavirus infection ranges from asymptomatic infection, to mild, watery diarrhoea of limited duration, to severe dehydrating diarrhoea with vomiting, fever, electrolyte imbalance, shock and death. Rotavirus infections are often more severe than other common causes of diarrhoea, and are more likely to result in dehydration and hospitalisation.[1,6] The incubation period is 1 to 3 days, after which illness can begin abruptly, with vomiting often preceding the onset of diarrhoea.[6] Up to one-third of patients have a temperature of >39°C in the first few days of illness. Symptoms generally resolve in 3 to 7 days.

4.17.3 Epidemiology

Rotaviruses are shed in high concentrations in the stools of infected children and are transmitted by the faecal–oral route, both through close person-to-person contact and via fomites.[7] In some instances, rotaviruses might also be transmitted by other modes, such as faecally contaminated food, water and respiratory droplets.[6,8]

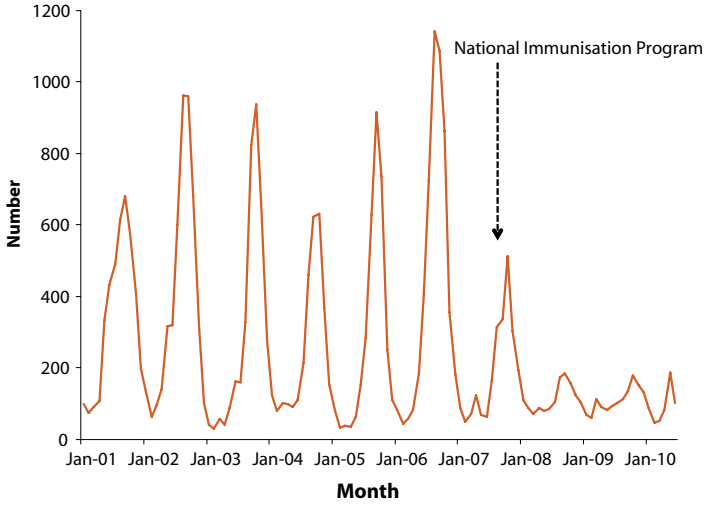
Infection in early childhood is thought to be universal. Although individuals can be infected several times during their lives, the first infection, typically between 3 and 36 months of age, is most likely to cause severe diarrhoea and dehydration.[9,10] The degree of protection following natural infection varies. After a single natural infection, 40% of children are protected against any subsequent infection with rotavirus, 75% are protected against diarrhoea from a subsequent rotavirus infection, and 88% are protected against severe diarrhoea.[10] Repeat infections provide even greater protection. Prior to the introduction of rotavirus vaccines in Australia, the best available estimates were that approximately 10 000 hospitalisations due to rotavirus occurred each year in children <5 years of age,[11] equating to around half the hospitalisations for acute gastroenteritis in this

age group[11,12] and affecting 3.8% of all children (1 in 27) by the age of 5 years. In addition to hospitalisations, an estimated 115 000 children <5 years of age visited a GP, and 22 000 children required an emergency department visit due to rotavirus.[11,13] On average, there was 1 death attributed to rotavirus each year in Australia, but this is likely to be a minimum estimate.[13] Following the introduction of rotavirus vaccines to the NIP in 2007, substantial reductions (>70%) in both rotavirus-specific and all-cause hospital presentations for gastroenteritis have been reported (Figure 4.17.1).[14-17] Emergency department visits for acute gastroenteritis have also declined, as have rotavirus notifications.[18,19]

In temperate Australia, rotavirus infections follow a seasonal pattern, with the peak incidence being in mid to late winter. In the northern tropical and arid regions, there is no consistent seasonal pattern – disease peaks are unpredictable[20] and widespread epidemics cause severe strain on healthcare services.[21,22] Overall, Indigenous infants and children are hospitalised with rotavirus gastroenteritis about 3 to 5 times more commonly than their non-Indigenous peers, are younger at hospitalisation, and have a longer duration of stay (an average of 5 days, compared with 2 days for non-Indigenous infants).[12,20,21,23]

Immunocompromised children and adults, such as those with congenital immunodeficiency, or post haematopoietic or solid organ transplantation, are at increased risk of severe, prolonged and even fatal rotavirus gastroenteritis.[1,24,25] Rotavirus is an important cause of nosocomial gastroenteritis,[26-30] and can also cause disease in adults, especially among those caring for children and those residing in aged care facilities.[1,31,32]

Figure 4.17.1: Rotavirus-coded hospitalisations per month, Australia, 2001 to 2010[17]



4.17.4 Vaccines

Two oral rotavirus vaccines are available in Australia, and their efficacy and safety in the prevention of rotavirus gastroenteritis have been extensively evaluated.[33-39] Both are live attenuated vaccines administered orally to infants, but the component vaccine viruses differ. The human rotavirus vaccine, Rotarix (GlaxoSmithKline), is a live attenuated vaccine containing one strain of attenuated human rotavirus (G1P1A[8] strain). Rotarix protects against non-G1 serotypes on the basis of other shared epitopes. A pentavalent vaccine, RotaTeq (CSL Limited/Merck & Co Inc), contains five human–bovine rotavirus reassortants with the human serotypes G1, G2, G3, G4 and P1A[8] and the bovine serotypes G6 and P7.

In middle- and high-income countries, a course of vaccination with either Rotarix or RotaTeq prevents rotavirus gastroenteritis of any severity in approximately 70% of recipients and prevents severe rotavirus gastroenteritis and rotavirus hospitalisation for 85 to 100% of recipients for up to 3 years.[33,34,40,41] Vaccination is also highly effective in preventing emergency department and clinic/GP visits.[33,40] Overall, in pre-market clinical trials, rotavirus vaccination prevented around half (42–58%) of hospital admissions for acute gastroenteritis of any cause in young children, suggesting that rotavirus is responsible for more gastroenteritis than detected using routine testing and admission practices.[33,34,40] post-marketing studies in the United States and Australia have confirmed high vaccine effectiveness and impressive reductions in both rotavirus-coded and all-cause gastroenteritis hospitalisations.[15,19,42-46] Reductions have also been observed in age groups not eligible for vaccination, suggesting that herd protective effects are also likely to exist for rotavirus vaccines.[15,19,45]

Although more modest estimates of efficacy have been reported in resource-poor settings,[36-38,47] post-marketing evaluation in the middle income countries Mexico and Brazil have revealed substantial reductions in diarrhoea-related mortality since vaccine introduction.[48,49] Studies of Rotarix during consecutive epidemics in Central Australia gave generally lower and wide-ranging vaccine effectiveness estimates, which require further investigation.[46,50] Considering the uniqueness of the remote Australian setting, these results should not be extrapolated to elsewhere in Australia, where the weight of evidence indicates a substantial reduction in the burden of rotavirus disease following vaccine introduction. To date, there has been no convincing evidence of important differences between the two vaccines with regard to protective efficacy against different serotypes.[33,34,39]

RotaShield, a tetravalent rhesus-reassortant vaccine, which was licensed in the United States (but not elsewhere) in 1998–99, was subsequently associated with intussusception (IS, an uncommon form of bowel obstruction in young children) in approximately 1 in 10 000 vaccine recipients.[51] The pathogenesis of RotaShield-associated IS has not been determined. The greatest risk of IS occurred within 3 to 14 days after the 1st dose, with a smaller risk after the 2nd dose.[51,52] There is evidence suggesting that when the 1st dose of RotaShield was given at >3 months

of age, the risk of IS was increased.[52] The current rotavirus vaccines (Rotarix and RotaTeq) differ in composition to RotaShield, which was more reactogenic.[53-55] The large-scale safety studies of Rotarix and RotaTeq included approximately 140 000 infants, and found the risk of IS in vaccine recipients to be similar to that of placebo recipients, and less than that estimated for RotaShield.[33,34] A meta-analysis of clinical trial data also did not find evidence of an increased risk of IS among vaccine recipients.[39] The clinical trials of Rotarix and RotaTeq limited administration of the 1st dose of vaccine to infants under 14 and 12 weeks of age, respectively, and did not give subsequent doses to infants beyond 24 weeks for Rotarix and 32 weeks for RotaTeq.[33,34] There are no data from clinical trials on the use of rotavirus vaccines given outside the recommended dosing age ranges. While clinical trials excluded an association between Rotarix or RotaTeq and IS of the magnitude associated with RotaShield, post-marketing studies in Australia and in Mexico indicate that a smaller increase in the absolute risk of IS might exist, particularly post dose 1 (see 4.17.11 *Adverse events* below).[56,57]

Vaccine viruses replicate in the intestinal mucosa and can be shed in the stool of vaccine recipients, particularly after the 1st dose. Vaccine virus shedding is more common with Rotarix and is detected in the stool a week after vaccination in up to 80% of 1st dose recipients, and in up to 30% of 2nd dose recipients.[58,59] RotaTeq is only shed after the 1st dose (in up to 13% of recipients).[33] In one study of 80 sets of twins, transmission of Rotarix was observed to occur from 15 vaccinated infants to their unvaccinated twin,[60] indicating that transmission of vaccine virus to unvaccinated contacts is likely to occur, but the clinical implication of this has not been studied (see 4.17.10 *Precautions* below).

Adventitious DNA fragments of porcine circoviruses have been detected in both Rotarix and RotaTeq vaccines. However, porcine circoviruses have never been shown to cause illness in humans and are considered non-pathogenic.

- ***Rotarix*** – GlaxoSmithKline (live attenuated RIX4414 human rotavirus strain, type G1P1A[8]). Each 1.5 mL monodose pre-filled oral applicator or squeezable tube contains $\geq 10^{6.0}$ cell culture infectious dose 50% ($CCID_{50}$) of the RIX4414 strain; di-sodium adipate; Dulbecco's Modified Eagle Medium; sterile water. Manufacture involves exposure to bovine-derived material.
- ***RotaTeq*** – CSL Limited/Merck & Co Inc (live attenuated human–bovine reassortant rotavirus strains, types G1, G2, G3, G4 and P1A[8]). Each 2.0 mL monodose pre-filled dosing tube contains a minimum dose level of at least 2.0×10^6 infectious units of each of the rotavirus reassortants G1, G2, G3, G4 and P1A[8]; sodium citrate; sodium phosphate monobasic monohydrate; sodium hydroxide; polysorbate 80; cell culture medium. Manufacture involves exposure to bovine-derived material.

4.17.5 Transport, storage and handling

Transport according to *National vaccine storage guidelines: Strive for 5*.[61] Store at +2°C to +8°C. Do not freeze. Protect from light.

4.17.6 Dosage and administration

Rotavirus vaccines are for oral administration only. Under *no* circumstances should rotavirus vaccines be injected.

Rotarix is recommended for use in a 2-dose course in infants and upper age limits apply; see Table 4.17.1. The liquid formulation is presented as a clear, colourless liquid contained within an oral applicator (syringe-type applicator with a plunger stopper or a squeezable tube). The 1.5 mL dose of vaccine should be administered *orally* from the oral applicator onto the inside of the infant's cheek. Rotarix does not require reconstitution or dilution.

RotaTeq is recommended for use in a 3-dose course in infants and upper age limits apply; see Table 4.17.1. It is supplied in a container consisting of a squeezable plastic, latex-free dosing tube with a twist-off cap, allowing for direct *oral* administration of the 2 mL dose onto the inside of the infant's cheek. RotaTeq does not require reconstitution or dilution. RotaTeq is a pale yellow, clear liquid that may have a pink tint.

There are limited data available on the safety of administering higher than the recommended dose of rotavirus vaccines or the efficacy of a partially administered dose(s). If *most* of an oral rotavirus vaccine dose has been spat out or vomited within minutes of administration, a single repeat dose can be administered during the same visit. If an infant regurgitates or vomits only a *small part* of a vaccine dose, it is not necessary to repeat the dose. Therefore, the regurgitated (and incomplete volume) dose is still considered as the valid dose.

Co-administration with other vaccines

Rotavirus vaccines can be co-administered with other vaccines included on the NIP schedule at 2 and 4 months of age (Rotarix) or 2, 4 and 6 months of age (RotaTeq). The available evidence from clinical trials suggests co-administration of oral rotavirus vaccines is safe and effective and does not interfere with the immune response to other vaccine antigens (DTPa, Hib, IPV, hepB, and pneumococcal conjugate vaccines).[58,59,62]

There are no restrictions on the timing of administration of any other live vaccines in relation to rotavirus vaccines, including BCG or oral poliomyelitis vaccine (OPV), for example, in infants who have received OPV overseas. Delay of rotavirus vaccination for 4 weeks following vaccination with BCG or vice versa is *not* necessary.

Interchangeability of rotavirus vaccines

Completion of a course of rotavirus vaccine should be with vaccine from the same manufacturer whenever possible. There are no studies that address the interchangeability of the two available rotavirus vaccines. However, if either dose 1 or 2 of vaccine is given as RotaTeq, a 3rd dose of either rotavirus vaccine should be given, provided that the upper age limit and inter-vaccine interval, as defined in Table 4.17.1, are met.

4.17.7 Recommendations

Infants

Administration of a course of oral rotavirus vaccination is recommended for all infants in the first half of the 1st year of life. Vaccination of older infants and children is not recommended as there are theoretical concerns regarding use in older age groups (see 4.17.4 *Vaccines* above). Vaccination should occur at either 2 and 4 months of age (Rotarix), or 2, 4 and 6 months of age (RotaTeq), according to the following schedules and upper age limits (see Table 4.17.1). The 1st dose of either rotavirus vaccine can be given as early as 6 weeks of age, where necessary (see Table 4.17.1). If the 1st dose is given at 6 weeks of age, the next scheduled rotavirus vaccine dose(s) should still be given according to the age limits specified for dosing in Table 4.17.1 below.

Rotarix (human monovalent rotavirus vaccine)

The vaccination course of Rotarix consists of 2 doses, at 2 and 4 months of age. The 1st dose should be given between 6 and 14 weeks of age (i.e. prior to turning 15 weeks old), and the 2nd dose should be given by 24 weeks of age (i.e. prior to turning 25 weeks old). The interval between the 2 doses should not be less than 4 weeks.

RotaTeq (pentavalent human–bovine reassortant rotavirus vaccine)

The vaccination course of RotaTeq consists of 3 doses, at 2, 4, and 6 months of age. The 1st dose should be given between 6 and 12 weeks of age (i.e. prior to turning 13 weeks old), and all doses should be given by 32 weeks of age (i.e. prior to turning 33 weeks old). The interval between doses should be at least 4 weeks.

Table 4.17.1: Upper age limits for dosing of oral rotavirus vaccines

	Doses	Age of routine oral administration	Recommended age limits for dosing			Minimum interval between doses
			1st dose	2nd dose	3rd dose	
Rotarix (GlaxoSmithKline)	2 oral doses (1.5 mL/dose)	2 and 4 months	6–14* weeks	10–24* weeks	N/A	4 weeks
RotaTeq (CSL Limited/Merck & Co Inc)	3 oral doses (2 mL/dose)	2, 4 and 6 months	6–12† weeks	10–32† weeks	14–32† weeks	4 weeks

* The upper age limit for receipt of the 1st dose of Rotarix is immediately prior to turning 15 weeks old, and the upper age limit for receipt of the 2nd dose is immediately prior to turning 25 weeks old.

† The upper age limit for receipt of the 1st dose of RotaTeq is immediately prior to turning 13 weeks old. The 2nd dose of vaccine should preferably be given by 28 weeks of age to allow for a minimum interval of 4 weeks before receipt of the 3rd dose. The upper age limit for the 3rd dose is immediately prior to turning 33 weeks old. For infants presenting for their 2nd dose after reaching 29 weeks of age, a 2nd and final dose can be given, provided the upper age limit of 32 weeks (immediately prior to turning 33 weeks old) has not been reached.

For infants in whom the 1st dose of rotavirus vaccine is inadvertently administered at an age greater than the suggested cut-off (i.e. after the 14th week of age for Rotarix or the 12th week of age for RotaTeq), the remaining vaccine doses should be administered as per the schedule, providing the minimum interval between doses can be maintained within the recommended age limits for subsequent doses. The timing of the 1st dose should not affect the safety and efficacy of the 2nd and 3rd doses.[6] Infants who develop rotavirus gastroenteritis before receiving the full course of rotavirus vaccination should still complete the full 2- or 3-dose schedule (dependent on the brand of vaccine), because one rotavirus infection only provides partial immunity.[6]

Older infants

Vaccination of older infants, children or adults is *not* recommended. Infants should commence the course of rotavirus vaccination within the recommended age limits for the 1st dose and doses should not be given beyond the upper age limits for the final dose of the vaccine course (see 'Infants' above). The incidence of severe rotavirus infection decreases with increasing age and the benefit and safety profile of rotavirus vaccination in older infants and children has not been established.

Preterm infants

Vaccination of preterm infants using either rotavirus vaccine is indicated at a chronologic age (without correction for prematurity) of at least 6 weeks, if the infant is clinically stable. Preterm infants (born at <37 weeks gestation) appear to be at increased risk of hospitalisation from viral gastroenteritis.[63] In clinical trials, RotaTeq or placebo was administered to 2070 preterm infants (25–36 weeks

gestational age; median 34 weeks) who experienced rates of adverse events after vaccination similar to matched placebo recipients.[6] Efficacy against rotavirus gastroenteritis of any severity appeared comparable to efficacy in full-term infants (73%; 95% CI: –2 to 95%).[64] These conclusions would also be expected to apply to Rotarix vaccine, which appears safe and immunogenic in preterm infants.[65] If standard infection control precautions are maintained, administration of rotavirus vaccine to hospitalised infants, including hospitalised preterm infants, would be expected to carry a low risk for transmission of vaccine viruses.

See also 4.17.10 *Precautions* below for other special risk groups and hospitalised infants.

4.17.8 Pregnancy and breastfeeding

There are no restrictions on the infant's consumption of food or liquid, including breast milk, either before or after vaccination with either rotavirus vaccine.[6,62]

Infants living in households of pregnant women can receive rotavirus vaccines. Most pregnant women will have pre-existing immunity to rotavirus, but protection from transmission of wild-type infection through the vaccination of infant contacts may benefit adults, including pregnant women, and outweighs any theoretical concern regarding exposure to vaccine viruses.

4.17.9 Contraindications

The contraindications to rotavirus vaccines are:

- anaphylaxis following a previous dose of either rotavirus vaccine
- anaphylaxis following any vaccine component
- previous history of intussusception or a congenital abnormality that may predispose to IS

  The risk of recurrence of IS unrelated to rotavirus vaccination is in the order of 10%.[66] In addition, certain congenital malformations affecting the gut (e.g. Meckel's diverticulum) increase the risk of IS. Because of the possible association of rotavirus vaccination with an increased risk of IS (see 4.17.11 *Adverse events* below), it is considered prudent to withhold administration of rotavirus vaccines to an infant with a previous history of IS or with a known uncorrected congenital malformation associated with increased risk of IS.
- severe combined immunodeficiency (SCID) in infants

  Case reports from the United States[67-69] indicate prolonged vaccine virus-associated gastrointestinal disease following receipt of rotavirus vaccines among infants with SCID. Because these infants are unlikely to generate a protective immune response to vaccination and because of potential harm, rotavirus vaccines are contraindicated for infants with SCID. For infants with less severe forms of immunocompromise, the risk of vaccine-associated disease is likely to be less than the risk of natural infection (see 4.17.10 *Precautions* below).

4.17.10 Precautions

Infants with acute gastroenteritis

Infants with moderate to severe acute gastroenteritis should not be vaccinated until after recovery from their acute illness. Infants with mild gastroenteritis (including mild diarrhoea) can be vaccinated. The use of rotavirus vaccines has not been studied in infants with acute gastroenteritis.

Infants with moderate to severe illness

As with other vaccines, infants with a moderate to severe illness should be vaccinated after recovery. In addition to the factors mentioned above, this avoids superimposing potential adverse events related to vaccination with the concurrent illness.

Infants with underlying conditions predisposing to severe rotavirus gastroenteritis

Conditions predisposing to severe or complicated rotavirus gastroenteritis include metabolic disorders and chronic gastrointestinal disease, such as Hirschsprung's disease, malabsorption syndromes or short gut syndrome.[1] Data on the safety of live rotavirus vaccines among such infants is limited. In one report, RotaTeq was reported to be tolerated in 8 of 9 infants with high-output ileostomies, while 1 infant experienced an increase in ileostomy losses.[70] However, because of the greater risk of serious rotavirus disease, the benefits from vaccination are expected to outweigh the risk in these infants.

Infants who are immunocompromised

There are theoretical concerns that vaccine-associated gastrointestinal disease could occur in immunocompromised infants who receive rotavirus vaccines, and infants with the most severe forms of immunocompromise (SCID) should not receive rotavirus vaccine (see 4.17.9 *Contraindications* above). However, the risk for those infants with less severe immunocompromise may be less than the risk from natural infection. The risks and benefits of vaccination should be considered in the context of the infant's specific immunocompromise with appropriate specialist advice[6] (see 3.3.3 *Vaccination of immunocompromised persons*).

Rotavirus vaccines have been administered to HIV-infected infants in clinical trial settings.[36-38] Specific data on the safety and efficacy of rotavirus vaccines in these infants are limited, but suggest that the vaccines are safe and immunogenic in HIV-infected, but clinically stable, children.[71,72] (See also 3.3.3 *Vaccination of immunocompromised persons* and Table 3.3.4 *Categories of immunocompromise in HIV-infected persons, based on age-specific CD4⁺ counts and percentage of total lymphocytes*.) There are no data on the use of rotavirus vaccines in infants born to women who have received immunosuppressive therapy in pregnancy (see 'Use of immunosuppressive therapy during pregnancy' in 3.3.2 *Vaccination of women who are planning pregnancy, pregnant or breastfeeding, and preterm infants*).

Infants living in households with people who are immunocompromised

Infants living in households with immunocompromised persons should be vaccinated. In general, immunocompromised household members are afforded protection by vaccination of young children in the household and this is considered to outweigh the risk of transmitting vaccine virus shed in stools to the immunocompromised household member. However, there have been no studies to specifically address this question.[6] Hand washing and the careful disposal of soiled nappies are likely to minimise any risk of vaccine transmission to other household members. (See also 3.3.3 *Vaccination of immunocompromised persons*.)

Recent administration of antibody-containing blood products

Infants who have recently received antibody-containing blood products and are at an eligible age should be vaccinated. The interval between vaccination and receipt of the blood product should be as long as possible, but without delaying administration of vaccine beyond the suggested age limits for dosing (as per Table 4.17.1 above). This recommendation for maximising the interval between receipt of antibody-containing blood products and rotavirus vaccination is based on theoretical concern that passively acquired antibody to rotavirus may interfere with vaccine immunogenicity.[6]

Hospitalised infants

Administration of rotavirus vaccine to hospitalised infants, including premature infants, is likely to carry a low risk for transmission of vaccine viruses if standard infection control precautions are maintained. Provided that the infant is medically stable, vaccination should not be delayed, particularly if the delay would result in an infant being beyond the upper age limit for vaccination (see 4.17.7 *Recommendations* above). If a recently vaccinated child is hospitalised for any reason, no precautions other than routine standard precautions need be taken to prevent the spread of vaccine virus in the hospital setting.

4.17.11 Adverse events

Intussusception

Although clinical trials of the two available vaccines did not find an association between vaccination and intussusception (IS)[39] (see 4.17.4 *Vaccines* above), one post-marketing study in Australia found evidence of a 4- to 5-fold increase in the risk of IS in the 7 days following the 1st dose of either Rotarix or RotaTeq.[56] However, no overall increase in the risk of IS was detectable over the first 9 months of life.[56] A similar apparent increase in risk for IS following the 1st dose of Rotarix has been observed in Mexico, and a smaller increase after the 2nd dose of Rotarix in Brazil.[57] A study in the United States found no increased risk of IS following RotaTeq; however, the study was limited by small numbers, which reduced power to determine a low range risk increase.[73] A subsequent Australian study estimated the increased risk of IS to be approximately 9-fold in the first

7 days after dose 1, and 2-fold in the first 7 days after dose 2 of either vaccine.[74] The baseline risk of intussusception for Australian infants is around 80 cases per 100 000 infants.[75] The increased risk of IS following rotavirus vaccination, from the most recent Australian study, is estimated as approximately 6 additional cases of intussusception among every 100 000 infants vaccinated, or 14 additional cases per year in Australia.[74] This estimate assumes that infants in which an episode of IS occurs shortly after vaccination would not have otherwise experienced a 'natural' episode of intussusception; however, this cannot be determined from current data. Importantly, studies from both Australia[14-17] and overseas[57] have demonstrated the substantial impact of vaccination in preventing rotavirus morbidity and mortality (see also 4.17.3 *Epidemiology* above). Rotavirus vaccines continue to be recommended for use on the basis of this positive benefit to risk profile.[76] Immunisation providers should inform parents and carers of the rare risk of intussusception and how to be alert for the signs and symptoms of the condition.

Rotavirus vaccine should not be given to an infant who has had a confirmed intussusception because there may be an increased risk of the condition recurring (see 4.17.9 *Contraindications* above).

Other adverse events

No significant increase in post-vaccination vomiting, diarrhoea or fever has been reported during follow-up of several thousand recipients of Rotarix compared to those who were unvaccinated.[39,77] Detailed follow-up of 11 700 recipients of RotaTeq or placebo reported no increase in fever or irritability in the week after vaccination among vaccinated infants, but a small increase in the incidence of vomiting (7% versus 5%) and diarrhoea (10% versus 9%).[78] Vomiting and diarrhoea have not emerged as important adverse events following immunisation in post-marketing surveillance of rotavirus vaccines.

Infants who report an episode of diarrhoea or vomiting following vaccination should still receive subsequent rotavirus vaccine doses, as required and age eligible. The potential causes of diarrhoea/vomiting following vaccination include: gastroenteritis unrelated to rotavirus vaccination or infection (e.g. another viral agent); natural rotavirus infection (as vaccination is neither immediately protective nor 100% protective against all disease); or symptoms from vaccine virus replication (less likely). If rotavirus is detected by routine stool testing on a recently vaccinated infant, a positive test result can represent either natural infection or vaccine virus (as vaccine virus shedding occurs commonly after vaccination (see 4.17.4 *Vaccines* above). Specific testing is required to differentiate between vaccine virus and natural infection; however, this is rarely clinically indicated.

4.17.12 Variations from product information

The product information for Rotarix states that the vaccine should not be administered to subjects with any chronic gastrointestinal disease. The ATAGI recommends instead that pre-existing chronic gastrointestinal disease is *not* a contraindication to rotavirus vaccination, with the exception of those conditions that may predispose to IS (see 4.17.9 *Contraindications* and 4.17.10 *Precautions* above).

The product information for RotaTeq states that in the event that a dose of vaccine is spat out or vomited post vaccination, a replacement dose should not be given. The ATAGI recommends instead that if *most* of a dose is spat out or vomited then a single replacement dose may be given (see 4.17.6 *Dosage and administration* above.)

References

A full reference list is available on the electronic *Handbook* or website www.immunise.health.gov.au

4.18 RUBELLA

4.18.1 Virology

Rubella is an enveloped togavirus, genus *Rubivirus.* The virus has an RNA genome and is closely related to group A arboviruses, but does not require a vector for transmission. It is relatively unstable, and is inactivated by lipid solvents, trypsin, formalin, extremes of heat and pH, and light.[1]

4.18.2 Clinical features

Rubella is generally a mild and self-limiting infectious disease, spread from person to person by respiratory secretions, possibly including aerosol transmission.[1,2] It causes a transient, generalised, erythematous, maculopapular rash; lymphadenopathy involving the post-auricular and sub-occipital glands; and, occasionally, arthritis and arthralgia. Other complications, such as neurological disorders and thrombocytopenia, may occur but are rare. Clinical diagnosis is unreliable since the symptoms are often fleeting and can be caused by other viruses; in particular, the rash is not unique to rubella and may be absent.[1,2] Up to 50% of rubella virus infections are subclinical or asymptomatic.[1] A history of rubella should, therefore, not be accepted without serological evidence of previous infection.[1] The incubation period is 14 to 21 days, and the period of infectivity is from 1 week before until 4 days after the onset of the rash.[2]

Rubella infection in pregnancy can result in fetal infection, causing congenital rubella syndrome (CRS) in a high proportion of cases. Up to 90% of infants born to women who had rubella infection in the first trimester of pregnancy have abnormalities (often multiple) characteristic of CRS.[3-5] The risk of damage declines to 10 to 20% by 16 weeks gestation. After this stage of pregnancy, fetal damage is rare but has been reported up to 20 weeks gestation.[3] The characteristics of CRS include intellectual disabilities, cataracts, deafness, cardiac abnormalities, intrauterine growth retardation, and inflammatory lesions of the brain, liver, lungs and bone marrow.[3] Any combination of these defects may occur, but defects that commonly occur alone following infection after the first 8 weeks of pregnancy are deafness and pigmentary retinopathy. Some infected infants may appear normal at birth, but defects, especially sensorineural deafness, may be detected later.[6]

Rubella infection has been reported in some persons who already have either natural or vaccine-induced antibody.[3] Occasional cases of CRS after reinfection in pregnancy have been documented. However, fetal damage is very rare in cases of infection in women in whom antibody has previously been detected.[4,7-9]

4.18.3 Epidemiology

Evidence suggests that endemic rubella is well controlled in Australia.[10] The incidence of rubella has fallen rapidly since vaccine registration, and notifications of rubella have been low since high vaccine coverage was achieved with the National Measles Control Campaign in late 1998 and then maintained.[10] Since

2003, rubella notifications in Australia have been less than 0.3 per 100 000. There has been a shift in the age distribution of cases, with comparatively more cases seen in older age groups, particularly the 25–29 years age group.[10]

Rubella vaccines have been registered in Australia since 1970, and mass vaccination of schoolgirls commenced in 1971.[1,11] Non-pregnant, seronegative adult women were also vaccinated. These programs were successful and there was a significant reduction in the incidence of CRS from 1977.[12-14] Successful vaccination campaigns and high vaccination coverage resulted in no cases of congenital rubella syndrome occurring in infants of Australian-born mothers between 1998 and 2002. However, 5 cases resulting from infection acquired outside of Australia were reported during this time.[15] In 2003, 2 cases of CRS occurred in Australian-born mothers from infection that occurred in Australia,[16] which reinforces the need for high vaccination coverage of women of child-bearing age. Between 2004 and 2008, 2 confirmed cases of CRS were reported in Australia, in children whose mothers were born outside Australia.[17-19]

There has also been a significant increase in the percentage of pregnant women immune to rubella (e.g. in New South Wales from 82% in 1971 to 96% in 1983).[20] Based on a study conducted in Melbourne in 2000, it was estimated that only 2.5% of women of child-bearing age in Australia were seronegative.[21] However, susceptibility was higher among certain groups of women, particularly overseas-born women (see 'Women of child-bearing age, including post-partum women' in 4.18.7 *Recommendations* below).[21]

Young adult males may not be immune to rubella, because they did not receive a measles-mumps-rubella (MMR) vaccine.[22] The MMR vaccination program for all adolescents replaced the rubella program for girls in 1993/94.[11] A serosurvey conducted in 1999 showed that only 84% of males aged 14–18 years (compared to 95% of females) and 89% of males aged 19–49 years (compared to 98% of females) were immune to rubella.[22] For this reason, young adult males, as well as females, who do not have a documented history of receipt of 2 doses of MMR vaccine should be vaccinated (see 4.18.7 *Recommendations* below). This is both for their own protection and to prevent transmission of the infection in the community.

Goals for the elimination of rubella and CRS have been set by a number of World Health Organization (WHO) regions, and elimination has been declared by the Pan American Health Organization.[23] The WHO Western Pacific Region has set goals for increased rubella and CRS control efforts, with a number of member states yet to incorporate rubella vaccination into their routine schedule.[24] As with elimination of measles, rubella and CRS elimination requires continued strengthening of immunisation and surveillance efforts, particularly identification of rubella virus genotypes to confirm the absence of an endemic strain.[25]

4.18.4 Vaccines

Monovalent rubella vaccine is not available in Australia. Rubella vaccination is provided using either MMR or measles-mumps-rubella-varicella (MMRV) vaccines. Two quadrivalent combination vaccines containing live attenuated measles, mumps, rubella and varicella viruses (MMRV) are registered in Australia.

A single dose of rubella vaccine produces an antibody response in over 95% of vaccine recipients, but antibody levels are lower than after natural infection.[3,7,8] A 2nd dose aims to confer immunity in those who fail to seroconvert to the 1st dose. Vaccine-induced antibodies have been shown to persist for at least 16 years in the absence of endemic disease.[7,8,26,27] Protection against clinical rubella appears to be long-term in those who seroconvert.[3]

Combination MMRV vaccines have been shown, in clinical trials, to produce similar rates of seroconversion to all four vaccine components compared with MMR and monovalent varicella vaccines administered concomitantly at separate injection sites.[28-31]

Trivalent measles–mumps–rubella (MMR) vaccines

- ***M-M-R II*** – CSL Limited/Merck & Co Inc (live attenuated measles virus [Enders' attenuated Edmonston strain], mumps virus [Jeryl Lynn B level strain] and rubella virus [Wistar RA 27/3 strain]). Lyophilised pellet in a monodose vial with separate diluent. Each 0.5 mL reconstituted dose contains ≥1000 tissue culture infectious dose 50% ($TCID_{50}$) of Enders' attenuated Edmonston measles virus, ≥12 500 $TCID_{50}$ of the Jeryl Lynn B level mumps virus, and ≥1000 $TCID_{50}$ of the Wistar RA 27/3 rubella virus; sorbitol; sucrose; hydrolysed gelatin; human albumin; fetal bovine serum; neomycin.
- ***Priorix*** – GlaxoSmithKline (live attenuated measles virus [Schwarz strain], mumps virus [RIT 4385 strain, derived from the Jeryl Lynn strain] and rubella virus [Wistar RA 27/3 strain]). Lyophilised pellet in a monodose vial with a pre-filled diluent syringe. Each 0.5 mL reconstituted dose contains ≥$10^{3.0}$ cell culture infectious dose 50% ($CCID_{50}$) of the Schwarz measles virus, ≥$10^{3.7}$ $CCID_{50}$ of the RIT 4385 mumps virus, and ≥$10^{3.0}$ $CCID_{50}$ of the Wistar RA 27/3 rubella virus; lactose; neomycin; sorbitol; mannitol.

Quadrivalent measles-mumps-rubella-varicella (MMRV) vaccines

- ***Priorix-tetra*** – GlaxoSmithKline (live attenuated measles virus [Schwarz strain], mumps virus [RIT 4385 strain, derived from the Jeryl Lynn strain], rubella virus [Wistar RA 27/3 strain] and varicella-

zoster virus [Oka strain]). Lyophilised pellet in a monodose vial with a pre-filled diluent syringe. Each 0.5 mL reconstituted dose contains $\geq 10^{3.0}$ $CCID_{50}$ of the Schwarz measles virus, $\geq 10^{4.4}$ $CCID_{50}$ of the RIT 4385 mumps virus, $\geq 10^{3.0}$ $CCID_{50}$ of the Wistar RA 27/3 rubella virus, and $\geq 10^{3.3}$ plaque-forming units (PFU) of Oka varicella-zoster virus; lactose; neomycin; sorbitol; mannitol.

- ***ProQuad*** – CSL Limited/Merck & Co Inc (live attenuated measles virus [Enders' attenuated Edmonston strain], mumps virus [Jeryl Lynn B level strain], rubella virus [Wistar RA 27/3 strain] and varicella-zoster virus [Oka/Merck strain]). Lyophilised powder in a monodose vial with a pre-filled diluent syringe. Each 0.5 mL reconstituted dose contains $\geq 10^{3.0}$ $TCID_{50}$ of Enders' attenuated Edmonston measles virus, $\geq 10^{4.3}$ $TCID_{50}$ of the Jeryl Lynn B level mumps virus, $\geq 10^{3.0}$ $TCID_{50}$ of the Wistar RA 27/3 rubella virus, and $\geq 10^{3.99}$ PFU of Oka/Merck varicella virus; sucrose; hydrolysed gelatin; urea; sorbitol; monosodium L-glutamate; human albumin; neomycin; residual components of MRC-5 cells; bovine serum albumin.

4.18.5 Transport, storage and handling

Transport according to *National vaccine storage guidelines: Strive for 5*.[32] Store at +2°C to +8°C. Do not freeze. Protect from light.

Both MMR and MMRV vaccines *must be reconstituted* by adding the entire contents of the diluent container to the vial containing the pellet and shaking until the pellet is completely dissolved.

Reconstituted Priorix (MMR), M-M-R II (MMR) and Priorix-tetra (MMRV) vaccines should be used as soon as practicable. If storage is necessary, hold at +2°C to +8°C for not more than 8 hours.

Reconstituted ProQuad (MMRV) vaccine must be used within 30 minutes.

4.18.6 Dosage and administration

The dose of Priorix (MMR) vaccine for both children and adults is 0.5 mL, to be given by either SC or IM injection.

The dose of M-M-R II (MMR) vaccine for both children and adults is 0.5 mL, to be given by SC injection.

For children <14 years of age, the dose of MMRV vaccine is 0.5 mL, to be given by SC injection. Priorix-tetra may also be given by IM injection.[33]

MMRV vaccines are not recommended for use in persons aged ≥14 years.

When 2 doses of MMR-containing vaccine are required, the minimum interval between doses is 4 weeks.

Co-administration with other vaccines

MMR or MMRV vaccines can be given at the same time as other live attenuated parenteral vaccines (e.g. varicella, BCG, yellow fever) or other inactivated vaccines (including DTPa, hepatitis B, Hib, IPV, MenCCV, hepatitis A and pneumococcal conjugate vaccine),[34] using separate syringes and injection sites. If MMR or MMRV vaccine is not given simultaneously with other live attenuated parenteral vaccines, they should be given at least 4 weeks apart.

If MMR vaccine is given at the same time as monovalent varicella vaccine (VV), they should be given using separate syringes and injection sites. MMR vaccine and monovalent VV should *not* be mixed together prior to injection.

Separate administration of measles, mumps or rubella vaccine is not available as an alternative to MMR vaccine, although a monovalent varicella vaccine is available (see 4.22 *Varicella*).

Interchangeability of MMR-containing vaccines

In general, the two brands of MMR vaccine can be considered interchangeable, that is, the 2nd MMR dose does not have to be of the same brand as the 1st. The same principle applies to the two available MMRV vaccines,[34] although they are not routinely recommended in a 2-dose schedule.

4.18.7 Recommendations

For further information on the recommendations for MMR and MMRV vaccines, see 4.9 *Measles* and 4.22 *Varicella*.

The principal aim of rubella vaccination is to prevent congenital rubella syndrome by stopping the circulation of rubella virus in the community. Susceptible pregnant women will continue to be at risk of rubella infection in pregnancy until the transmission of rubella virus is interrupted by continued high-level coverage of rubella-containing vaccine.

A history of rubella is not a contraindication to vaccination. Persons who are already immune to rubella have no increased risk of side effects from vaccination.[3,7]

Infants aged <12 months

MMR-containing vaccines are not routinely recommended for infants <12 months of age. However, MMR vaccine can be given to children from as early as 9 months of age in high-risk circumstances (see 4.9 *Measles*).

If MMR vaccine is given at <12 months of age, there is still a need for 2 vaccine doses to be administered at ≥12 months of age (see 4.9 *Measles*).

Children

Two doses of rubella-containing vaccine are recommended for all children. The 1st dose should be given at 12 months of age as MMR vaccine. MMRV vaccines are *not* recommended for use as the 1st dose of MMR-containing vaccine in

children <4 years of age, due to a small but increased risk of fever and febrile seizures when given as the 1st MMR-containing vaccine dose in this age group (see Table 4.9.1 in 4.9 *Measles* and Table 4.22.1 in 4.22 *Varicella*). (See also 4.9.11 *Adverse events* in 4.9 *Measles* and 4.22.11 *Adverse events* in 4.22 *Varicella*.)

The 2nd dose of rubella-containing vaccine is recommended to be given routinely at 18 months of age as MMRV vaccine. This is to commence from July 2013, once MMRV vaccine(s) are available under the NIP (see Table 4.9.1 in 4.9 *Measles* and Table 4.22.1 in 4.22 *Varicella*). The recommended age for administration of the 2nd dose of rubella-containing vaccine will be moved down from 4 years of age, to provide earlier 2-dose protection against measles, mumps and rubella, and to improve vaccine uptake (see 4.18.3 *Epidemiology* above).

If MMRV vaccine is inadvertently administered as dose 1 of MMR-containing vaccine, the dose does not need to be repeated (providing it was given at ≥12 months of age); however, parents/carers should be advised regarding the small but increased risk of fever and febrile seizures (compared with that expected following MMR vaccine).

Adults and adolescents

Two doses of rubella-containing vaccine are recommended for all non-immune adolescents and adults (see 4.9 *Measles*). All persons born during or since 1966 who are ≥18 months of age (or, until catch-up following the move of the 2nd NIP dose of measles-containing vaccine to 18 months of age is completed, are ≥4 years of age) should have documented evidence of 2 doses of MMR-containing vaccine (administered at least 4 weeks apart with both doses administered at ≥12 months of age) or have serological evidence of protection for measles, mumps and rubella.

It is particularly important to ensure that women of child-bearing age are immune to rubella (see 'Women of child-bearing age, including post-partum women' below).

It is recommended that all males born during or after 1966 (particularly those born from 1966 up to the 1990s) have their vaccination records reviewed to ensure they have received 2 doses of MMR vaccine, as they are more likely, than females, to have not received 2 doses of rubella-containing vaccine (see 4.18.3 *Epidemiology* above).

MMRV vaccines are not recommended for use in persons ≥14 years of age, due to a lack of data on safety and immunogenicity/efficacy in this age group. If a dose of MMRV vaccine is inadvertently given to an older person, this dose does not need to be repeated.

Healthcare workers and those who work with children

All healthcare workers and persons working with children, born during or since 1966, either without vaccination records or seronegative upon screening, should receive 2 doses of MMR vaccine, both for their own protection and to

avoid the risk of transmitting rubella to pregnant women[35] (see 3.3 *Groups with special vaccination requirements*, Table 3.3.7 *Recommended vaccinations for persons at increased risk of certain occupationally acquired vaccine-preventable diseases*).

Women of child-bearing age, including post-partum women

Every effort should be made to identify and immunise non-pregnant seronegative women of child-bearing age (see 'Serological testing for immunity to rubella' below). The following women are more likely to be seronegative to rubella: women born overseas (especially in Asia, Pacific islands, sub-Saharan Africa and South America) who entered Australia after the age of routine vaccination; Indigenous women living in rural and remote regions; non-English speaking women; women over the age of 35 years; and Australian-born Muslim women.[12,13,21,36-38]

Seronegative women should be given MMR vaccine and advised to avoid pregnancy for 28 days after vaccination. Vaccinated women should be tested for seroconversion 6 to 8 weeks after vaccination (see 'Serological testing for immunity to rubella' below). Women who have negative or very low antibody levels after vaccination should be revaccinated. However, if antibody levels remain low after a 2nd documented vaccination, it is unlikely that further vaccinations will improve this.[3] Further testing and vaccination is not usually warranted; however, consultation with the laboratory that performed the serological testing may also be helpful (see also 'Serological testing for immunity to rubella' below). Negative serology after 2 documented doses of rubella-containing vaccine may represent a false negative (i.e. an antibody titre too low to be detected using routine commercial assays).

Although 2 doses of MMR vaccine are routinely recommended, if rubella immunity is demonstrated after receipt of 1 dose of a rubella-containing vaccine, no further dose is required, unless indicated by subsequent serological testing (see 'Serological testing for immunity to rubella' below) or if indicated for protection against measles and mumps (see 4.9 *Measles* and 4.11 *Mumps*).

Women found to be seronegative on antenatal testing for rubella immunity should be vaccinated after delivery and before discharge from the maternity unit, as discussed above. These women should be tested for rubella immunity 6 to 8 weeks following vaccination.[1,7] (See also 'Serological testing for immunity to rubella' below.)

Serological testing for immunity to rubella

Serological testing for immunity to rubella after routine vaccination of children is not recommended. However, serological testing for rubella immunity can be performed in cases where a history of natural immunity or 2 doses of vaccine administration is uncertain. It is particularly important to ensure that women of child-bearing age are immune to rubella (see 'Women of child-bearing age, including post-partum women' above).

A number of commercial assays for testing immunity to rubella are available. These vary according to the method used to determine the positive cut-off value (the WHO cut-off is 10 IU/mL, but, at present, there is no recommended Australian minimal level). Available data support the presumption that an antibody level found by use of a licensed assay to be above the standard positive cut-off for that assay can be considered evidence of past exposure to rubella virus.[7] Rubella vaccine induces immune responses that are similar in quality, but lesser in quantity, than those after natural disease.[3] Measurement of antibody by commercial assays is not a perfect correlate of protection in vaccinated persons.[3] While on the one hand, those with low levels of vaccine-induced antibodies are often protected, conversely, reinfection may take place in some individuals with measurable antibodies. If a person is found to be rubella IgG seronegative, vaccination should be provided according to the recommendations above. Interpretation of the results of serological testing may be enhanced by discussion with the laboratory that performed the test, ensuring that relevant clinical information is provided. In addition, expert consultation and referral of sera to a reference laboratory are recommended if there is difficulty interpreting results, particularly for women of child-bearing age (see 'Women of child-bearing age, including post-partum women' above).

All women of child-bearing age should be advised by a medical practitioner of the result of their antibody test, as it is a clinically significant test.[39] Women should be screened for rubella antibodies shortly before every pregnancy, or early in the pregnancy, or if pregnancy is contemplated, irrespective of a previous positive rubella antibody result.[3,14] Very occasionally, errors may result in patients who are seronegative being reported as seropositive. Specimens from pregnant women are required to be stored until the completion of the pregnancy for parallel serological testing if required.[40]

4.18.8 Pregnancy and breastfeeding

Rubella-containing vaccines are contraindicated in pregnant women (see 4.18.9 *Contraindications* below). Pregnancy should be avoided for 28 days after vaccination.[41]

MMR vaccines can be given to breastfeeding women. The rubella vaccine virus may be secreted in human breast milk, and rare cases of transmission of vaccine virus through breast milk have been reported. However, symptoms in the newborn have been absent or mild.[42-44] Post-partum vaccination of women without evidence of rubella immunity need not be delayed because of breastfeeding.

MMRV vaccines are not recommended for use in persons aged ≥14 years.

There is no risk to pregnant women from contact with recently vaccinated persons. The vaccine virus is not transmitted from vaccinated persons to susceptible contacts.[1]

Refer to 3.3 *Groups with special vaccination requirements*, Table 3.3.1 *Recommendations for vaccination in pregnancy* for more information.

4.18.9 Contraindications

Anaphylaxis to vaccine components

MMR and MMRV vaccines are contraindicated in persons who have had:

- anaphylaxis following a previous dose of any MMR-containing vaccine
- anaphylaxis following any vaccine component.

Persons who are immunocompromised

Measles-, mumps-, and rubella-containing vaccines contain live attenuated vaccine viruses and are contraindicated in persons who are immunocompromised. Thus, MMR-containing vaccines are contraindicated in the following groups:

- Persons immunocompromised due to HIV/AIDS. MMR vaccination of asymptomatic HIV-infected persons >12 months of age with an age-specific $CD4^+$ count of ≥15% may be considered[45-48] (see 'HIV-infected persons' in 3.3.3 *Vaccination of immunocompromised persons*). Since studies have not been performed using combination MMRV vaccines in asymptomatic HIV-infected persons or persons with an age-specific $CD4^+$ count of ≥15%, it is recommended that only MMR vaccine (and monovalent VV, see 4.22 *Varicella*) be considered for use in this setting.[47,49-51]
- Persons with other medical conditions associated with significant immunocompromise (see 3.3.3 *Vaccination of immunocompromised persons*)
- Persons receiving high-dose systemic immunosuppressive therapy, such as chemotherapy, radiation therapy or oral corticosteroids. MMR-containing vaccines are contraindicated in persons taking high-dose oral corticosteroids for more than 1 week (in children equivalent to >2 mg/kg per day prednisolone, and in adults >60 mg per day) (see 3.3.3 *Vaccination of immunocompromised persons*). Those who have been receiving high-dose systemic steroids for more than 1 week may be vaccinated with live attenuated vaccines after corticosteroid therapy has been discontinued for at least 1 month[52] (see 3.3.3 *Vaccination of immunocompromised persons*).

See also 3.3 *Groups with special vaccination requirements* and 4.22 *Varicella* for more information.

Pregnant women

See also 4.18.8 *Pregnancy and breastfeeding* above.

Rubella-containing vaccines are contraindicated in pregnant women.

This is due to the theoretical risk of transmission of the rubella component of the vaccine to a susceptible fetus. However, no evidence of vaccine-induced CRS has been reported.[1] Active surveillance in the United States, the United Kingdom and

Germany indicates that no case of vaccine-induced congenital rubella syndrome occurred among more than 500 women inadvertently vaccinated with rubella vaccine during pregnancy, whose pregnancies continued.[53] In an Iranian study performed after mass vaccination with a measles–rubella vaccine, 117 susceptible women were inadvertently vaccinated while pregnant or became pregnant within 3 months after vaccination. There were no CRS-related abnormalities among the infants born to these women.[54] Based on this evidence, the vaccine cannot be considered to be teratogenic, and termination of pregnancy following inadvertent vaccination is *not* indicated.[1,8] (See also 3.3.2 *Vaccination of women who are planning pregnancy, pregnant or breastfeeding, and preterm infants*.)

4.18.10 Precautions

For additional precautions related to MMR and MMRV vaccines, see 4.9 *Measles* and 4.22 *Varicella*.

Vaccination with other live attenuated parenteral vaccines

If MMR or MMRV vaccine is not given simultaneously with other live attenuated parenteral vaccines (e.g. varicella, BCG, yellow fever), the vaccines should be given at least 4 weeks apart.

Vaccination after immunoglobulin or blood product administration

Administration of a MMR or MMRV vaccine should be delayed after administration of immunoglobulin-containing products. After receipt of immunoglobulin-containing blood products, the expected immune response to measles, mumps, rubella and varicella vaccination may be impaired.[7,55,56] MMR-containing vaccines should not be given for between 3 and 11 months following the administration of immunoglobulin-containing blood products. The interval between receipt of the blood product and vaccination depends on the amount of immunoglobulin in each product, and is indicated in 3.3 *Groups with special vaccination requirements*, Table 3.3.6 *Recommended intervals between either immunoglobulins or blood products and MMR, MMRV or varicella vaccination*.[55] For further information, see 3.3.4 *Vaccination of recent recipients of normal human immunoglobulin and other blood products*.

Recent blood transfusion with washed red blood cells is *not* a contraindication to MMR or MMRV vaccines.

MMR vaccine may be administered concomitantly with, or at any time in relation to, anti-D immunoglobulin, but at a separate injection site. Anti-D immunoglobulin does not interfere with the antibody response to vaccine.[1,3,8]

Immunoglobulin or blood product administration after vaccination

Immunoglobulin-containing products should not be administered for 3 weeks following vaccination with rubella-containing vaccines, unless the benefits exceed those of vaccination. If immunoglobulin-containing products are administered within this interval, the vaccinated person should either be

revaccinated later at the appropriate time following the product (as indicated in Table 3.3.6), or be tested for immunity 6 months later and then revaccinated if seronegative.

Rh (D) immunoglobulin (anti-D) may be given at the same time in different sites with separate syringes or at any time in relation to MMR vaccine, as it does not interfere with the antibody response to the vaccine.

4.18.11 Adverse events

Adverse events following administration of MMR-containing vaccines are generally mild and well tolerated.[3] Adverse events are much less common after the 2nd dose of MMR or MMRV vaccine than after the 1st dose.

Mild adverse events such as fever, sore throat, lymphadenopathy, rash, arthralgia and arthritis may occur following MMR vaccination.[1,7] Symptoms most often begin 1 to 3 weeks after vaccination and are usually transient.

Thrombocytopenia (usually self-limiting) has been very rarely associated with the rubella or measles component of MMR vaccine, occurring in 3 to 5 per 100 000 doses of MMR vaccine administered.[7,57-59] This is considerably less frequent than after natural measles, mumps and rubella infections.[59]

For further information on adverse events related to MMR and MMRV vaccines, see 4.9 *Measles* and 4.22 *Varicella*.

4.18.12 Public health management of rubella

Rubella is a notifiable disease in all states and territories in Australia.

Further instructions about the public health management of rubella, including management of cases of rubella and their contacts, should be obtained from state/territory public health authorities (see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*).

Rubella-containing vaccine does not provide protection if given after exposure to rubella.[7] However, if the exposure did not result in infection, the vaccine would induce protection against subsequent infection. Normal human immunoglobulin (NHIG) has been shown *not* to be of value in post-exposure prophylaxis for rubella.[7] However, NHIG may be recommended in certain circumstances (see 'Use of normal human immunoglobulin in pregnant women exposed to rubella' below).

Suspected rubella contacts

All contacts of persons with suspected rubella infection should be identified, especially those who are pregnant (see 'Pregnant women with suspected rubella or exposure to rubella' below).

Contacts >12 months of age without adequate proof of immunity should receive 1 dose of MMR vaccine (or MMRV vaccine, if appropriate). This will not prevent rubella disease if already exposed. If vaccination is refused, the contact should avoid further contact with cases until at least 4 days after onset of the rash in the

case. Seronegative women of child-bearing age should be vaccinated and tested for seroconversion 6 to 8 weeks after vaccination (see 4.18.7 *Recommendations* above).

Exposed healthcare workers without adequate proof of immunity should be excluded from work for 21 days from exposure or for at least 4 days after the onset of rash.[60]

Testing for rubella infection

All cases of suspected rubella infection should be laboratory tested and false positive results excluded (see 'Serological testing for immunity to rubella' in 4.18.7 *Recommendations* above).

Acute rubella infection is indicated by the presence of rubella IgM or a 4-fold or greater increase in rubella IgG. Rubella IgM may not appear until a week after clinical symptoms. Sera for testing should be taken 7 to 10 days after onset of illness and repeated 2 to 3 weeks later. The most recent date of potential exposure should be obtained, if possible, to calculate the potential incubation period. As some patients may have more than one exposure to a person with a rubella-like illness, and because exposure may occur over a prolonged period, it is important to ascertain the dates of the first and last exposures.[60] Testing for infection can also be done, particularly early in the course of a clinical illness, using virus-detection methods, such as nucleic acid amplification testing (PCR).[60]

Infected persons should be excluded from school/work/institution and should avoid contact with women of child-bearing age for at least 4 days after the onset of the rash.[60]

Pregnant women with suspected rubella or exposure to rubella

All pregnant women with suspected rubella or exposure to rubella should be serologically tested (for IgM and IgG), irrespective of a history of prior vaccination, clinical rubella or a previous positive rubella antibody result (for more details, see 'Testing for rubella infection' above). Testing is essential because of the serious consequences of the infection, the rash of rubella is not diagnostic, asymptomatic infection can occur, and the diagnosis requires confirmation by laboratory tests.[3,7,8] In addition, infection has been reported in women who have previous evidence of antibody.[7]

Serologic specimens should include information regarding the date of the last menstrual period and the date of presumed exposure (or date of onset of symptoms).[60] If the woman has an antibody titre below the protective level, or a low level of antibodies and remains asymptomatic, a second specimen should be collected 28 days after the exposure (or onset of symptoms) and tested in parallel with the first. Alternatively, if the woman develops symptoms/signs of rubella infection, a second serum specimen should be tested as soon as possible. A third blood specimen may be required in some circumstances.[8] Testing for infection

can also be done, particularly early in the course of a clinical illness, using virus-detection methods, such as nucleic acid amplification testing (PCR).[60]

Pregnant women should be counselled to restrict contact with persons with confirmed, probable or suspected rubella for 6 weeks (2 incubation periods).[60] Counselling of pregnant women with confirmed rubella regarding the risk to the fetus should be given in conjunction with the woman's obstetric service.

Use of normal human immunoglobulin in pregnant women exposed to rubella

Post-exposure prophylaxis with normal human immunoglobulin (NHIG) does not prevent infection in non-immune contacts and is, therefore, of little value for protection of susceptible contacts exposed to rubella.[7] However, it may prolong the incubation period. If given to non-immune pregnant contacts, this may marginally reduce the risk to the fetus. It may also reduce the likelihood of clinical symptoms in the mother. In such cases, IM administration of 20 mL of NHIG within 72 hours of rubella exposure might reduce, but will not eliminate, the risk for rubella.[60] Serological follow-up of recipients is essential, and should continue for up to 2 months.

There is some evidence to suggest that, in outbreak situations, pre-exposure NHIG may be effective in preventing infection in women who are likely to be pregnant, and its use may be indicated for such women with low antibody titres in high-risk occupations.[61]

4.18.13 Variations from product information

The product information for MMR and MMRV vaccines recommends that women of child-bearing age should be advised not to become pregnant for 3 months after vaccination. The ATAGI instead recommends avoiding pregnancy for 28 days after vaccination.[41]

For further information on MMR and MMRV vaccines, see 4.9 *Measles* and 4.22 *Varicella*.

References

A full reference list is available on the electronic *Handbook* or website www.immunise.health.gov.au

4.19 TETANUS

4.19.1 Bacteriology

Tetanus is caused by *Clostridium tetani*, a motile, non-capsulated, Gram-positive rod that forms endospores. Spores of the bacillus are found in manured soil and can enter wounds. Once in a wound site, the bacillus can grow anaerobically. *C. tetani* produces a potent protein toxin, which has two components, tetanospasmin (a neurotoxin) and tetanolysin (a haemolysin).

4.19.2 Clinical features

Tetanus is an acute, often fatal, disease caused by the toxin produced by *C. tetani*. The neurotoxin acts on the central nervous system to cause muscle rigidity with painful spasms. The disease usually occurs after an incubation period of 3 to 21 days (range 1 day to several months), with a median time of onset after injury of 10 days. Generally, a shorter incubation period is associated with a more heavily contaminated wound, more severe disease and a worse prognosis. Generalised tetanus, the most common form of the disease, is characterised by increased muscle tone and generalised spasms. Early symptoms and signs include increased tone in the masseter muscles (trismus, or lockjaw), dysphagia, and stiffness or pain in the neck, shoulder and back muscles. Some patients develop paroxysmal, violent, painful, generalised muscle spasms. A constant threat during generalised spasms is reduced ventilation, apnoea or laryngospasm. The patient may be febrile, although many have no fever; mental state is unimpaired. Sudden cardiac arrest sometimes occurs, but its basis is unknown. Other complications include pneumonia, fractures, muscle rupture, deep vein thrombophlebitis, pulmonary emboli, decubitus ulcers and rhabdomyolysis. Death results from respiratory failure, hypertension, hypotension or cardiac arrhythmia.

Tetanus is uncommon in people who have received 4 or more doses of a tetanus-containing vaccine and in those who received their last dose within 10 years.[1,2] However, cases have been reported[3,4] and clinicians should consider tetanus when there are appropriate symptoms and signs, irrespective of the person's vaccination status. A high level of diagnostic awareness of tetanus is particularly important in the elderly in industrialised countries, including Australia, as most deaths occur in people over 70 years of age, especially women, and may be associated with apparently minor injury.[1,2,5]

Neonatal tetanus is usually associated with generalised symptoms, and fatal if left untreated. It usually occurs following contamination of the umbilical cord stump. Neonatal tetanus was effectively eliminated in Australia and other developed countries over a century ago. Introduction of maternal immunisation during pregnancy with tetanus toxoid has seen neonatal tetanus almost eliminated in developing countries.[6]

4.19.3 Epidemiology

In Australia, tetanus is rare, occurring primarily in older adults who have never been vaccinated or who were vaccinated in the remote past. There were 24 notified cases of tetanus during 2001–2007, but 156 hospitalisations (July 2000–June 2007) where tetanus was coded as the principal diagnosis.[5,7,8] This discrepancy suggests under-notification. During 2001–2006, there were 3 deaths recorded from tetanus.[5,7,8] The case-fatality rate in Australia is about 2%. Effective protection against tetanus can be provided only by active immunisation. This is because the amount of tetanus toxin required to produce clinical symptoms is too small to induce a protective antibody response; second cases of tetanus in unimmunised persons have been recorded. Tetanus vaccine was introduced progressively into the childhood vaccination schedule after World War II. The effectiveness of the vaccine was demonstrated in that war; all Australian servicemen were vaccinated against tetanus and none contracted the disease. As tetanus can follow apparently trivial, even unnoticed wounds, active immunisation is the only certain protection.[1] A completed course of vaccination provides protection for many years.

4.19.4 Vaccines

Tetanus toxoid is available in Australia only in combination with diphtheria and other antigens.

The acronym DTPa, using capital letters, signifies child formulations of diphtheria, tetanus and acellular pertussis-containing vaccines. The acronym dTpa is used for formulations that contain substantially lesser amounts of diphtheria toxoid and pertussis antigens than child (DTPa-containing) formulations; dTpa vaccines are usually used in adolescents and adults.

Tetanus vaccination stimulates the production of antitoxin. Hence, vaccination does not prevent growth of *C. tetani* in contaminated wounds, but protects against the toxin produced by the organism. The immunogen is prepared by treating a cell-free preparation of toxin with formaldehyde, thereby converting it into the innocuous tetanus toxoid. Tetanus toxoid is usually adsorbed onto an adjuvant, either aluminium phosphate or aluminium hydroxide, to increase its immunogenicity. Antigens from *Bordetella pertussis*, in combination vaccines, also act as an effective adjuvant.

Complete immunisation (a 3-dose primary schedule and 2 booster doses) induces protective levels of antitoxin throughout childhood and into adulthood but, by middle age, about 50% of vaccinated persons have low or undetectable levels.[9-11] A single dose of tetanus toxoid produces a rapid anamnestic response in such persons.[12-15]

Formulations for children aged <10 years

- ***Infanrix hexa*** – GlaxoSmithKline (DTPa-hepB-IPV-Hib; diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus-*Haemophilus influenzae* type b). The vaccine consists of *both* a 0.5 mL pre-filled syringe containing ≥30 IU diphtheria toxoid, ≥40 IU tetanus toxoid, 25 µg pertussis toxoid (PT), 25 µg filamentous haemagglutinin (FHA), 8 µg pertactin (PRN), 10 µg recombinant HBsAg, 40 D-antigen units inactivated poliovirus type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett), adsorbed onto aluminium hydroxide/phosphate; traces of formaldehyde, polysorbate 80, polysorbate 20, polymyxin and neomycin; *and* a vial containing a lyophilised pellet of 10 µg purified Hib capsular polysaccharide (PRP) conjugated to 20–40 µg tetanus toxoid. May contain yeast proteins.
- ***Infanrix IPV*** – GlaxoSmithKline (DTPa-IPV; diphtheria-tetanus-acellular pertussis-inactivated poliovirus). Each 0.5 mL pre-filled syringe contains ≥30 IU diphtheria toxoid, ≥40 IU tetanus toxoid, 25 µg PT, 25 µg FHA, 8 µg PRN, 40 D-antigen units inactivated poliovirus type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett), adsorbed onto aluminium hydroxide; traces of formaldehyde, polysorbate 80, polymyxin and neomycin.
- ***Pediacel*** – Sanofi Pasteur Pty Ltd (DTPa-IPV-Hib; diphtheria-tetanus-acellular pertussis-inactivated poliovirus-*Haemophilus influenzae* type b). Each 0.5 mL monodose vial contains ≥30 IU diphtheria toxoid, ≥40 IU tetanus toxoid, 20 µg PT, 20 µg FHA, 3 µg PRN, 5 µg pertussis fimbriae (FIM) 2+3, 40 D-antigen units inactivated poliovirus type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett), 10 µg Hib capsular polysaccharide conjugated to 20 µg tetanus protein; 1.5 mg aluminium phosphate; ≤50 ng bovine serum albumin; phenoxyethanol as preservative; traces of formaldehyde, glutaraldehyde, polysorbate 80, polymyxin, neomycin and streptomycin.
- ***Quadracel*** – Sanofi Pasteur Pty Ltd (DTPa-IPV; diphtheria-tetanus-acellular pertussis-inactivated poliovirus). Each 0.5 mL monodose vial contains ≥30 IU diphtheria toxoid, ≥40 IU tetanus toxoid, 20 µg PT, 20 µg FHA, 3 µg PRN, 5 µg FIM 2+3, 40 D-antigen units inactivated poliovirus type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett); 1.5 mg aluminium phosphate; ≤50 ng bovine serum albumin; phenoxyethanol as preservative; traces of formaldehyde, glutaraldehyde, polysorbate 80, polymyxin and neomycin.

- ***Tripacel*** – Sanofi Pasteur Pty Ltd (DTPa; diphtheria-tetanus-acellular pertussis). Each 0.5 mL monodose vial contains ≥30 IU diphtheria toxoid, ≥40 IU tetanus toxoid, 10 µg PT, 5 µg FHA, 3 µg PRN, 5 µg FIM 2+3; 1.5 mg aluminium phosphate; 3.4 mg phenoxyethanol.

Reduced antigen formulations for adults, adolescents and children aged ≥10 years

- ***ADT Booster*** – CSL Limited/Statens Serum Institut (dT; diphtheria-tetanus). Each 0.5 mL monodose vial or pre-filled syringe contains ≥2 IU diphtheria toxoid and ≥20 IU tetanus toxoid, adsorbed onto 0.5 mg aluminium as aluminium hydroxide.
- ***Adacel*** – Sanofi Pasteur Pty Ltd (dTpa; diphtheria-tetanus-acellular pertussis). Each 0.5 mL monodose vial contains ≥2 IU diphtheria toxoid, ≥20 IU tetanus toxoid, 2.5 µg PT, 5 µg FHA, 3 µg PRN, 5 µg FIM 2+3; 0.33 mg aluminium as aluminium phosphate; phenoxyethanol as preservative; traces of formaldehyde and glutaraldehyde.
- ***Adacel Polio*** – Sanofi Pasteur Pty Ltd (dTpa-IPV; diphtheria-tetanus-acellular pertussis-inactivated poliovirus). Each 0.5 mL monodose vial or pre-filled syringe contains ≥2 IU diphtheria toxoid, ≥20 IU tetanus toxoid, 2.5 µg PT, 5 µg FHA, 3 µg PRN, 5 µg FIM 2+3, 40 D-antigen units inactivated poliovirus type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett); 0.33 mg aluminium as aluminium phosphate; phenoxyethanol as preservative; traces of formaldehyde, glutaraldehyde, polysorbate 80, polymyxin, neomycin and streptomycin.
- ***Boostrix*** – GlaxoSmithKline (dTpa; diphtheria-tetanus-acellular pertussis). Each 0.5 mL monodose vial or pre-filled syringe contains ≥2 IU diphtheria toxoid, ≥20 IU tetanus toxoid, 8 µg PT, 8 µg FHA, 2.5 µg PRN, adsorbed onto 0.5 mg aluminium as aluminium hydroxide/phosphate; traces of formaldehyde, polysorbate 80 and glycine.
- ***Boostrix-IPV*** – GlaxoSmithKline (dTpa-IPV; diphtheria-tetanus-acellular pertussis-inactivated poliovirus). Each 0.5 mL pre-filled syringe contains ≥2 IU diphtheria toxoid, ≥20 IU tetanus toxoid, 8 µg PT, 8 µg FHA, 2.5 µg PRN, 40 D-antigen units inactivated poliovirus type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett), adsorbed onto 0.5 mg aluminium as aluminium hydroxide/phosphate; traces of formaldehyde, polysorbate 80, polymyxin and neomycin.

4.19.5 Transport, storage and handling

Transport according to *National vaccine storage guidelines: Strive for 5*.[16] Store at +2°C to +8°C. Do not freeze. Protect from light.

Infanrix hexa *must be reconstituted* by adding the entire contents of the syringe to the vial and shaking until the pellet is completely dissolved. Reconstituted vaccine should be used as soon as practicable. If storage is necessary, hold at room temperature for not more than 8 hours.

4.19.6 Dosage and administration

The dose of all tetanus-containing vaccines is 0.5 mL, to be given by IM injection.

Do not mix DTPa- or dTpa-containing vaccines or dT vaccine with any other vaccine in the same syringe, unless specifically registered for use in this way.

4.19.7 Recommendations

Infants and children

Tetanus toxoid is given in combination with diphtheria toxoid and acellular pertussis as DTPa vaccine. The recommended 3-dose primary schedule is at 2, 4 and 6 months of age. The 1st dose can be given as early as 6 weeks of age, due to the high morbidity and occasional mortality associated with pertussis in very young infants. If the 1st dose is given at 6 weeks of age, the next scheduled doses should still be given at 4 months and 6 months of age (see 4.12 *Pertussis*).

A booster dose of tetanus-containing vaccine, usually provided as DTPa-IPV, is recommended at 4 years of age, but can be given as early as 3.5 years. For this booster dose, all brands of DTPa-containing vaccines are considered interchangeable.

Where required, DTPa-containing vaccines can be given for catch-up for either the primary doses or booster dose in children aged <10 years (see 2.1.5 *Catch-up*).

Older children and adolescents

A 2nd booster dose is recommended for adolescents between 10 and 17 years of age, using the reduced antigen content dTpa. The optimal age for administering this dose is 11–13 years, due to waning immunity (particularly the pertussis antibody responses) following the 1st booster dose recommended at 4 years of age. (See also 4.12 *Pertussis*.) This 2nd booster dose of tetanus-containing vaccine is also essential for maintaining immunity to tetanus (and diphtheria and pertussis) into adulthood.

It is recommended to use the reduced antigen content dTpa for booster doses. However, when necessary, dT can also be used for the booster dose or, if necessary, for the primary dT course, in persons aged ≥10 years (see 4.19.14 *Variations from product information* below).

For details on the management of children and adolescents who require catch-up vaccination for tetanus, see 2.1.5 *Catch-up*.

Adults

Booster vaccination

All adults who reach the age of 50 years without having received a booster dose of dT in the previous 10 years should receive a further tetanus booster dose. This should be given as dTpa, to also provide protection against pertussis (see 4.12 *Pertussis*). This stimulates further production of circulating tetanus antibodies at an age when waning of diphtheria and tetanus immunity is commencing in the Australian population.[9] Travellers to countries where health services are difficult to access should be adequately protected against tetanus before departure. They should receive a booster dose of dT (or dTpa if not given previously) if more than 10 years have elapsed since the last dose of dT-containing vaccine.

For persons undertaking high-risk travel, consider giving a booster dose of either dTpa or dT (as appropriate) if more than 5 years have elapsed since the last dose of a dT-containing vaccine.

Primary vaccination

Persons who have not received any tetanus vaccines are also likely to have missed diphtheria vaccination. Therefore, 3 doses of dT should be given at minimum intervals of 4 weeks, followed by booster doses at 10 and 20 years after the primary course. One of these 3 doses (preferably the 1st) should be given as dTpa, to also provide additional protection against pertussis. In the event that dT vaccine is *not* available, dTpa can be used for all primary doses. However, this is not recommended routinely because there are no data on the safety, immunogenicity or efficacy of dTpa in multiple doses for primary vaccination.

For additional information on adults with no history of a primary course of dT vaccine requiring catch-up, see 2.1.5 *Catch-up*.

4.19.8 Pregnancy and breastfeeding

Although dT or dTpa vaccines are not routinely recommended for pregnant women, they can be given under certain circumstances, such as for management of a tetanus-prone wound (see 4.19.9 *Tetanus-prone wounds* below) or to prevent pertussis in pregnant women and their newborns (see 4.12 *Pertussis*).[17]

dT or dTpa vaccines can be given to breastfeeding women.

Refer to 3.3 *Groups with special vaccination requirements*, Table 3.3.1 *Recommendations for vaccination in pregnancy* for more information.

4.19.9 Tetanus-prone wounds

The definition of a tetanus-prone injury is not straightforward, as tetanus may occur after apparently trivial injury, such as from a rose thorn, or with no history of injury. It is for this reason that all wounds other than clean, minor cuts are considered 'tetanus-prone'. However, there are certain types of wounds that are more likely to favour the growth of tetanus organisms. These include compound fractures, bite wounds, deep penetrating wounds, wounds containing

foreign bodies (especially wood splinters), wounds complicated by pyogenic infections, wounds with extensive tissue damage (e.g. contusions or burns) and any superficial wound obviously contaminated with soil, dust or horse manure (especially if topical disinfection is delayed more than 4 hours). Reimplantation of an avulsed tooth is also a tetanus-prone event, as minimal washing and cleaning of the tooth is conducted to increase the likelihood of successful reimplantation. Persons who inject drugs are also at risk of tetanus, particularly if skin 'popping' is practised.[18] Appropriate tetanus prophylaxis measures in wound management, including use of tetanus immunoglobulin (TIG), are outlined in Table 4.19.1.

Adults who have sustained injuries deemed to be tetanus-prone (all wounds other than clean minor cuts) should receive a booster dose of dT if more than 5 years have elapsed since the last dose of tetanus-containing vaccine (see Table 4.19.1). As an alternative to dT vaccine after a tetanus-prone wound, adults can receive dTpa vaccine (see 4.12 *Pertussis*) to also provide additional protection against pertussis.[19] In children <10 years of age, this dose of vaccine should be given as DTPa or a DTPa-combination vaccine, consistent with the child's vaccination history and the recommended schedule. For details on the management of children who have missed doses in the recommended schedule, see 2.1.5 *Catch-up*. If there is any doubt about the adequacy of previous tetanus immunisation in a person who has a tetanus-prone wound, TIG must be given as soon as possible, as well as tetanus toxoid-containing vaccine, to provide both *immediate passive* and active protection (see Table 4.19.1). The recommended dose for TIG is 250 IU, given by IM injection, as soon as practicable after the injury. If more than 24 hours have elapsed, 500 IU should be given. Persons with a significant humoral immune deficiency may not have developed or maintained adequate immunity to tetanus, despite vaccination, and require TIG for tetanus-prone wounds.

Clean minor cuts are not categorised as tetanus-prone wounds and, for these wounds, TIG is unnecessary, independent of previous tetanus vaccination history.

Information regarding accessing tetanus immunoglobulin (for intramuscular use for management of tetanus-prone wounds, or intravenous tetanus immunoglobulin for the treatment of clinical tetanus) should be obtained from the Australian Red Cross Blood Service (see Part 5 *Passive immunisation*). For further information on TIG see 4.19.13 *Public health management of tetanus* below.

General measures for treatment of tetanus-prone wounds[20-25]

Whatever the immune status of a person with a tetanus-prone wound, local disinfection and, where appropriate, surgical treatment of tetanus-prone wounds, must never be omitted. Antibiotic prophylaxis is not indicated for the prevention of tetanus; however, the use of antibiotics (such as penicillin, amoxycillin + clavulanate, or metronidazole) for preventing other bacterial infection of the wound is a matter for clinical judgment.

Table 4.19.1: Guide to tetanus prophylaxis in wound management

History of tetanus vaccination	Time since last dose	Type of wound	DTPa, DTPa-combinations, dT, dTpa, as appropriate	Tetanus immunoglobulin* (TIG)
≥3 doses	<5 years	Clean minor wounds	NO	NO
		All other wounds†	NO	NO‡
≥3 doses	5–10 years	Clean minor wounds	NO	NO
		All other wounds†	YES	NO‡
≥3 doses	>10 years	Clean minor wounds	YES	NO
		All other wounds†	YES	NO‡
<3 doses or uncertain§		Clean minor wounds	YES	NO
		All other wounds†	YES	YES

* The recommended dose for TIG is 250 IU, given by IM injection, as soon as practicable after the injury. If more than 24 hours have elapsed, 500 IU should be given. Because of its viscosity, TIG should be given to adults using a 21 gauge needle. For children, it can be given slowly using a 23 gauge needle.

† All wounds, other than clean minor wounds, should be considered 'tetanus-prone'. For more detail, see 4.19.9 *Tetanus-prone wounds* above.

‡ Individuals with a humoral immune deficiency (including HIV-infected persons who have immunodeficiency) should be given TIG if they have received a tetanus-prone injury, regardless of the time since their last dose of tetanus-containing vaccine.

§ Persons who have no documented history of a primary vaccination course (3 doses) with a tetanus toxoid-containing vaccine should receive all missing doses and must receive TIG. See 2.1.5 *Catch-up*.

4.19.10 Contraindications

The only absolute contraindications to tetanus-containing vaccines are:

- anaphylaxis following a previous dose of any tetanus-containing vaccine
- anaphylaxis following any vaccine component.

If a person has a tetanus-prone wound and has previously had a severe adverse event following tetanus vaccination, alternative measures, including the use of tetanus immunoglobulin, can be considered.

4.19.11 Precautions

Administration of more than 1 dose of a tetanus-containing vaccine in a 5-year period in previously immunised adults had previously been thought to be associated with an increased risk of injection site reactions. However, recent

studies indicate that the adverse reactions to a single dose of dTpa are similar in adults and adolescents, whether administered shortly (18 months) or at a longer interval after a previous dose of a vaccine containing tetanus/diphtheria toxoids.[26-29] (See also 4.12 *Pertussis*.)

4.19.12 Adverse events

Mild discomfort or pain at the injection site persisting for up to a few days is common. Uncommon general adverse events following dT vaccine include headache, lethargy, malaise, myalgia and fever. Anaphylaxis, urticaria and peripheral neuropathy occur very rarely. Brachial neuritis (inflammation of a nerve in the arm, causing weakness or numbness) has been described following the administration of tetanus toxoid-containing vaccines, with an estimated excess risk of approximately 0.5–1 in 100 000 doses in adults.[30,31] For specific adverse events following combination vaccines containing both tetanus and pertussis antigens, see 4.12 *Pertussis*.

4.19.13 Public health management of tetanus

Tetanus is a notifiable disease in all states and territories in Australia.

Further instructions about the public health management of tetanus, including management of cases of tetanus, should be obtained from state/territory public health authorities (see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*).

- ***Tetanus Immunoglobulin-VF (human; for intramuscular use)*** – CSL Limited. 160 mg/mL immunoglobulin (mainly IgG) prepared from human plasma containing high levels of antibody to the toxin of *Clostridium tetani*. Single vials contain 250 IU of human tetanus antitoxin, with the actual volume stated on the label on the vial. Also contains glycine.

For information on the definition and management of tetanus-prone wounds, see 4.19. 9 *Tetanus-prone wounds* and Table 4.19.1 above. To access tetanus immunoglobulin (for intramuscular use for management of tetanus-prone wounds, or intravenous tetanus immunoglobulin for the treatment of clinical tetanus), contact the Australian Red Cross Blood Service (see Part 5 *Passive immunisation*).

4.19.14 Variations from product information

The product information for Infanrix hexa states that this vaccine is indicated for primary immunisation of infants from the age of 6 weeks. The ATAGI recommends that this vaccine may also be used for catch-up of the primary schedule in children <10 years of age.

The product information for Infanrix IPV states that this vaccine is indicated for use in a 3-dose primary schedule for immunisation of infants from the age of 6 weeks and as a single booster dose for children ≤6 years of age who have previously been vaccinated against diphtheria, tetanus, pertussis and poliomyelitis. In addition, the ATAGI recommends that this product may also be used for catch-up of the primary schedule or as a booster in children <10 years of age.

The product information for Quadracel states that this vaccine is indicated for use in a 3-dose primary schedule from the age of 2 months to 12 months and may also be used as a booster dose for children from 15 months to 6 years of age who have previously been vaccinated against diphtheria, tetanus, pertussis and poliomyelitis. The ATAGI recommends that, when appropriate, this product may also be used for either catch-up of the primary schedule or as a booster dose in children aged <10 years. The ATAGI also recommends that the primary schedule may be commenced at 6 weeks of age, if required.

The product information for Tripacel states that this vaccine is indicated for use in a 3-dose primary schedule from the age of 2 months to 12 months and may also be used as a booster dose for children from 15 months to 8 years of age who have previously been vaccinated against diphtheria, tetanus and pertussis. The ATAGI recommends that, when appropriate, this product may also be used for either catch-up of the primary schedule or as a booster dose in children aged <10 years. The ATAGI also recommends that the primary schedule may be commenced at 6 weeks of age, if required.

The product information for Pediacel states that this vaccine is indicated for primary immunisation of infants from the age of 6 weeks and may also be used as a booster dose for children from 15 to 20 months of age who have previously been vaccinated against diphtheria, tetanus, pertussis, poliomyelitis and *Haemophilus influenzae* type b. The ATAGI recommends that, when appropriate, this product may also be used for either catch-up of the primary schedule or as a booster dose in children aged <10 years.

The product information for ADT Booster states that this vaccine is indicated for use as a booster dose only in children aged ≥5 years and adults who have previously received at least 3 doses of diphtheria and tetanus vaccines. The ATAGI recommends instead that, where a dT vaccine is required, ADT Booster can be used, including for primary immunisation against diphtheria and tetanus (for any person ≥10 years of age).

The product information for Adacel and Boostrix (reduced antigen content dTpa) states that these vaccines are indicated for booster doses only. The ATAGI recommends instead that, when a 3-dose primary course of diphtheria/tetanus toxoids is given to an adolescent/adult, dTpa should replace the 1st dose of dT, with 2 subsequent doses of dT. If dT is *not* available, dTpa can be used for all 3 primary doses, but this is *not* routinely recommended.

The product information for Adacel and Boostrix states that there is no recommendation regarding the timing and frequency of booster doses against pertussis in adults; however, the ATAGI recommends that pregnant or post-partum women can receive a booster dose every 5 years and that other adults in contact with infants and/or at increased risk from pertussis can receive a booster dose every 10 years.

The product information for Boostrix, Boostrix-IPV and Adacel states that dTpa-containing vaccine should not be given within 5 years of a tetanus toxoid-containing vaccine. The product information for Adacel Polio states that dTpa-containing vaccine should not be given within 3 years of a tetanus toxoid-containing vaccine. The ATAGI recommends instead that, if protection against pertussis is required, dTpa-containing vaccines can be administered at any time following receipt of a dT-containing vaccine.

The product information for Boostrix, Boostrix-IPV, Infanrix hexa and Infanrix IPV states that these vaccines are contraindicated in children with encephalopathy of unknown aetiology or with neurologic complications occurring within 7 days following a vaccine dose. The ATAGI recommends instead that the only contraindication is a history of anaphylaxis to a previous dose or to any of the vaccine components.

The product information for Adacel Polio states that this vaccine is not indicated following a tetanus-prone wound. The ATAGI recommends instead that Adacel Polio can be administered following a tetanus-prone wound.

References

A full reference list is available on the electronic *Handbook* or website www.immunise.health.gov.au

4.20 TUBERCULOSIS

4.20.1 Bacteriology

Tuberculosis (TB) is caused by organisms of the *Mycobacterium tuberculosis* complex (M.TB complex), which are slow-growing, aerobic, acid-fast bacilli. The M.TB complex consists of *Mycobacterium tuberculosis*, *M. bovis*, *M. microti*, *M. canetti* and *M. africanum*,[1] of which *M. tuberculosis* is the cause of almost all TB in Australia.[2]

4.20.2 Clinical features

As infection is usually air-borne, lung disease is the most common form of tuberculosis, accounting for approximately 60% of notified TB cases in Australia.[3] Cough, fever, sweats, weight loss and haemoptysis are common symptoms of pulmonary TB. TB lymphadenitis is the most common extrapulmonary manifestation, but the disease can occur in any part of the body. Disseminated disease (miliary TB) and meningeal TB are more common in very young children, and are among the most serious manifestations of TB disease.[1]

Most persons infected with *M. tuberculosis* remain asymptomatic, but there is a 10% lifetime risk of developing clinical illness (although the risk can vary depending on age and immune status), sometimes many years after the original infection. Infants, the elderly and persons who are immunocompromised, due to drugs or disease or as a result of adverse socioenvironmental circumstances (e.g. malnutrition, alcoholism), are more prone to rapidly progressive or generalised infection.[1,4]

4.20.3 Epidemiology

The World Health Organization (WHO) declared tuberculosis a global emergency in 1993, and recent reports have reaffirmed the threat to human health.[5] It is estimated that in 2010 there were 8.8 million incident cases of TB globally. The majority of these cases (81%) were accounted for by 22 high-burden countries, which all have estimated TB incidences of greater than 40 per 100 000.[6] Approximately 1200 cases of TB are notified to Australian health authorities each year. The annual notification rate for TB has been relatively stable at approximately 5 to 6 cases per 100 000 population since 1985.[2,3] In the southern states, rates among Indigenous Australians overall are comparable with rates among Australian-born non-Indigenous Australians; however, in some specific settings (e.g. in the Northern Territory, Far North Queensland and northern South Australia) rates are higher in Indigenous Australians[3] (see 3.1 *Vaccination for Aboriginal and Torres Strait Islander people*). Most TB cases in Australia (over 85%) occur in persons born overseas, particularly those born in Asia, southern and eastern European countries, Pacific island nations, and north and sub-Saharan Africa. The rate of TB in the overseas-born population has been slowly increasing over the past decade.[3] The rate of multi-drug resistant (MDR) TB in Australia has been low (less than 2% of notified cases); however, the proportion

of MDR-TB cases identified has increased in recent years.[2,3,7-9] Tuberculosis in animals (*M. bovis*) has been eradicated by screening and culling programs.[10]

Patients who are immunocompromised are at high risk of developing active TB if they are infected with *M. tuberculosis*.[4,5,11] Screening programs in Australia concentrate on contacts of notified cases and others at increased risk of TB infection, including refugees and healthcare workers.

4.20.4 Vaccine

- ***BCG vaccine*** – Sanofi Pasteur Pty Ltd (live vaccine prepared from an attenuated strain of *Mycobacterium bovis*). 1.5 mg lyophilised powder in a multi-dose vial with separate diluent. Reconstituted vaccine contains 8–32 x 10^6 colony forming units per mL and monosodium glutamate 1.5% w/v. May contain trace amounts of polysorbate 80. Reconstituted volume provides about 10 adult or 20 infant doses.

BCG (bacille Calmette-Guérin) vaccine is a suspension of a live attenuated strain of *M. bovis*. Worldwide, there are many BCG vaccines available, but they are all derived from the strain propagated by the Institute Pasteur, which was first tested in humans in 1921.[12] BCG vaccination probably has little effect on preventing infection per se, or reactivation among those already infected with TB, so the role of BCG vaccination in preventing overall transmission is probably limited.[13] However, there is strong evidence that BCG vaccination in infancy provides greater than 70% protection against severe disseminated forms of TB disease in young children, including miliary TB and TB meningitis.[14-18] TB can be difficult to diagnose in young children and progression to disseminated TB can be rapid; they are therefore the primary target for the use of BCG vaccine. The efficacy of BCG vaccine against pulmonary disease in adults is less consistent and has ranged from no protection to 80% in controlled trials.[19] The greatest protection has been observed among skin test-negative adults in North America and Europe, and the lowest among skin test-positive persons in tropical settings.[13] The reason for the wide variation in measured effectiveness is not clear, but has been attributed to variability in study quality, differences in BCG strains, host factors such as age at vaccination and nutritional status, and differences in the prevalence of infection with environmental mycobacteria. The duration of protection following BCG vaccination has been difficult to measure because the interval between infection and disease may extend to decades. Benefit from infant vaccination has been found in studies with follow-up of up to 12 years, but protection is commonly thought to decline over 10 to 20 years.[13] There is evidence that memory responses persist for up to 10 to 50 years.[20-22]

BCG vaccination has been shown to offer some protection against *Mycobacterium leprae*, the causative agent of leprosy.[23]

BCG vaccine is not used in the treatment of tuberculosis disease. BCG may be used as a therapeutic modality for transitional cell carcinoma of the bladder.

4.20.5 Transport, storage and handling

Transport according to *National vaccine storage guidelines: Strive for 5*.[24] Store at +2°C to +8°C. Do not freeze. Protect from light.

BCG vaccine *must be reconstituted* by adding the entire contents of the diluent container to the vial and shaking until the powder is completely dissolved. Reconstituted vaccine is very unstable and must be stored at +2°C to +8°C and used within one working session of 4 to 6 hours.

4.20.6 Dosage and administration

The dose of BCG vaccine in newborns and infants <12 months of age is 0.05 mL, given by intradermal injection.

The dose of BCG vaccine in children ≥12 months of age and in adults is 0.1 mL, given by intradermal injection.

BCG vaccine is given as a single dose. Due to the lack of evidence, BCG revaccination is not recommended in any person.

BCG vaccine is available from state/territory tuberculosis services.

Before vaccination

Tuberculin skin test (Mantoux)

All individuals, except infants <6 months of age, should undergo a tuberculin skin test (TST; Mantoux) before BCG vaccination. A hypersensitivity reaction to tuberculin purified protein derivative (PPD; Tubersol) used in the TST assists in the identification of those infected with M.TB. A hypersensitivity reaction may also occur in those infected with other mycobacteria and those previously vaccinated with BCG. Only immunocompetent persons who have induration <5 mm following correctly administered and interpreted TST should receive BCG vaccination. Guidelines to assist in the undertaking and interpretation of TST are available by contacting local state/territory tuberculosis services.

It should be noted that live viral vaccines inhibit the response to tuberculin and tuberculin-positive persons may become tuberculin-negative for up to a month after measles infection.[25,26] As such, tuberculin skin testing may be unreliable for at least 4 weeks after the administration of live viral vaccines.

Interferon-gamma (γ) release assays

Newly available blood tests (Interferon-gamma release assays; IGRAs) are available for the detection of tuberculosis infection. TST, however, remains the preferred method of screening for tuberculosis infection, pending further evaluation of IGRAs. Guidelines for the use of IGRAs in Australia have been developed by the National Tuberculosis Advisory Committee.[27]

BCG vaccination procedures

BCG vaccination should only be given by medical or nursing staff who are trained in BCG vaccination procedures.

- Use a short (10 mm) 26–27 gauge needle with a short bevel. The risk of spillage can be minimised by using an insulin syringe to which the needle is already attached.
- Wear protective eye-wear. The person to be vaccinated (and the parent/carer holding a small child being vaccinated) should also wear protective eye-wear. Eye splashes may ulcerate; if an eye splash occurs, wash the eye with saline or water immediately.
- Identify the correct injection site. BCG vaccine should be injected into the skin over the region of insertion of the deltoid muscle into the humerus. This is just above the midpoint of the upper arm. This site is recommended to minimise the risk of keloid formation. By convention, the left upper arm is used wherever possible to assist those who subsequently look for evidence of BCG vaccination.
- Stretch the skin between a finger and thumb and insert the bevel into the dermis, bevel uppermost, to a distance of about 2 mm. The bevel should be visible through the transparent epidermis.
- If the injection is not intradermal, withdraw the needle and try again at a new site. A truly intradermal injection should raise a blanched bleb of about 7 mm in diameter with the features of peau d'orange (the appearance of orange peel). Considerable resistance will be felt as the injection is given. If this resistance is not felt, the needle may be in the subcutaneous tissues.

Response to BCG vaccination

In response to BCG vaccination, a small red papule forms and eventually ulcerates, usually within 2 to 3 weeks of vaccination. The ulcer heals with minimal scarring over several weeks. There may be swelling and tenderness in local lymph nodes. While a local reaction represents a normal response to BCG vaccination, more extensive local reactions are less common (see 4.20. 11 *Adverse events* below). Subjects who are given BCG vaccine despite latent or previous TB infection are likely to experience an accelerated response characterised by induration within 24 to 48 hours, pustule formation in 5 to 7 days, and healing within 10 to 15 days.

Clinical trials have *not* shown a consistent relationship between the size of tuberculin reactions after BCG vaccination and the level of protection provided. TST is not recommended to demonstrate immunity after BCG vaccination.[28,29]

4.20.7 Recommendations

BCG is not recommended for routine use in the general population, given the low incidence of TB in Australia and the variable efficacy reported in adults. However, some groups are at increased of tuberculosis and BCG vaccination may be warranted for these persons, based on a risk assessment. BCG should be specifically considered for the following groups.

Aboriginal and Torres Strait Islander neonates[30]

In some parts of Australia, the incidence of TB is appreciably higher among Aboriginal and Torres Strait Islander people than Australian-born non-Indigenous Australians, and BCG is recommended for neonates living in those regions. State and territory guidelines should be consulted for local recommendations and the geographic areas where BCG vaccination of Aboriginal and Torres Strait Islander neonates is conducted (see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*). (See also 3.1 *Vaccination for Aboriginal and Torres Strait Islander people*.)

Infants born in Australia to migrant parents

TB is rare in infants and young children born in Australia, but infants born to parents who have migrated from countries with a high TB incidence (i.e. >40 cases per 100 000 population per year – see 4.20.3 *Epidemiology* above) may be at higher risk of TB exposure in their early life.[31] BCG vaccination of these infants is not routinely recommended because of the uncertainty of the risks and benefits.

Children who will be travelling to high TB incidence settings

The risk of TB disease in children travelling to countries with a high TB incidence (i.e. >40 cases per 100 000 population per year – see 4.20.3 *Epidemiology* above) depends on the age of the child, the duration of stay, and the TB incidence at the destination. Country-specific incidence data are available from the World Health Organization.[32]

The need for BCG vaccination should be assessed for young children, particularly those aged <5 years, who will be travelling to a country with high TB incidence for an extended period. This is best discussed with local state/territory TB services or with a paediatric infectious diseases specialist. BCG vaccination should ideally occur at least 3 months before departure and therefore consideration should be given to future travel plans at birth.

Neonates born to parents with leprosy or a family history of leprosy

There is strong evidence that BCG provides some protection against *Mycobacterium leprae*.[23]

Occupational groups

There is some evidence that specific occupational groups are at increased risk of TB, including embalmers, and healthcare workers likely to encounter patients with TB (e.g. chest clinic staff) or those involved in conducting autopsies. Due to the limited evidence of benefit of BCG vaccination in adults and interference of vaccination with interpretation of TST, routine BCG vaccination of persons within these occupations is not recommended. In occupational settings, TB prevention and control should be focused around infection control measures, employment-based TST screening and therapy for latent TB infection. However, BCG vaccination should be considered for TST-negative healthcare workers who are at high risk of exposure to drug-resistant TB, due to the difficulty in treating drug-resistant infection.

4.20.8 Pregnancy and breastfeeding

BCG vaccine is contraindicated in pregnant women.

BCG vaccine can be given to breastfeeding women.

Refer to 3.3 *Groups with special vaccination requirements*, Table 3.3.1 *Recommendations for vaccination in pregnancy* for more information.

4.20.9 Contraindications

BCG is a live vaccine and its use is contraindicated in the following groups:

- Persons with known or suspected HIV infection,[33] even if asymptomatic or with normal immune function, because of the risk of disseminated BCG infection.[34,35]
- Persons treated with corticosteroids or other immunosuppressive therapy, including monoclonal antibodies against tumour necrosis factor-alpha (TNF-alpha) (e.g. infliximab, etanercept, adalimulab). Infants born to mothers treated with bDMARDS (e.g. TNF-alpha blocking monoclonal antibodies) in the third trimester of pregnancy frequently have detectable antibodies for several months and they should not be vaccinated[36-38] (see also 3.3 *Groups with special vaccination requirements*).
- Persons with congenital cellular immunodeficiencies, including specific deficiencies of the interferon-gamma pathway.
- Persons with malignancies involving bone marrow or lymphoid systems (see also 3.3 *Groups with special vaccination requirements*).
- Persons with any serious underlying illness, including severe malnutrition.
- Pregnant women (BCG vaccine has not been shown to cause fetal damage, but use of live vaccines in pregnancy is not recommended).
- Persons who have previously had TB or a large (≥5 mm) reaction to a tuberculin skin test.

4.20.10 Precautions

For those who would otherwise be candidates for BCG, vaccination should be deferred in the following groups:

- Neonates who are medically unstable, until the neonate is in good medical condition and ready for discharge from hospital.
- Infants born to mothers who are suspected or known to be HIV-positive, until HIV infection of the infant can be confidently excluded.
- Persons with generalised septic skin disease and skin conditions such as eczema, dermatitis and psoriasis.
- Persons being treated for latent TB infection, as the therapy is likely to inactivate the BCG vaccine.
- Persons who have recently received another parenteral live vaccine (e.g. MMR, MMRV, varicella, zoster and yellow fever vaccines), until 4 weeks have elapsed, unless these vaccines are given concurrently with the BCG vaccine. There are no restrictions on the timing of BCG vaccine in relation to oral live vaccines.
- Persons with significant febrile illness, until 1 month after recovery.

4.20.11 Adverse events

The normal reaction to BCG vaccination has been described above (see 4.20.6 *Dosage and administration*). About 5% of vaccinated persons experience adverse events. Injection site abscesses occur in 2.5% of vaccinated persons and lymphadenitis in 1%, while up to 1% require medical attention.[39] Gross suppurative or generalised complications of BCG vaccination have been treated with anti-tuberculosis drugs; however, there is no consensus on the management of these complications and specialist advice should be sought from local state/territory tuberculosis services. Anaphylactic reactions have also been reported. Keloid formation can occur, but the risk is minimised if the injection is not given higher than the level of insertion of the deltoid muscle into the humerus. The overall risk of fatal disseminated infection is extremely low (approximately 1 case per million vaccinated persons).[13]

4.20.12 Public health management of tuberculosis

Tuberculosis is a notifiable disease in all states and territories in Australia.

Further instructions about the public health management of tuberculosis, including management of cases of tuberculosis and their contacts, should be obtained from state/territory public health authorities (see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*).

4.20.13 Variations from product information

Although the product information for BCG vaccine specifies that vaccine must be used within 8 hours of reconstitution, the National Tuberculosis Advisory Committee (NTAC) guidelines recommend that any unused vaccine is discarded after a working period of 4 to 6 hours.

References

A full reference list is available on the electronic *Handbook* or website www.immunise.health.gov.au

4.21 TYPHOID

4.21.1 Bacteriology

Typhoid fever is a clinical syndrome caused by a systemic infection with *Salmonella enterica* subspecies *enterica* serovar Typhi (*S.* Typhi). Paratyphoid fever, caused by infection with *S. enterica* serovar Paratyphi A or B, is similar to, and often indistinguishable from, typhoid fever.[1] The two infections are collectively known as enteric fever, have largely overlapping geographic distributions, and, although there is no vaccine specifically targeted against paratyphoid fever, there is evidence to suggest some cross-protection from the oral live attenuated typhoid vaccine against Paratyphi B.[2-4]

4.21.2 Clinical features

Typhoid fever has a usual incubation period of 7 to 14 days (range 3 to 60 days).[5] Although clinical presentations of typhoid fever can be quite variable, a typical case presents with a low-grade fever, dull frontal headache, malaise, myalgia, anorexia and a dry cough.[5] The fever tends to increase as the disease progresses; constipation (more typically diarrhoea in young children), abdominal tenderness, relative bradycardia and splenomegaly are common. Complications occur in 10 to 15% of patients and tend to occur in patients who have been ill for more than 2 weeks. The more important complications include gastrointestinal bleeding, intestinal perforation and typhoid encephalopathy.[5]

Relapse occurs in up to 10% of patients, usually 2 to 3 weeks after the initial fever resolves. Chronic asymptomatic biliary carriage of *S.* Typhi occurs in up to 5% of patients with typhoid fever, even after treatment. Chronic carriage is defined by the continued shedding of the organism for longer than 1 year. Carriers serve as an important reservoir in endemic areas and are of public health significance (e.g. if a carrier works in the food industry).[5]

4.21.3 Epidemiology

Humans are the sole reservoir of *S.* Typhi. It is shed in the faeces of those who are acutely ill and those who are chronic asymptomatic carriers of the organism; transmission usually occurs via the ingestion of faecally contaminated food or water.

The vast majority of typhoid fever cases occur in less developed countries, where poor sanitation, poor food hygiene and untreated drinking water all contribute to endemic disease, with moderate to high incidence and considerable mortality.[6] Geographic regions with high incidence (>100 cases per 100 000 population per year) include the Indian subcontinent, most Southeast Asian countries and several South Pacific nations, including Papua New Guinea. Estimates of incidence from African countries are more limited. In many regions, particularly the Indian subcontinent, strains partially or completely resistant to many antibiotics (including ciprofloxacin) are detected with increasing frequency.[7]

In developed countries, typhoid fever is predominantly a travel-related disease, with a considerably greater risk following travel to the Indian subcontinent than to other regions.[8,9] Those who travel to endemic regions to visit friends and relatives (e.g. immigrants who travel to their former homelands) appear to be at considerably greater risk of acquiring typhoid fever than other travellers.[8-10] There are typically fewer than 150 cases of typhoid fever reported in Australia each year, with most following travel to regions with endemic disease.[11]

4.21.4 Vaccines

Monovalent typhoid vaccines

- ***Vivotif Oral*** – CSL Limited/Crucell Switzerland AG (oral live attenuated typhoid vaccine). Each enteric-coated capsule contains ≥2 x 10^9 viable organisms of attenuated *S.* Typhi strain Ty21a; gelatin; ethylene glycol; sucrose. 3 capsules in a blister pack.
- ***Typherix*** – GlaxoSmithKline (purified Vi capsular polysaccharide vaccine). Each 0.5 mL pre-filled syringe contains 25 µg Vi polysaccharide of *S.* Typhi strain Ty2; phenol as preservative; phosphate buffer.
- ***Typhim Vi*** – Sanofi Pasteur Pty Ltd (purified Vi capsular polysaccharide vaccine). Each 0.5 mL pre-filled syringe contains 25 µg Vi polysaccharide of *S.* Typhi strain Ty2; phenol as preservative; phosphate buffer.

Combination vaccine that contains *S.* Typhi

- ***Vivaxim*** – Sanofi Pasteur Pty Ltd (formaldehyde-inactivated hepatitis A virus [GBM strain] and typhoid Vi capsular polysaccharide). Supplied in a dual-chamber syringe which enables the two vaccines to be mixed just before administration. Each 1.0 mL dose of mixed vaccine contains 160 ELISA units of inactivated hepatitis A virus antigens, 25 µg purified typhoid Vi capsular polysaccharide strain Ty2; 0.3 mg aluminium as aluminium hydroxide; 2.5 µL phenoxyethanol; 12.5 µg formaldehyde; traces of neomycin, bovine serum albumin and polysorbate 80.

The attenuated non-pathogenic *S.* Typhi strain Ty21a was derived by chemical attenuation of a wild-type strain. Attenuated features of Ty21a include the absence of the enzyme UDP-galactose-4-epimerase and the Vi capsular polysaccharide antigen (an important virulence determinant of *S.* Typhi). These features partially contribute to the non-pathogenicity and, therefore, the safety of the oral live vaccine.[12]

The oral vaccine Ty21a strain cannot be detected in faeces more than 3 days after administration of the vaccine. It stimulates serum IgG, vigorous secretory intestinal IgA and cell-mediated immune responses.[12] Clinical trials, with different formulations of the vaccine and with a variety of schedules, have been undertaken in several countries with endemic typhoid fever (Egypt, Chile, Indonesia). These have documented varying degrees of protection against the disease.[5,12]

Parenteral Vi polysaccharide vaccines are produced by fermentation of the Ty2 strain, followed by inactivation with formaldehyde, and then extraction of the polysaccharide from the supernatant using a detergent.[12] The vaccines elicit prompt serum IgG anti-Vi responses in 85 to 95% of adults and children >2 years of age. The vaccines have also been used in clinical trials in endemic regions (Nepal, South Africa, China), indicating moderate protection against typhoid fever.[5,12] As with oral typhoid vaccine, herd protection of unvaccinated persons living in areas with moderate coverage of parenteral vaccine has been demonstrated.[13,14]

Neither the oral nor the parenteral vaccines have been studied in prospective clinical trials in travellers to endemic regions. Because many travellers do not have any naturally acquired immunity, the protection conferred through typhoid vaccination may be less than that documented in the clinical trials mentioned above. However, there is circumstantial evidence that the vaccines do provide protection to travellers to endemic regions,[8,9] and that 3-yearly revaccination is necessary to prolong the protection.[15]

4.21.5 Transport, storage and handling

Transport according to *National vaccine storage guidelines: Strive for 5*.[16] Store at +2°C to +8°C. Do not freeze. Protect from light.

Because the person to be vaccinated will be responsible for looking after the course of the oral live attenuated vaccine following purchase, details of how it should be transported (from the pharmacy to home) and stored in the refrigerator (at home) must be carefully explained.

4.21.6 Dosage and administration

Oral live attenuated vaccine

The vaccine is registered for use in persons ≥6 years of age; it is presented in a pack of 3 capsules. Each dose (a whole capsule) is the same for both adults and children.

The vaccination schedule consists of 1 capsule of vaccine on days 1, 3 and 5, taken 1 hour before food. The capsule must be swallowed whole with water and must not be chewed, since the organisms can be killed by gastric acid. Do not give the vaccine concurrently with antibiotics, or other drugs that are active against *Salmonellae*. If possible, antibiotics and other relevant drugs should be delayed for 3 days after the last dose of the vaccine (see 4.21.10 *Precautions* below).

A 4th capsule taken on day 7 has been shown in one large clinical trial to result in a lower incidence of typhoid fever compared with 3 doses.[12,17] However, giving a 4th dose requires partial use of a second pack.

Co-administration with other vaccines

Oral typhoid vaccine can be administered at the same time as any of the live parenteral vaccines (including yellow fever vaccine or BCG).[12]

The oral live attenuated typhoid vaccine should be separated from the administration of inactivated oral cholera vaccine by an interval of at least 8 hours, and separated from the administration of antibiotics by an interval of at least 3 days (see 4.21.10 *Precautions* below).

The oral live attenuated typhoid vaccine may be given concurrently with mefloquine or with atovaquone/proguanil combination (Malarone) (see 4.21.10 *Precautions* below).

Parenteral Vi polysaccharide vaccines

Both monovalent typhoid vaccines (Typherix and Typhim Vi) are registered for use in persons ≥2 years of age. The dose of both vaccines is 0.5 mL (for both adults and children), to be given by IM injection.

The dose of the combination typhoid Vi polysaccharide/hepatitis A vaccine (Vivaxim) is 1 mL to be given by IM injection. Vivaxim is registered for use in persons aged ≥16 years. (See also 4.4 *Hepatitis A*.)

Co-administration with other vaccines

Parenteral Vi polysaccharide typhoid vaccines can be given with, or at any time before or after, other travel vaccines, such as oral cholera or yellow fever vaccines.

4.21.7 Recommendations

It is recommended that travellers be advised about personal hygiene, food safety and drinking boiled or bottled water only. They should be advised that raw (or undercooked) shellfish, salads, cold meats, untreated water and ice (in drinks) are all potentially 'high-risk', as are short (day) trips away from higher quality accommodation venues.

Oral live attenuated vaccine

Children aged <6 years

Oral typhoid vaccine is not recommended for use in children aged <6 years.

Children aged ≥6 years and adults

Oral typhoid vaccine in either a 3- or 4-dose schedule is recommended for children aged ≥6 years and adults who are:

- travelling to endemic regions, where food hygiene may be suboptimal and drinking water may not be adequately treated
- travelling to endemic regions to visit friends and relatives
- military personnel
- laboratory personnel routinely working with *S.* Typhi.

The addition of a 4th oral dose, on day 7, is an option as there is evidence that 4 doses provides greater protection.[12,17]

Revaccination of children aged ≥6 years and adults

The optimal timing of revaccination against typhoid fever is uncertain and, therefore, international recommendations vary considerably.[5,7,9,12]

Where continued exposure to *S.* Typhi exists (such as occurs with either prolonged travel or residence in an endemic region) and the oral live attenuated vaccine was used initially, a repeat 3-dose or 4-dose course can be given 3 years after a 3-dose course, or 5 years after a 4-dose course.

Parenteral Vi polysaccharide vaccines

For further recommendations on the use of the combination typhoid Vi polysaccharide/hepatitis A vaccine see 4.4 *Hepatitis A*.

Children aged <2 years

The parenteral typhoid vaccine is not recommended for use in children aged <2 years.

Children aged ≥2 years and adults

A single dose of parenteral typhoid vaccine is recommended for children aged ≥2 years and adults who are:

- travelling to endemic regions, where food hygiene may be suboptimal and drinking water may not be adequately treated
- travelling to endemic regions to visit friends and relatives
- military personnel
- laboratory personnel routinely working with *S.* Typhi.

Revaccination of children aged ≥2 years and adults

The optimal timing of revaccination against typhoid fever is uncertain and, therefore, international recommendations vary considerably.[5,7,9,12]

Where continued exposure to *S.* Typhi exists (such as occurs with either prolonged travel or residence in an endemic region) and the parenteral vaccine was used initially, revaccinate with the parenteral vaccine every 3 years. See also 4.4 *Hepatitis A* for more information.

4.21.8 Pregnancy and breastfeeding

The oral live attenuated typhoid vaccine is contraindicated in pregnant women (see 4.21.9 *Contraindications* below).

The oral live attenuated typhoid vaccine can be given to breastfeeding women.

Parenteral Vi polysaccharide vaccines are not routinely recommended for pregnant or breastfeeding women, but can be given where vaccination is considered necessary (see 4.21.7 *Recommendations* above).

Refer to 3.3 *Groups with special vaccination requirements*, Table 3.3.1 *Recommendations for vaccination in pregnancy* for more information.

4.21.9 Contraindications

The only absolute contraindications to typhoid vaccines are:

- anaphylaxis following a previous dose of any typhoid vaccine
- anaphylaxis following any vaccine component.

Oral live attenuated vaccine

The oral live attenuated vaccine should *not* be administered to:

- children <6 years of age; parenteral Vi polysaccharide vaccine should be used instead in children 2–5 years of age
- pregnant women; parenteral Vi polysaccharide vaccine should be used instead
- persons who are immunocompromised, including those with known HIV infection; parenteral Vi polysaccharide vaccine should be used instead
- persons taking antibiotics; parenteral Vi polysaccharide vaccine should be used instead.

Parenteral Vi polysaccharide vaccines

The parenteral Vi polysaccharide vaccines should *not* be administered to children <2 years of age.

4.21.10 Precautions

The oral live attenuated vaccine strain may be destroyed by gastric acid, so capsules must be swallowed whole, rather than chewed or opened.

There should be an interval of at least 8 hours between the administration of the oral live attenuated typhoid vaccine and the inactivated oral cholera vaccine, as the buffer in the cholera vaccine may affect the transit of the capsules of oral typhoid vaccine through the gastrointestinal tract.

The oral live attenuated typhoid vaccine may be susceptible to inactivation by some antibiotics and antimalarial agents, although concurrent administration of either mefloquine or atovaquone/proguanil combination (Malarone) has not been shown to interfere with immune responses or efficacy. If the oral vaccine is

used, it is recommended that vaccination should be timed so that the last dose of vaccine is administered at least 3 days before starting antibiotics or antimalarial prophylaxis.

4.21.11 Adverse events

Typhoid vaccines, both oral and parenteral, are associated with very few adverse events and, when adverse events do occur, they tend to be mild and transient.[18]

Oral live attenuated vaccine

Abdominal discomfort, diarrhoea, nausea, vomiting and rashes have occasionally been reported.

Parenteral Vi polysaccharide vaccines

Local adverse events such as erythema, swelling and pain at the injection site occur very commonly in 10 to 20% of vaccine recipients. Systemic adverse events are common and include fever (3% of recipients), malaise and nausea.

4.21.12 Public health management of typhoid fever

Typhoid fever is a notifiable disease in all states and territories in Australia.

Further instructions about the public health management of typhoid fever, including management of cases of typhoid fever and their contacts, should be obtained from state/territory public health authorities (see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*).

4.21.13 Variations from product information

The Australian product information for Vivotif Oral live attenuated vaccine does not mention the use of a 4-dose course of the vaccine for either initial or repeat vaccination, although this vaccine is registered for use in some other countries (e.g. Canada and the United States) in a 4-dose schedule. The ATAGI recommends that a 4-dose course can be given to provide increased protection against typhoid fever.

The product information for Vivotif Oral live attenuated vaccine does not include pregnancy among the listed contraindications. The ATAGI recommends that pregnancy *is* a contraindication to the oral live attenuated typhoid vaccine.

The product information for Typhim Vi recommends a booster dose every 2 to 3 years, and the product information for Vivotif Oral live attenuated vaccine recommends a booster every 3 years. The ATAGI also recommends, for those at continuing risk, revaccination with a dose of parenteral Vi polysaccharide vaccine every 3 years after a previous dose, or revaccination with a 3- or 4-dose course of the oral live attenuated vaccine 3 years after a 3-dose course or 5 years after a 4-dose course.

References

A full reference list is available on the electronic *Handbook* or website www.immunise.health.gov.au

4.22 VARICELLA

4.22.1 Virology

Varicella-zoster virus (VZV) is a DNA virus within the herpes virus family.[1] Primary infection with VZV causes varicella (chickenpox). Following primary infection, VZV establishes latency in the dorsal root ganglia. Reactivation of the latent virus manifests as herpes zoster (shingles)[2] (see 4.24 *Zoster*).

4.22.2 Clinical features

Varicella is a highly contagious infection spread by respiratory secretions, including aerosol transmission, or from the vesicle fluid of the skin lesions of varicella or zoster infection.[1] Varicella is usually a mild disease of childhood. However, complications occur in approximately 1% of cases.[3] It is more severe in adults and in persons of any age who are immunocompromised, in whom complications, disseminated disease and fatal illness can occur.[1]

The average incubation period is 14 to 16 days (range 10 to 21 days), but may be longer in persons who are immunocompromised, especially after receipt of zoster immunoglobulin (ZIG).[2] The period of infectivity is from 48 hours before the onset of rash until crusting of all lesions has occurred.[4] A short prodromal period of 1 to 2 days may precede the onset of the rash, especially in adults.[1,2] In otherwise healthy children, skin lesions usually number between 200 and 500.[1,2] Acute varicella may be complicated by secondary bacterial skin infection, pneumonia, acute cerebellar ataxia (1 in 4000 cases), aseptic meningitis, transverse myelitis, encephalitis (1 in 100 000 cases) and thrombocytopenia. In rare cases, it involves the viscera and joints.[1]

Congenital varicella syndrome has been reported after varicella infection in pregnancy and may result in skin scarring, limb defects, ocular anomalies and neurologic malformations.[1,5] There is a higher risk to the fetus if maternal infection occurs in the second trimester compared with infection in the first trimester (1.4% versus 0.55%).[6] Infants with intrauterine exposure also risk developing herpes zoster in infancy (0.8–1.7%), with the greatest risk following exposure in the third trimester.[5] Severe neonatal varicella infection can result from perinatal maternal varicella.[7] The onset of varicella in pregnant women from 5 days before delivery to 2 days after delivery is estimated to result in severe varicella in 17 to 30% of their newborn infants.[1,7]

Reactivation of latent VZV as a result of waning cellular immunity results in herpes zoster (HZ), a localised vesicular rash. HZ can occur at any age, but is more common in older adults and persons who are immunocompromised. Complications may include post-herpetic neuralgia and disseminated zoster with visceral, central nervous system and pulmonary involvement[1] (see 4.24 *Zoster*).

There is no specific therapy for uncomplicated varicella infection. Antiviral therapy is used in the treatment of complicated or severe varicella, herpes zoster disease, and disease in persons who are immunocompromised.

4.22.3 Epidemiology

In an unimmunised population in temperate climates, the annual number of cases of varicella approximates the birth cohort.[8] Tropical regions have a higher proportion of cases in adults. Approximately 5% of cases are subclinical. A serosurvey conducted in 1997–1999 found that 83% of the Australian population were seropositive by 10–14 years of age.[9] Prior to the introduction of a varicella vaccination program in Australia, there were about 240 000 cases, 1500 hospitalisations and an average of 7 to 8 deaths each year from varicella in Australia.[10-12] The highest rates of hospitalisation occur in children <5 years of age.[13]

In Australia, there was a 69% decline in varicella hospitalisations in children aged 1.5–4 years in the first 2.5 years following the inclusion of varicella vaccine on the NIP in late 2005.[14] Declines have also been observed in hospitalisation rates in other age groups and in general practice consultations.[14-16] In the United States, where universal varicella vaccination has been in place since 1995, there has been an even greater decline in varicella disease (85%) and hospitalisations (70–88%).[17-19] The greatest decline in hospitalisation rates has been in 0–4-year olds. However, reductions in hospitalisation rates have also occurred in infants,[20] older children and adults, due to herd immunity.[17]

There has been no evidence of a change in the rates of herpes zoster incidence, healthcare utilisation or hospitalisations in the United States[21,22] or hospitalisations in Australia[14,15] attributable to the introduction of the varicella vaccine, although herpes zoster rates in children have declined in the United States.[23,24]

4.22.4 Vaccines

Live attenuated varicella vaccine (VV) is currently available as a monovalent vaccine. Two quadrivalent combination vaccines containing live attenuated measles, mumps, rubella and varicella viruses (MMRV) are also registered in Australia.

All available varicella-containing vaccines are derived from the Oka VZV strain, but have some genetic differences.[25]

Monovalent VVs have been available in Australia since 2000, and, since November 2005, a single dose of VV has been funded under the NIP for all children at 18 months of age, with a catch-up dose funded for children 10 to <14 years of age who have not received varicella vaccine and who have not had the disease.[26] At the time of implementation of a universal varicella vaccination program in Australia, a single dose was considered adequate for protection of infants and children <14 years of age. However, recent data from the United States suggest that a 2nd dose of varicella-containing vaccine in children is optimal to provide an immune response more like that acquired after natural infection, reducing the risk of vaccine failure and increasing population immunity.[27] Vaccine failure, also known as breakthrough varicella, is defined

as a case of wild-type varicella occurring more than 42 days after vaccination. The majority of cases of breakthrough varicella are mild with fewer lesions than natural infection. However, breakthrough varicella infections can be contagious, particularly if many lesions are present.[28]

Post-marketing studies in the United States have estimated the effectiveness of 1 dose of VV in children to be 80 to 85% against any disease and 95 to 98% against severe varicella.[28-32] Although earlier data suggested persistence of immunity in most healthy vaccine recipients,[1] some, but not all, long-term follow-up studies have shown that rates of vaccine failure increased over time in 1-dose vaccine recipients. For example, in one study, vaccine failure was increased 2.6 times in children who received 1 dose of vaccine more than 5 years previously, compared with those who had received 1 dose of vaccine within 5 years.[33] Follow-up from a randomised controlled trial in children 12 months to 12 years of age, comparing 1 dose with 2 doses of VV over a 10-year period, showed significantly higher protection with 2 doses (98.3% versus 94.4%).[34] Based on current evidence, 2 doses of a varicella-containing vaccine in children from 12 months of age will minimise the risk of breakthrough varicella (see 4.22.7 *Recommendations* below).

Healthy adolescents (≥14 years of age) and adults require 2 doses of varicella vaccine, at least 4 weeks apart, as the response to a single dose of VV decreases progressively as age increases and is insufficient to provide adequate protection.[35]

Combination MMRV vaccines have been shown in clinical trials, conducted predominantly in children 12 months to 6 years of age, to produce similar rates of seroconversion to all four vaccine components compared with MMR and monovalent varicella vaccines administered concomitantly at separate injection sites.[36-39] In one comparative study assessing seroresponses to a single MMRV vaccine dose in 12–14-month-old children, the seroresponse rates to measles, mumps and rubella were similar, but varicella seroresponses were lower in Priorix-tetra recipients than in ProQuad recipients.[40] However, the clinical significance of this is not clear, particularly for MMRV given after MMR vaccine.

Monovalent varicella vaccines (VV)

- ***Varilrix***– GlaxoSmithKline (live attenuated Oka strain of varicella-zoster virus). Lyophilised powder in a monodose vial with separate diluent. Each 0.5 mL reconstituted dose contains $\geq 10^{3.3}$ plaque-forming units (PFU) of attenuated varicella-zoster virus; human albumin; lactose; neomycin; polyalcohols.
- ***Varivax Refrigerated*** – CSL Limited/Merck & Co Inc (live attenuated Oka/Merck strain of varicella-zoster virus). Lyophilised powder in a monodose vial with a pre-filled diluent syringe. Each 0.5 mL

reconstituted dose contains ≥1350 PFU of attenuated varicella-zoster virus; sucrose; hydrolysed gelatin; urea; monosodium glutamate; residual components of MRC-5 cells; traces of neomycin and bovine serum.

Quadrivalent measles-mumps-rubella-varicella (MMRV) vaccines

- ***Priorix-tetra*** – GlaxoSmithKline (live attenuated measles virus [Schwarz strain], mumps virus [RIT 4385 strain, derived from the Jeryl Lynn strain], rubella virus [Wistar RA 27/3 strain] and varicella-zoster virus [Oka strain]). Lyophilised pellet in a monodose vial with a pre-filled diluent syringe. Each 0.5 mL reconstituted dose contains $\geq 10^{3.0}$ cell culture infectious dose 50% ($CCID_{50}$) of the Schwarz measles virus, $\geq 10^{4.4}$ $CCID_{50}$ of the RIT 4385 mumps virus, $\geq 10^{3.0}$ $CCID_{50}$ of the Wistar RA 27/3 rubella virus, and $\geq 10^{3.3}$ PFU of Oka varicella-zoster virus; lactose; neomycin; sorbitol; mannitol.
- ***ProQuad*** – CSL Limited/Merck & Co Inc (live attenuated measles virus [Enders' attenuated Edmonston strain], mumps virus [Jeryl Lynn B level strain], rubella virus [Wistar RA 27/3 strain] and varicella-zoster virus [Oka/Merck strain]). Lyophilised powder in a monodose vial with a pre-filled diluent syringe. Each 0.5 mL reconstituted dose contains $\geq 10^{3.0}$ tissue culture infectious dose 50% ($TCID_{50}$) of Enders' attenuated Edmonston measles virus, $\geq 10^{4.3}$ $TCID_{50}$ of the Jeryl Lynn B level mumps virus, $\geq 10^{3.0}$ $TCID_{50}$ of the Wistar RA 27/3 rubella virus, and $\geq 10^{3.99}$ PFU of Oka/Merck varicella virus; sucrose; hydrolysed gelatin; urea; sorbitol; monosodium L-glutamate; human albumin; neomycin; residual components of MRC-5 cells; bovine serum albumin.

4.22.5 Transport, storage and handling

Transport according to *National vaccine storage guidelines: Strive for 5*.[41] Store at +2°C to +8°C. Do not freeze. Protect from light.

Varicella-containing vaccines are less stable than other commonly used live viral vaccines, and adherence to storage and reconstitution requirements is very important. All vaccines *must be reconstituted* by adding the entire contents of the diluent to the vial containing the pellet, and shaking until the pellet is completely dissolved. Available monovalent VVs and MMRV vaccines have different requirements following reconstitution.

Reconstituted Varilrix vaccine should be used as soon as practicable. If storage is necessary, hold at ambient temperature for not more than 90 minutes, or at +2°C to +8°C for not more than 8 hours.

Reconstituted Varivax Refrigerated vaccine must be used within 2½ hours.

Reconstituted Priorix-tetra (MMRV) vaccine should be used as soon as practicable. If storage is necessary, hold at +2°C to +8°C for not more than 8 hours.

Reconstituted ProQuad (MMRV) vaccine must be used within 30 minutes.

4.22.6 Dosage and administration

The dose of VV and MMRV vaccines is 0.5 mL, to be given by SC injection. Priorix-tetra may also be given by IM injection.[42]

MMRV vaccines are not recommended for use in persons aged ≥14 years.

The minimum interval between doses of varicella-containing vaccine is 4 weeks.

Co-administration with other vaccines

VV and MMRV vaccines can be given at the same time as other live attenuated parenteral vaccines (e.g. BCG, yellow fever) or other inactivated vaccines (including DTPa, hepatitis B, Hib, IPV, MenCCV, hepatitis A and pneumococcal conjugate vaccine),[40] using separate syringes and injection sites. If VV or MMRV vaccine is not given simultaneously with other live attenuated parenteral vaccines, they should be given at least 4 weeks apart.

If VV is given at the same time as MMR vaccine, they should be given using separate syringes and injection sites. MMR vaccine and monovalent VV should *not* be mixed together prior to injection.

Interchangeability of varicella-containing vaccines

In general, the two brands of varicella vaccine can be considered interchangeable; that is, the 2nd varicella dose does not have to be of the same brand as the 1st. The same principle applies to the two available MMRV vaccines,[40] although they are not routinely recommended in a 2-dose schedule.

4.22.7 Recommendations

Children (aged <14 years)

It is recommended that at least 1 dose of a varicella-containing vaccine be given to all children <14 years of age. One dose of varicella-containing vaccine is recommended to be given routinely at 18 months of age as either VV or as MMRV vaccine; see Table 4.22.1. (See also 4.9 *Measles*.) Prior varicella infection is *not* a contraindication and such children can still receive either VV or MMRV, as appropriate. (See also 'Serological testing for varicella immunity from infection and/or vaccination' below.) There is no known increase in adverse events from vaccinating those with pre-existing immunity to one or more of the vaccine components (see 4.22.11 *Adverse events* below).

Administration of varicella vaccine from as early as 12 months of age will provide earlier protection from varicella and can be considered on a case-by-case basis when appropriate, for example, in the context of travel or a varicella

outbreak. However, note that MMRV vaccine is *not* recommended for use as the 1st dose of MMR-containing vaccine in children aged <4 years, due to a small but increased risk of fever and febrile seizures when given as the 1st MMR-containing vaccine dose in this age group (see 4.9 *Measles* and 4.22.11 *Adverse events* below).

If MMRV is inadvertently administered as dose 1 of MMR-containing vaccine, the dose does not need to be repeated (providing it was given at ≥12 months of age); however, parents/carers should be advised regarding the small but increased risk of fever and febrile seizures (compared with that expected following MMR vaccine).

Receipt of 2 doses of varicella-containing vaccine provides increased protection and minimises the chance of breakthrough varicella in children <14 years of age.[34] However, routine administration of a 2nd dose of varicella-containing vaccine for children is not included on the NIP schedule. If parents/carers wish to minimise the risk of breakthrough varicella, administration of 2 doses of varicella-containing vaccine is recommended (see 4.22.4 *Vaccines* above). MMRV vaccine is also suitable for use as the 2nd dose of varicella-containing vaccine in children <14 years of age. (For further information, see also 4.9 *Measles*.) The minimum interval between doses of varicella-containing vaccine in children (and adults) is 4 weeks.

Table 4.22.1: Recommendations for varicella vaccination with (a) monovalent varicella vaccine (VV) (currently available), and (b) once measles-mumps-rubella-varicella (MMRV) vaccines are available from July 2013

Vaccines	Schedule point (age)		
	12 months	18 months	4 years
(a) Only monovalent varicella vaccine available	MMR	VV	MMR*
(b) When MMRV vaccine available (from July 2013)	MMR	MMRV	–

* The 2nd dose of MMR-containing vaccine is recommended to be provided at 18 months of age to improve 2-dose coverage and protection against measles in young children. However, until June 2013 the 2nd dose of MMR vaccine is included under the NIP schedule for administration at 4 years of age. From July 2013, the 2nd dose of MMR vaccine will move to the 18-month NIP schedule point and be provided as MMRV vaccine.

Adolescents (aged ≥14 years) and adults

Vaccination is recommended for all non-immune adolescents (≥14 years of age) and adults. Every effort should be made to identify and immunise non-pregnant seronegative women of child-bearing age (see 4.22.2 *Clinical features* above). Adolescents (≥14 years of age) and adults *must* receive 2 doses of VV to achieve

adequate protection from varicella.[35,43] The 2 doses should be administered at least 4 weeks apart. However, a longer interval between vaccine doses is acceptable. Lack of immunity to varicella should be based on a negative history of previous varicella infection and can be supplemented by serological testing for evidence of past infection (see 'Serological testing for varicella immunity from infection and/or vaccination' below).

MMRV vaccines are not recommended for use in persons ≥14 years of age, due to a lack of data on safety and immunogenicity/efficacy in this age group. If a dose of MMRV vaccine is inadvertently given to an older person, this dose does not need to be repeated.

Serological testing for varicella immunity from infection and/or vaccination

Children who have an uncertain clinical history or no documentation of age-appropriate varicella vaccination should be considered susceptible and offered vaccination. Although a reliable history of varicella infection correlates highly with serological evidence of immunity in young children,[44,45] due to the decreasing incidence of varicella in Australia and reduced familiarity with the disease, vaccination should be offered, unless confident clinical diagnosis of prior natural infection is made. Testing of children to assess serologic status prior to vaccination is generally not recommended. Provided there are no contraindications, children can safely receive either VV or MMRV vaccine, even if prior infection with VZV has occurred (see 'Children (aged <14 years)' above).

In older adolescents and adults with a negative history of varicella infection and no documented history of age-appropriate vaccination, serological testing before vaccination is more likely to be helpful, as a majority of those with a negative history are immune, and thus may not require vaccination.[46,47] Screening for varicella immunity (from natural infection) or a past history of vaccination should be undertaken as part of pre-pregnancy planning and varicella vaccine given to non-immune women prior to conception.

Testing to check for seroconversion after varicella vaccination is *not* recommended. Commercially available laboratory tests are not usually sufficiently sensitive to detect antibody levels following vaccination, which may be up to 10-fold lower than levels induced by natural infection.[48-50] Protection (commensurate with the number of vaccine doses received, see 4.22.4 *Vaccines* above) should be assumed if a child or adult has documented evidence of receipt of age-appropriate dose(s) of a varicella-containing vaccine. If serological tests to investigate existing immunity to varicella are performed, interpretation of the results may be enhanced by discussion with the laboratory that performed the test, ensuring the relevant clinical information described above is provided.

Post-exposure vaccination

If varicella-containing vaccines are not contraindicated, vaccination can be offered to non-immune age-eligible children and adults who have a significant exposure to varicella or HZ, and wish to be protected against primary infection

with VZV. (See also 4.22.12 *Public health management of varicella* below.) Post-exposure vaccination is generally successful when given within 3 days, and up to 5 days, after exposure, with earlier administration being preferable.[51-55] MMRV vaccine can be given to children in this setting, particularly if MMR vaccination is also indicated (see 4.22.7 *Recommendations* above).

Household contacts of persons who are immunocompromised

Vaccination of household contacts of persons who are immunocompromised is strongly recommended. This is based on evidence that transmission of varicella vaccine virus strain is extremely rare and it is likely to cause only mild disease (see 4.22.11 *Adverse events* below). This compares with the relatively high risk of severe varicella disease from exposure to wild-type varicella-zoster virus in persons who are immunocompromised.[49,56] If vaccinated persons develop a rash, they should cover the rash and avoid contact with persons who are immunocompromised for the duration of the rash. Zoster immunoglobulin (ZIG) need not be given to an immunocompromised contact of a vaccinated person with a rash, because the disease associated with this type of transmission (should it occur) is expected to be mild (see 4.22.12 *Public health management of varicella* below).

Healthcare workers, staff working in early childhood education and care, and in long-term care facilities

Refer to 3.3 *Groups with special vaccination requirements*, Table 3.3.7 *Recommended vaccinations for persons at increased risk of certain occupationally acquired vaccine-preventable diseases* for more information.

Vaccination against varicella is recommended for all non-immune adults, but especially for all healthcare workers (HCW), staff working in early childhood education and care, and staff working in long-term care facilities. Persons in such occupations who have a negative or uncertain history of varicella infection, and who do not have documentation of 2 doses of varicella vaccine, should be vaccinated with 2 doses of varicella vaccine or have serological evidence of immunity to varicella[57] (see 'Adolescents (aged ≥14 years) and adults' above). Testing to check for seroconversion after VV is *not* recommended (see 'Serological testing for varicella immunity from infection and/or vaccination' above). However, since varicella vaccination is not 100% effective, HCWs and other carers should still be advised of the signs and symptoms of infection and how to manage them appropriately according to local protocols if they develop varicella.

4.22.8 Pregnancy and breastfeeding

Varicella-containing vaccines are contraindicated in pregnant women (see 4.22.9 *Contraindications* below). Pregnancy should be avoided for 28 days after vaccination.

Varicella-containing vaccines can be given to breastfeeding women. Most live vaccines have not been demonstrated to be secreted in breast milk. Women who

received varicella vaccine while breastfeeding showed no evidence of VZV DNA in breast milk samples, and no effects on breastfed infants have been reported.[58] Post-partum vaccination of women without evidence of varicella immunity need not be delayed because of breastfeeding.

MMRV vaccines are not recommended for use in persons aged ≥14 years.

Refer to 3.3 *Groups with special vaccination requirements*, Table 3.3.1 *Recommendations for vaccination in pregnancy* for more information.

4.22.9 Contraindications

Anaphylaxis to vaccine components

Varicella-containing vaccines are contraindicated in persons who have had:

- anaphylaxis following a previous dose of any varicella-containing vaccine
- anaphylaxis following any vaccine component.

Persons who are immunocompromised

Measles-, mumps-, rubella- and varicella-containing vaccines contain live attenuated vaccine viruses and are contraindicated in persons who are immunocompromised. Thus, both VV and MMRV vaccines are contraindicated in the following groups:

- Persons immunocompromised due to HIV/AIDS. Vaccination with live attenuated vaccines can result in a more extensive vaccine-associated rash or disseminated infection in persons with AIDS.[59-62] However, varicella vaccination (with a 2-dose schedule of VV) of asymptomatic HIV-infected persons >12 months of age with an age-specific $CD4^+$ count of ≥15% may be considered[63-65] (see 'HIV-infected persons' in 3.3.3 *Vaccination of immunocompromised persons*). Since studies have not been performed using combination MMRV vaccines in asymptomatic HIV-infected persons or persons with an age-specific $CD4^+$ count of ≥15%, it is recommended that only MMR vaccine and monovalent VV be considered for use in this setting.[60,64,65]
- Persons with other medical conditions associated with significant immunocompromise (see 3.3.3 *Vaccination of immunocompromised persons*).
- Persons receiving high-dose systemic immunosuppressive therapy, such as chemotherapy, radiation therapy or oral corticosteroids. Varicella-containing vaccines are contraindicated in persons taking high-dose oral corticosteroids for more than 1 week (in children equivalent to >2 mg/kg per day prednisolone, and in adults >60 mg per day) (see 3.3.3 *Vaccination of immunocompromised persons*). Those who have been receiving high-dose systemic steroids for more than 1 week may be vaccinated with live attenuated vaccines after corticosteroid therapy has been discontinued for at least 1 month[66] (see 3.3.3 *Vaccination of immunocompromised persons*).

See also 3.3 *Groups with special vaccination requirements* and 4.9 *Measles* for more information.

Pregnant women

See also 4.22.8 *Pregnancy and breastfeeding* above.

Varicella-containing vaccines are contraindicated in pregnant women.

This is due to the theoretical risk of transmission of the varicella component of the vaccine to a susceptible fetus. However, no evidence of vaccine-induced congenital varicella syndrome has been reported. Data from a registry, established in the United States to monitor the maternal–fetal outcomes of pregnant women who were inadvertently administered VV either 3 months before, or at any time during, pregnancy, showed that, among the 587 prospectively enrolled women (including 131 live births to women known to be varicella-zoster virus-seronegative), there was no evidence of congenital varicella syndrome.[67] The rate of occurrence of congenital anomalies from prospective reports in the registry was similar to reported rates in the general United States population (3.2%) and the anomalies showed no specific pattern or target organ.

A non-immune pregnant household contact is *not* a contraindication to vaccination with varicella-containing vaccines of a healthy child or adult in the same household. The benefit of reducing the exposure to varicella by vaccinating healthy contacts of non-immune pregnant women outweighs any theoretical risks of transmission of vaccine virus to these women.

4.22.10 Precautions

For additional precautions related to MMRV vaccines, see 4.9 *Measles*.

Vaccination with other live attenuated parenteral vaccines

If a varicella-containing vaccine is not given simultaneously with other live attenuated parenteral vaccines (e.g. MMR, BCG, yellow fever), the vaccines should be given at least 4 weeks apart.

Vaccination after immunoglobulin or blood product administration

Administration of MMR or MMRV vaccine should be delayed after administration of immunoglobulin-containing products. After receipt of immunoglobulin-containing blood products, the expected immune response to measles, mumps, rubella and varicella vaccination may be impaired.[68-70] VV or MMRV vaccine should not be given for between 3 and 11 months following the administration of immunoglobulin-containing products. The interval between receipt of the blood product and vaccination depends on the amount of immunoglobulin in each product, and is indicated in 3.3 *Groups with special vaccination requirements*, Table 3.3.6 *Recommended intervals between either immunoglobulins or blood products and MMR, MMRV or varicella vaccination*.[69] For further information, see 3.3.4 *Vaccination of recent recipients of normal human*

immunoglobulin and other blood products and 4.22.13 *Variations from product information* below.

Recent blood transfusion with washed red blood cells is *not* a contraindication to VV or MMRV vaccines.

Varicella vaccine may be administered concomitantly with, or at any time in relation to, anti-D immunoglobulin, but at a separate injection site. Anti-D immunoglobulin does not interfere with the antibody response to vaccine.

Immunoglobulin or blood product administration after vaccination

Immunoglobulin-containing products should not be administered for 3 weeks following vaccination with varicella-containing vaccines, unless the benefits exceed those of vaccination. If immunoglobulin-containing products are administered within this interval, the vaccinated person should be revaccinated later at the appropriate time following the product (as indicated in Table 3.3.6 *Recommended intervals between either immunoglobulins or blood products and MMR, MMRV or varicella vaccination*).

Rh (D) immunoglobulin (anti-D) may be given at the same time, in different sites with separate syringes, or at any time in relation to varicella vaccine, as it does not interfere with the antibody response to the vaccine.

Persons receiving long-term aspirin or salicylate therapy

Persons receiving long-term salicylate therapy (aspirin) should be vaccinated if indicated, as the benefit is likely to outweigh any possible risk of Reye syndrome occurring after vaccination. Natural varicella infection and salicylate use has been associated with an increased risk of developing Reye syndrome. However, there have been no reports of an association between Reye syndrome and varicella vaccination (see 4.22.13 *Variations from product information* below).

4.22.11 Adverse events

If using MMRV vaccine, additional adverse events relating to the measles, mumps and rubella vaccine components are discussed in 4.9 *Measles*, 4.11 *Mumps* and 4.18 *Rubella*.

Adverse events following administration of varicella-containing vaccines are generally mild and well tolerated.[71]

Injection site reactions (pain, redness or swelling) are the most common adverse events reported after varicella vaccination, occurring in 7 to 30% of vaccine recipients, but are generally well tolerated.[2,71]

A maculopapular or papulovesicular rash may develop after varicella vaccination (usually within 5 to 26 days). A VV-associated rash is likely to occur in less than 5% of vaccine recipients, and to last for less than 1 week.[72,73] Rashes typically consist of 2 to 5 lesions and may be generalised (3–5%), or also commonly occur at the injection site (3–5%).[66] VV-associated rash may be atypical and may not be vesicular. Most varicelliform rashes that occur within the first

2 weeks after vaccination are due to wild-type VZV, with median onset 8 days after vaccination (range 1 to 24 days), while vaccine-strain VZV rashes occur at a median of 21 days after vaccination (range 5 to 42 days).[74,75]

Transmission of vaccine virus to contacts of vaccinated persons is rare. In the United States, where more than 56 million doses of VV were distributed between 1995 and 2005, there have been only six well-documented cases of transmission of the vaccine-type virus from five healthy vaccine recipients who had a vaccine-associated rash.[66,76] Contact cases have been mild.[66,76-78]

Fever >39°C has been observed in 15% of healthy children after varicella vaccination, but this was comparable to that seen in children receiving placebo.[66] In adults and adolescents, fever has been reported in 10% of VV recipients. It is recommended that parents/carers/vaccine recipients be advised about possible symptoms, and given advice for reducing fever, including the use of paracetamol for fever in the period 5 to 12 days after vaccination. Higher rates of fever were observed in clinical trials of both MMRV vaccines, particularly following dose 1, when compared with giving MMR vaccine and monovalent VV at the same time but at separate sites.[36-39] Two post-marketing studies in the United States identified an approximately 2-fold increased risk of fever and febrile convulsions in 1st dose recipients of MMRV vaccine, who were predominantly 12–23 months of age, in the period 7 to 10 days[79] (or 5 to 12 days)[80] after vaccination, compared with recipients of separate MMR and VV vaccines. MMRV vaccination resulted in 1 additional febrile seizure for every 2300 doses compared to separate MMR and VV vaccination.[79] An increase in fever or febrile convulsions has not been identified after the 2nd dose of MMRV vaccine in the United States, although most 2nd dose recipients were aged 4–6 years, an age at which the incidence of febrile convulsions is low.[81] These post-marketing studies were in children who received ProQuad; however, it is anticipated that this side effect profile would be similar in Priorix-tetra recipients.

A post-marketing study in the United States reported serious adverse events temporally, but not necessarily causally, linked to varicella vaccination, such as encephalitis, ataxia, thrombocytopenia and anaphylaxis, were very rare and occurred in <0.01% of doses distributed.[49,75] There were no neurological adverse events following VV in which the Oka vaccine virus strain was detected in cerebrospinal fluid (CSF).

Herpes zoster (HZ) has been reported rarely in vaccine recipients and has been attributed to both the vaccine strain and to wild-type varicella virus reactivation.[74] Reactivation of the vaccine virus resulting in HZ is rare and most cases of HZ in vaccine recipients can be attributed to reactivation of wild-type virus following unrecognised prior infection. The risk of developing HZ is currently thought to be lower after vaccination than after natural varicella virus infection, and reported cases have been mild.[2] Rates of herpes zoster in children 0–9 years of age after natural VZV infection were estimated to be between 30 and 74 per 100 000 per year,[82,83] while a rate of 22 per 100 000 person-years was

reported in a 9-year follow-up of 7000 varicella vaccinated children.[27] (See also 4.24 *Zoster*.)

4.22.12 Public health management of varicella

Varicella is a notifiable disease in most states and territories in Australia.

Further instructions about the public health management of varicella, including management of cases of varicella and their contacts, should be obtained from state/territory public health authorities (see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*).

- ***Zoster Immunoglobulin-VF (human)*** – CSL Limited. 160 mg/mL immunoglobulin (mainly IgG) prepared from human plasma containing high levels of antibody to the varicella-zoster virus. Single vials contain 200 IU of varicella-zoster antibody, with the actual volume stated on the label on the vial. Also contains glycine.

High-titre zoster immunoglobulin (ZIG) is available from the Australian Red Cross Blood Service on a restricted basis for the prevention of varicella in high-risk subjects who report a significant exposure to varicella or HZ. ZIG has no proven use in the treatment of established varicella or zoster infection. ZIG is highly efficacious, but is often in short supply. Normal human immunoglobulin (NHIG) can be used for the prevention of varicella if ZIG is unavailable. Post-exposure prophylaxis using varicella vaccine may also be indicated, if vaccination is not contraindicated (see below).

Zoster immunoglobulin should only be given by IM injection.

'Significant exposure' to VZV is defined as living in the same household as a person with active varicella or HZ, or direct face-to-face contact with a person with varicella or HZ for at least 5 minutes, or being in the same room for at least 1 hour. In the case of varicella infection, the period of infectivity is from 48 hours before the onset of rash until crusting of all lesions has occurred. Transmission from a person with localised zoster is less likely than from a person with varicella.[4]

Immunocompetent varicella contacts should be tested for varicella-zoster antibodies.

ZIG must be given early in the incubation period (within 96 hours of exposure), but may have some efficacy if administered out to as late as 10 days post exposure. ZIG is able to prevent or ameliorate varicella in infants <1 month of age, in children who are being treated with immunosuppressive therapy, and in pregnant women. Persons with primary or acquired diseases associated with cellular immune deficiency and those receiving immunosuppressive therapy

should be tested for varicella-zoster antibodies following contact with a person with confirmed varicella. However, testing should not delay ZIG administration after initial exposure to a case.[84-86]

ZIG administration (preferably within 96 hours and up to 10 days after exposure) is required for the following groups and should not be delayed by testing (if indicated below):

- Pregnant women who are presumed to be susceptible to varicella infection. If practicable, they should be tested for varicella-zoster antibodies before ZIG is given.[5]
- Neonates whose mothers develop varicella from 7 or fewer days before delivery to 2 days after delivery. ZIG *must* be given, as the neonatal mortality without ZIG is up to 30% in this setting.[1,7] ZIG must be given as early as possible in the incubation period.
- Neonates exposed to varicella in the 1st month of life, if the mother has no personal history of infection with VZV and is seronegative.[27] ZIG *should* be given, due to the increased risk of severe varicella in newborns of seronegative women.
- Premature infants (born at <28 weeks gestation or whose birth weight is <1000 g) exposed to VZV while still hospitalised should be given ZIG *regardless of maternal history of varicella*.
- Patients suffering from primary or acquired diseases associated with cellular immune deficiency, and those receiving immunosuppressive therapy.[85,86]

Note: If an immunocompromised VZV contact is shown to have recent evidence of detectable antibodies, it is not necessary to give ZIG, as its administration will not significantly increase varicella-zoster antibody titres in those who are already antibody positive. Note that varicella-zoster antibodies detected in patients who have been transfused or who have received intravenous immunoglobulin or ZIG in the previous 3 months may be passively acquired and transient.

The dose schedule recommended for ZIG administration is shown in Table 4.22.2.

Table 4.22.2: Zoster immunoglobulin-VF (ZIG) dose based on weight

Weight of patient (kg)	Dose (IU)
0–10	200
11–30	400
>30	600

A dose of ZIG may be repeated if a 2nd exposure occurs more than 3 weeks after the 1st dose of ZIG. However, testing for varicella antibodies is also recommended (see above). NHIG can be used for the prevention of varicella if ZIG is unavailable (see Part 5 *Passive immunisation*). Persons receiving monthly

high-dose intravenous NHIG are likely to be protected and probably do not require ZIG if the last dose of NHIG was given 3 weeks or less before exposure.

Vaccination for post-exposure prophylaxis

If VV is not contraindicated, it can be offered to non-immune age-eligible children and adults who have a significant exposure to varicella or HZ and wish to be protected against primary infection with VZV (see 'Post-exposure vaccination' in 4.22.7 *Recommendations* above).[51-55] Vaccination has the added benefit of reducing the likelihood of varicella infection, particularly moderate to severe disease, following exposure, and also provides long-term protection. Vaccination of exposed persons during outbreaks has also been shown to prevent further cases and to control outbreaks.[55] If MMR vaccination is also indicated, MMRV vaccine can be used in children <14 years of age, although MMRV vaccine is not routinely recommended as the 1st dose of MMR-containing vaccine in children aged <4 years (see 4.22.7 *Recommendations* above).

Post-exposure vaccination should be administered within 5 days, and preferably within 3 days, after exposure.[51-55]

4.22.13 Variations from product information

Varilrix and Varivax Refrigerated are registered for use as 2 doses of 0.5 mL (1–2 months apart) in adolescents ≥13 years of age and adults. The ATAGI instead recommends a single dose of varicella vaccine for children <14 years of age and 2 doses of varicella vaccine in those aged ≥14 years.

In adults and adolescents where 2 doses of varicella vaccine are required, the product information for Varilrix states that the 2nd dose should be given at least 6 weeks after the 1st dose. The ATAGI recommends instead that the 2nd dose may be given at least 4 weeks after the 1st dose.

The product information for both monovalent varicella vaccines and both MMRV vaccines recommends that women of child-bearing age should be advised not to become pregnant for 3 months after vaccination. The ATAGI instead recommends avoiding pregnancy for 28 days after vaccination.[87]

The product information for Priorix-tetra and ProQuad states that persons with a history of anaphylactic or anaphylactoid reactions to egg should not be vaccinated. The ATAGI recommends instead that either Priorix-tetra or ProQuad can be given in this situation.[68]

The product information for Priorix-tetra states that it should be given by SC injection. The ATAGI recommends that it may also be given by IM injection.

The product information for ProQuad states that this vaccine is indicated for vaccination in individuals 12 months through 12 years of age. The product information for Priorix-tetra states that this vaccine can be used in persons from 9 months of age. The ATAGI recommends instead that both MMRV vaccines can be given to persons up to 14 years of age. The ATAGI also recommends that

MMRV vaccine should *not* be used routinely as the 1st dose of MMR-containing vaccine in children aged <4 years.

The product information for all varicella-containing vaccines states that salicylates should be avoided for 6 weeks after vaccination, as Reye syndrome has been reported following the use of salicylates during natural varicella infection. The ATAGI recommends instead that non-immune persons receiving long-term salicylate therapy can receive varicella-containing vaccine, as the benefit is likely to outweigh any possible risk of Reye syndrome occurring after vaccination.

The product information for Varivax Refrigerated recommends delaying vaccination for 5 months after receipt of NHIG by IM injection or blood transfusion. The ATAGI recommends instead that varicella-containing vaccines should not be given for at least 3 months after receipt of immunoglobulin-containing blood products according to the intervals contained in Table 3.3.6 *Recommended intervals between either immunoglobulins or blood products and MMR, MMRV or varicella vaccination*.

The dosage of ZIG recommended in the product information differs from that in Table 4.22.2, which has been revised in order to minimise wastage of ZIG.

References

A full reference list is available on the electronic *Handbook* or website www.immunise.health.gov.au

4.23 YELLOW FEVER

4.23.1 Virology

Yellow fever is a viral haemorrhagic fever caused by an RNA flavivirus that is transmitted by mosquitoes. *Aedes aegypti*, a highly domesticated mosquito found throughout the tropics, is the vector responsible for person-to-person transmission of the yellow fever virus in urban and inhabited rural areas in endemic countries.

4.23.2 Clinical features

The clinical spectrum of yellow fever varies from a non-specific febrile illness to fatal haemorrhagic fever.[1] After an incubation period of 3 to 6 days, the disease begins abruptly with fever, prostration, myalgia and headache. The patient appears acutely ill with congestion of the conjunctivae; there is an intense viraemia during this 'period of infection', which lasts 3 to 4 days.[1] This may be followed by the 'period of remission', in which the fever and symptoms settle over 24 to 48 hours, during which the virus is cleared by immune responses.[1]

Approximately 15 to 25% of patients may then relapse with a high fever, vomiting, epigastric pain, jaundice, renal failure and haemorrhage: 'the period of intoxication'.[1] These complications can be severe, and reflect the viscerotropic nature of the yellow fever virus (its ability to infect the liver, heart and kidneys). The case-fatality rate varies widely, but can be more than 20% in local populations.[2]

4.23.3 Epidemiology

Yellow fever occurs in tropical regions of Africa and Central and South America. In both regions the virus is enzootic in rainforest monkeys and canopy mosquito species; sporadic human cases occur when people venture into these forests ('sylvatic or jungle yellow fever').[1]

In moist savannah regions in Africa, especially those adjacent to rainforests, tree hole-breeding *Aedes* mosquito species are able to transfer yellow fever virus from monkeys to people and then between people, leading to small-scale outbreaks ('intermediate yellow fever').

Ae. aegypti occurs in both heavily urbanised areas and settled rural areas in tropical Africa and the Americas.[1] Epidemics of 'urban yellow fever' occur when a viraemic individual (with yellow fever) infects local populations of *Ae. aegypti*; such epidemics can be large and very difficult to control. Although *Ae. aegypti* also occurs throughout much of tropical Asia and Oceania (including north Queensland), yellow fever has never been reported from these regions.

Although yellow fever is undoubtedly markedly under-reported, it is clear that there has been a considerable increase in the reported number of outbreaks, and therefore cases, of yellow fever in past decades.[3] Most of this increase was in

Africa, particularly in West African countries.[3,4] In 2008, there were 24 cases of yellow fever reported near Asunción in Paraguay with 8 deaths.[5]

The risk of susceptible travellers acquiring yellow fever varies considerably with season, location, duration of travel and utilisation of mosquito avoidance measures. There have been reported cases of yellow fever, all fatal, in unvaccinated travellers to Africa and South America.[6]

4.23.4 Vaccine

- ***Stamaril*** – Sanofi Pasteur Pty Ltd (live attenuated yellow fever virus [17D strain]). Lyophilised powder in a monodose vial with a pre-filled diluent syringe. Each 0.5 mL reconstituted dose contains ≥1000 mouse LD_{50} units; 16.0 mg lactose; 8.0 mg sorbitol; 0.833 mg L-histidine hydrochloride. May contain traces of egg proteins.

Yellow fever vaccine is a live, freeze-dried preparation of attenuated 17D strain yellow fever virus cultured in, and harvested from, embryonated chicken eggs. The vaccine does not contain antibiotics, preservatives or gelatin.

Vaccination elicits protective levels of neutralising antibodies in approximately 90% of adult vaccine recipients by day 14, and in virtually all by day 28.[7] Immunity is long-lasting and perhaps life-long; regardless, revaccination is required after 10 years under International Health Regulations for a valid International Certificate of Vaccination or Prophylaxis (ICVP) against yellow fever. Because the vaccine produces a transient very low level viraemia in healthy adult recipients, they cannot serve as a source of infection for mosquitoes.[7]

Although the efficacy of the yellow fever vaccine has never been determined in prospective clinical trials, there is considerable observational evidence that it is very effective in preventing the disease.[7]

4.23.5 Transport, storage and handling

Transport according to *National vaccine storage guidelines: Strive for 5*.[8] Store at +2°C to +8°C. Do not freeze. Protect from light.

Stamaril *must be reconstituted* by adding the entire contents of the diluent syringe to the vial and shaking until the powder is completely dissolved. Reconstituted vaccine must be used within 1 hour.

4.23.6 Dosage and administration

The dose of yellow fever vaccine for children and adults is 0.5 mL, to be given by either IM or SC injection.

Test doses of yellow fever vaccine should never be used (see 4.23.13 *Variations from product information* below).

Co-administration with other vaccines

If administration of both yellow fever and other parenteral live viral vaccines is indicated, the vaccines should be given either on the same day or at least 4 weeks apart (see 4.23.10 *Precautions* below).

Inactivated vaccines and oral live vaccines relevant to travel (e.g. cholera, typhoid) can be given with, or at any time before or after, yellow fever vaccine.

Yellow fever vaccine can be given at the same time as the Imojev Japanese encephalitis vaccine,[9] using separate syringes and separate injection sites.

4.23.7 Recommendations

Children aged <9 months

Yellow fever vaccine is contraindicated in infants aged <9 months.

Children aged ≥9 months and adults

A single dose of yellow fever vaccine is recommended for:

- persons ≥9 months of age travelling to, or living in, areas with a risk of yellow fever virus transmission. Information risk for specific destinations should be sought from a reputable source, such as the World Health Organization (WHO),[10] prior to travel.
- laboratory personnel who routinely work with yellow fever virus.

Those persons who are at ongoing risk of yellow fever virus exposure and who received a yellow fever vaccine more than 10 years ago will require a booster.

Vaccination is generally not recommended when travelling to areas where there is low potential for yellow fever virus exposure (i.e. no human yellow fever cases ever reported and evidence to suggest only low levels of yellow fever virus transmission in the past). However, vaccination might be considered for a small subset of travellers to these areas who are at increased risk of exposure to mosquitoes or unable to avoid mosquito bites.

International travel requirements

All those travelling to, or living in, countries with a risk of yellow fever virus transmission should be informed that the mosquito vectors of yellow fever usually bite during the day. They should be advised of the necessity for mosquito avoidance measures, even if vaccinated. These include the use of insect repellents, coils and sprays, the use of mosquito nets (preferably those that have been treated with an insecticide), and adequate screening of residential (and work) premises.

Many countries require that travellers arriving from countries with a risk of yellow fever virus transmission provide evidence of yellow fever vaccination prior to entry. This is because importation of the virus into these countries by an infected traveller could result in introduction and establishment of the virus in local *Ae. aegypti* mosquitoes. Under International Health Regulations, countries

are free to set their own requirements for entry and some countries require a valid International Certificate of Vaccination or Prophylaxis against yellow fever or a valid letter of exemption for all arriving travellers. A country may require such documentation even for travellers who are only in transit through that country. The most recent WHO list of individual country yellow fever vaccination requirements and recommendations for travellers can be found at www.who.int/ith/chapters/ith2012en_countrylist.pdf. As yellow fever disease patterns, like other diseases, are constantly changing, it is recommended that the entry requirements for yellow fever vaccination for the countries a traveller intends to enter or transit through be confirmed by contacting the country's foreign missions in Australia.

Travellers >1 year of age entering or returning to Australia within 6 days of leaving a country on Australia's list of yellow fever declared places are required to have a valid International Certificate of Vaccination or Prophylaxis with proof of valid yellow fever vaccination (see below). This list is developed based on the WHO list of countries with risk of yellow fever virus transmission and international surveillance data, and is available from the Australian Government Department of Health's yellow fever fact sheet (www.health.gov.au/yellowfever). Travellers who do not have a valid certificate are provided with information on yellow fever and required to promptly seek medical assessment if they develop relevant symptoms within 6 days of leaving the declared place.

Yellow fever vaccine can be administered only by Yellow Fever Vaccination Centres approved by the relevant state or territory health authorities. Each yellow fever vaccination is to be recorded in an International Certificate of Vaccination or Prophylaxis, with proof of valid yellow fever vaccine; the certificate must include the vaccinated person's name and signature (or the signature of a parent or guardian of a child), and the signature of a person approved by the relevant health authority. The date of the vaccination must be recorded in day–month–year sequence, with the month written in letters, and the official stamp provided by the state or territory health authority must be used. The certificate becomes valid 10 days after vaccination, and remains valid for 10 years.

Note: People with a true contraindication to yellow fever vaccine (see 4.23.9 *Contraindications* below) who intend to travel to yellow fever risk countries should obtain a letter from a doctor, clearly stating the reason for withholding the vaccine. The letter should be formal, signed and dated, and on the practice's letterhead. Arriving travellers who possess an exemption from the yellow fever vaccination are provided with information on yellow fever and required to promptly seek medical assessment if they develop relevant symptoms.

4.23.8 Pregnancy and breastfeeding

Yellow fever vaccine is not recommended for pregnant women or women breastfeeding infants aged <9 months.

As with all live attenuated virus vaccines, unless there is a risk of exposure to the virus, yellow fever vaccine should not routinely be given to pregnant women. Pregnant women should be advised against going to the rural areas of yellow fever endemic areas (and to urban areas of West African countries as well). However, where travel to an at-risk country is unavoidable, such women should be vaccinated (see 4.23.7 *Recommendations* above).[11-14]

The yellow fever vaccine has been given to considerable numbers of pregnant women[7,11,12] with no evidence of any adverse outcomes. Therefore, women vaccinated in early pregnancy can be reassured that there is no evidence of risk to themselves and very low (if any) risk to the fetus.[7]

Administration of yellow fever vaccine to women who are breastfeeding infants aged <9 months (and therefore unable to be vaccinated) should be avoided, except in situations where exposure to yellow fever virus cannot be avoided or postponed.[13,14] While extremely rare, there have been several case reports of transmission of the vaccine strain of yellow fever virus via breast milk.[13,14]

Refer to 3.3 *Groups with special vaccination requirements*, Table 3.3.1 *Recommendations for vaccination in pregnancy* for more information.

4.23.9 Contraindications

Anaphylaxis to vaccine components

Yellow fever vaccine is contraindicated in persons who have had:

- anaphylaxis following a previous dose of the vaccine
- anaphylaxis following any vaccine component.

In particular, the vaccine is contraindicated in persons with a known anaphylaxis to eggs. Persons with a known allergy to eggs wishing to receive yellow fever vaccination should discuss this with either an immunologist/allergist or be referred to a specialised immunisation adverse events clinic. Contact a specialist travel medicine clinic or your local state or territory health authority for further details (see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*).

Infants

Routine yellow fever vaccine is contraindicated in infants <9 months of age. Countries experiencing a mass outbreak of yellow fever may elect to immunise infants from as young as 6 months of age.

Altered immune status

As with all live viral vaccines, the yellow fever vaccine should generally not be given to people who are immunocompromised due to either disease or medical treatment (see 3.3.3 *Vaccination of immunocompromised persons*). However, studies of small numbers of HIV-infected participants, mainly travellers with $CD4^+$ counts >200 per µL, have shown reduced immune response, but good tolerability.[15]

Thymus disorders

People with a history of any thymus disorder, including myasthenia gravis, thymoma, thymectomy and DiGeorge syndrome, or thymic damage from chemoradiotherapy or graft-versus-host disease, should not be given the yellow fever vaccine due to the increased risk of yellow fever vaccine-associated viscerotropic disease (see 4.23.11 *Adverse events* below).

4.23.10 Precautions

Adults aged ≥60 years

The risk of severe adverse events following yellow fever vaccine is considerably greater in those aged ≥60 years than in younger adults.[16-19]

Adults ≥60 years of age should be given yellow fever vaccine only if they intend to travel to endemic countries (as recommended above) and they have been informed about the (albeit very low) risks of developing a severe complication.

Vaccination with other live attenuated parenteral vaccines

The administration of other parenteral live viral vaccines (e.g. MMR, MMRV, varicella or zoster vaccine) should be on the same day as yellow fever vaccine, or separated by a 4-week interval.

4.23.11 Adverse events

Mild adverse events

Adverse events following yellow fever vaccine are generally mild. Vaccine recipients often report mild headaches, myalgia and low-grade fevers or other minor symptoms for 5 to 10 days post vaccination. In clinical trials in which symptoms are actively elicited, up to 25% of vaccine recipients report mild adverse events and up to 1% curtail regular activities.[7,19,20]

Immediate hypersensitivity reactions

Immediate hypersensitivity reactions, including anaphylaxis, following yellow fever vaccine are very rare, with an incidence of less than 1 in 1 million, and occur principally in people with anaphylactic sensitivity to eggs.[7,18,19] Although it has been suggested that an anaphylactic sensitivity to gelatin (added as a stabiliser to some yellow fever vaccines) may also precipitate anaphylaxis following vaccination,[21] Stamaril does not contain gelatin.

Vaccine-associated neurotropic adverse events

Yellow fever vaccine-associated neurotropic disease (YF-AND) is rare.[18] At least 25 cases of meningoencephalitis following yellow fever vaccination have been reported.[7] However, 15 of these cases occurred in the 1950s in infants ≤7 months of age. Following recommendations in the early 1960s not to vaccinate young infants, the incidence of vaccine-associated meningoencephalitis declined considerably.[7] Nevertheless, these adverse events, albeit very rare, still occur in adults; the risk is greater in persons ≥60 years of age.[16,17]

Vaccine-associated viscerotropic adverse events

Recently, an apparently very rare (and often fatal) complication, yellow fever vaccine-associated viscerotropic disease (YF-AVD), characterised by multi-organ system failure, has been recognised following yellow fever vaccination. It appears that overwhelming infection with the 17D vaccine virus is responsible for these viscerotropic adverse events.[7,18]

Vaccine-associated viscerotropic adverse events do not appear to be caused by altered virulence of the vaccine virus, but rather appear to be related to host factors. Although cases have occurred in younger persons, it is apparent that the risk is increased with advanced age, particularly in those aged ≥60 years.[16,17,19] Another host factor associated with an increased risk of a viscerotropic adverse event is pre-existing thymus disease. Published reports of YF-AVD cases have indicated that 4 of the 27 reported cases had a history of thymic tumour and thymectomy, both uncommon conditions.[18,22]

4.23.12 Public health management of yellow fever

Yellow fever is a notifiable and quarantinable disease in all states and territories in Australia.

Further instructions about the public health management of yellow fever, including management of cases of yellow fever and their contacts, should be obtained from state/territory public health authorities (see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*).

4.23.13 Variations from product information

The product information states that pregnancy is a contraindication to the yellow fever vaccine. The ATAGI recommends instead that pregnant women who insist on travelling to endemic countries should be vaccinated.

The product information suggests that a 0.1 mL test dose of yellow fever vaccine can be used intradermally to assess an individual with suspected allergy to the vaccine. The ATAGI instead recommends that (with the exception of Q fever vaccine) test doses should never be used.

References

A full reference list is available on the electronic *Handbook* or website www.immunise.health.gov.au

4.24 ZOSTER (herpes zoster)

4.24.1 Virology

Varicella-zoster virus (VZV) is a DNA virus that is a member of the herpesvirus family. Primary infection with VZV is known as varicella or 'chickenpox'.[1] Herpes zoster (HZ), or 'shingles', is caused by reactivation of latent VZV, which typically resides in the dorsal root or trigeminal nerve ganglia following primary infection.[1]

4.24.2 Clinical features

Reactivation of VZV causing HZ is thought to be particularly due to a decline in cellular immunity to the virus, and presents clinically as a unilateral vesicular rash in a dermatomal distribution in the majority of cases. A prodromal phase occurs 48 to 72 hours prior to the appearance of the lesions in 80% of cases.[2] Associated symptoms may include headache, photophobia, malaise, and an itching, tingling or severe pain in the affected dermatome.[3,4] In the majority of patients, HZ is an acute and self-limiting disease, with the rash lasting 10 to 15 days.[1,3] However, complications can occur, especially with increasing age.

Post-herpetic neuralgia (PHN), the most frequent debilitating complication of HZ, is a neuropathic pain syndrome that persists or develops after the dermatomal rash has healed. By definition, PHN is established when pain persists for longer than 3 months after the onset of the rash.[5,6] Other complications may occur, depending on the site of reactivation. These include ophthalmic disease (such as keratitis and chorioretinitis), neurological complications (such as meningoencephalitis and myelitis), secondary bacterial skin infection, scarring and pneumonia.[7] Rarely, disseminated HZ may develop, with widespread vesicular rash, and visceral, central nervous system and pulmonary involvement. Disseminated disease is more common in persons who are immunocompromised.[4] Dermatomal pain without the appearance of rash is also documented (zoster siné herpéte).

Antiviral therapy, if initiated within 3 days of the onset of HZ, has been shown to reduce the severity and duration of HZ and may reduce the risk of developing PHN.[8-12] However, despite medical therapy, PHN may persist for years and can be refractory to treatment.[13]

4.24.3 Epidemiology

HZ occurs most commonly with increasing age (>50 years), immunocompromise, and following a history of varicella in the 1st year of life. The lifetime risk of reactivation of VZV causing HZ is estimated to be approximately 20 to 30% and it affects half of those who live to 85 years.[1,14-16] Second attacks of HZ occur in approximately 5% of immunocompetent persons, but are more frequent in persons who are immunocompromised.[3,17,18] Using Australian general practice and other data, approximately 490 cases per 100 000 (range 330–830 per 100 000) are estimated to occur annually in all ages, with approximately

1000 cases per 100 000 population in persons aged ≥50 years.[19-22] In the large efficacy study of zoster vaccine in the United States, the incidence of HZ in unimmunised participants ≥60 years of age was 1112 cases per 100 000 person-years.[23] The incidence in persons aged 50–59 years is lower, with one study estimating a rate of 470 per 100 000 person-years.[24] The risk of HZ increases with immunocompromise; for example, rates of HZ are up to 15 times higher in those who are immunocompromised due to HIV infection, and, in the 1st year following haematopoietic stem cell transplantation (HSCT), up to 30% of patients may develop HZ.[3,25]

Overall, an estimated 13 to 26% of patients with HZ develop complications. Complications occur more frequently with increasing age, and with immunocompromise.[26,27] PHN occurs infrequently in young people, but, in patients over the age of 50 years, it complicates HZ in 25 to 50% of cases.[26,27]

Modelling studies of the impact of universal childhood vaccination programs for varicella have predicted that a rise in the incidence of HZ could occur, based on the assumption that exposure to wild-type VZV circulating in the community boosts immunity.[28] However, to date, multiple studies and surveillance data do not demonstrate any consistent changes in overall HZ incidence in the United States, which has a universal varicella vaccination program that commenced in 1995.[29-31] Australian data show an increase in HZ GP consultation rates over time, commencing prior to varicella vaccine introduction, which is likely to be due to the increasing age of the population. Age-standardised HZ hospitalisation rates have not declined since introduction of varicella vaccine, and the use of zoster vaccine has not yet been extensive enough in any country to expect an impact on HZ epidemiology.[32-34] In the United States, the incidence of HZ in children <10 years of age has declined, indicating that HZ rates are lower in varicella vaccine recipients.[30]

4.24.4 Vaccine

Zostavax is a live attenuated vaccine formulated from the same VZV vaccine strain (Oka/Merck) as the registered varicella (chickenpox) vaccine Varivax, but is of higher potency (on average, at least 14 times greater). The higher viral titre in Zostavax is required to elicit a boost in immune response in adults who usually remain seropositive to VZV following primary infection, but have declining cellular immunity with increasing age.[35] Zostavax is used for the prevention of HZ in persons >50 years of age. It is important to note that the registered varicella vaccines are *not* indicated for use in preventing HZ in older people and Zostavax is *not* indicated for use in younger people who have not been previously immunised or infected with VZV. Zostavax is not indicated for use for therapeutic benefit during an acute HZ episode, nor for the treatment of PHN.

A single large, randomised, double-blind, placebo-controlled efficacy study of the frozen formulation of Zostavax (known as the 'Shingles Prevention Study'

[SPS]) was conducted among 38 546 adults aged ≥60 years and demonstrated that Zostavax significantly reduced the likelihood of developing both HZ and PHN.[23] Vaccination reduced the incidence of HZ by 51.3%, the incidence of PHN by 66.5%, and the burden of illness associated with HZ by 61.1% over a median of more than 3 years follow-up.[23] The vaccine was more efficacious in reducing HZ in persons aged 60–69 years than in those aged 70–79 years (64% compared with 41% efficacy). However, efficacy against PHN was similar in both age groups.[23] Efficacy against HZ in the ≥80 years age group was lower (18% and not statistically different to placebo). However, there were fewer participants of this age in the SPS.[36] In those who developed HZ despite vaccination, the severity of pain associated with the episode was also reduced.[37] Another randomised controlled study in >22 000 50–59-year olds demonstrated a reduction in the incidence of HZ after a follow-up period of 1 year or more, with a vaccine efficacy for preventing HZ of 69.8%.[38] In these clinical trials many participants were treated with antiviral and pain medication for their HZ, suggesting that the effect of the vaccine was in addition to any benefit obtained from medical therapy.[23,38] Efficacy of a single dose of zoster vaccine appears to decline over time, with recent data suggesting persistent efficacy through to the 5th year post vaccination, with uncertain efficacy beyond that point.[39] The need for a booster dose has not yet been determined.

The Shingles Prevention Study, together with other smaller studies, demonstrated that Zostavax is safe and generally well tolerated among adults ≥50 years of age.[23,38] In the SPS, the most common adverse events were injection site reactions, with Zostavax more likely to result in erythema, pain and swelling at the injection site than placebo (48% versus 17%, respectively). Varicella-like rashes at the injection site were also more common in vaccine recipients; however, varicella-like rash not localised to the injection site did not occur more often. Varicella- or zoster-like rashes that were PCR-positive for VZV were mostly due to wild-type VZV.[23] Fever was no more common in vaccine recipients; however, the rate of vaccine-related systemic symptoms was higher (Zostavax 6.3% versus placebo 4.9%), with the most frequently reported systemic symptoms being headache and fatigue.[23] Mild to moderate adverse events, particularly injection site reactions, were higher in vaccine recipients aged 50–59 years than in those aged ≥60 years.[38,40]

In Australia, a refrigerated form of Zostavax is registered on the basis of comparable immunogenicity and safety to the frozen vaccine formulation that was used in the SPS.[41] Zostavax was registered for use in persons 50–59 years of age based on a study that demonstrated similar immunogenicity in this age group compared with those ≥60 years of age,[40] and has since been shown to reduce the incidence of HZ in this population.[38] A study of the simultaneous administration of Zostavax with inactivated influenza vaccine (given separately and at different injection sites) demonstrated comparable immunogenicity and safety to giving the vaccines at different times.[42] A study of the simultaneous

administration of Zostavax with 23-valent pneumococcal polysaccharide vaccine (Pneumovax 23; 23vPPV) suggested that the immunogenicity of Zostavax was reduced when administered simultaneously with Pneumovax 23, compared with administration 4 weeks apart.[43] The immunogenicity of Pneumovax 23 was not affected. However, an observational study from the United States suggests this may not impact on Zostavax effectiveness.[44-46]

Zostavax availability in Australia has been limited due to manufacturer supply constraints.

- ***Zostavax*** – CSL Limited/Merck & Co Inc (live attenuated Oka/Merck strain of varicella-zoster virus). Lyophilised powder in a monodose vial with separate diluent. Each 0.65 mL reconstituted dose contains ≥19 400 plaque-forming units of attenuated varicella-zoster virus; sucrose; gelatin; urea; monosodium glutamate; residual components of MRC-5 cells; traces of neomycin and bovine serum albumin.

4.24.5 Transport, storage and handling

Transport according to *National vaccine storage guidelines: Strive for 5*.[47] Store at +2°C to +8°C. Do not freeze. Protect from light.

Zostavax is less stable than other commonly used live viral vaccines, and adherence to storage and reconstitution requirements is very important.

Zostavax *must be reconstituted* by adding the entire contents of the diluent container to the vial and shaking until the powder is completely dissolved. Reconstitute immediately upon removal from the refrigerator. Reconstituted vaccine must be used within 30 minutes.

4.24.6 Dosage and administration

The dose of Zostavax is 0.65 mL, to be given by SC injection.

Zostavax must never be given where varicella (chickenpox) vaccine is indicated. Zoster vaccine is only registered for use in adults ≥50 years of age.

Co-administration with other vaccines

Zostavax can be given at the same time as influenza vaccine,[42] using separate syringes and injection sites.

Simultaneous administration of Zostavax with pneumococcal polysaccharide vaccine is not routinely recommended; if possible the two vaccines should be given at least 4 weeks apart. However, inadvertent administration of Zostavax and pneumococcal polysaccharide vaccine at the same time or at an interval of less than 4 weeks does not require revaccination (see 4.24.4 *Vaccine* above).

Zostavax can be administered at the same visit as, or at any time following receipt of, other inactivated vaccines (e.g. tetanus-containing vaccines), if required.

If administration of both Zostavax and another live parenteral vaccine (e.g. MMR or yellow fever) is indicated, the vaccines should be given either on the same day or at least 4 weeks apart. (See also 4.22 *Varicella*.)

4.24.7 Recommendations

Adults aged ≥60 years

A single dose of zoster vaccine is recommended for adults ≥60 years of age who have not previously received a dose of zoster vaccine. Routine serological testing prior to receipt of zoster vaccine is not indicated and it is not necessary to elicit a history of previous varicella (chickenpox) infection (see 'Serological testing before and after zoster vaccination' below).

Persons with chronic medical conditions, such as arthritis, chronic renal failure, diabetes and other conditions, can be given zoster vaccine, unless a contraindication or precaution exists due to their condition or medical treatment (see 4.24.9 *Contraindications* and 4.24.10 *Precautions* below). Persons with significant immunocompromise should *not* receive zoster vaccine (see also 3.3.3 *Vaccination of immunocompromised persons*).

The zoster vaccine has been shown to be less efficacious in persons aged ≥80 years and may be less likely to provide a clinical benefit in this age group (see 4.24.4 *Vaccine* above).

Adults aged 50–59 years

Routine population-based use of zoster vaccine in persons aged 50–59 years is not recommended. Although the incidence of HZ in persons 50–59 years of age is higher than in younger age groups,[19,22] and zoster vaccine is efficacious in 50–59-year olds,[38] the likelihood of developing PHN and other complications of HZ is lower in this age group than in those ≥60 years of age.[24,48] Persons aged 50–59 years who wish to protect themselves against HZ can be vaccinated; however, the duration of efficacy, and need for a booster dose at a later age, is not yet determined (see 4.24.4 *Vaccine* above).

Persons aged <50 years

Zoster vaccination is not recommended for use in persons <50 years of age and is not registered for use in this age group. There have been very limited studies of the safety and immunogenicity of zoster vaccine in this age group (see 4.24.4 *Vaccine* above).

Persons with a history of a previous episode of HZ

Persons with a history of a previous episode of HZ can be given zoster vaccine. It is possible that a history of previous zoster may be inaccurate or a mistaken

diagnosis. In addition, the risk of a repeat episode of zoster has been estimated at approximately 5% in immunocompetent persons.[17,18,48] Persons with a history of HZ were excluded from the SPS, so no data on the efficacy of the vaccine in those with a history of HZ is available. The safety and immunogenicity of zoster vaccine in persons with a history of HZ has been studied in one small clinical trial; the vaccine was well tolerated and immunogenic.[49] Injection site reactions were more common in vaccine recipients than in placebo recipients, but similar to vaccine recipients in the SPS. Systemic adverse events were similar between groups.[23] The length of time following an episode of HZ after which it would be reasonable to vaccinate has not been established. However, it is suggested that the vaccine could be given at least 1 year after the episode of HZ.

Persons previously vaccinated with varicella vaccine

Zoster vaccination of persons who have previously received varicella vaccine is not recommended at this time. There have been limited studies of the safety and immunogenicity of zoster vaccine in this setting, and the currently available data are insufficient to suggest a benefit from vaccination. It is not yet known whether, in the future, populations vaccinated with varicella vaccine will experience rates of HZ sufficient to warrant zoster vaccination. Preliminary information suggests that the incidence of HZ in persons who have received varicella vaccine is lower than in those infected with wild-type varicella.[30]

Persons with immunocompromise due to HIV/AIDS

Studies of the use of zoster vaccine in HIV-infected persons have not been completed. However, persons with asymptomatic HIV infection may be considered for vaccination on a case-by-case basis after seeking appropriate specialist advice. Serological confirmation of previous VZV infection must be obtained prior to vaccination (see 'Serological testing before and after zoster vaccination' below). Although asymptomatic HIV-infected persons are likely to have a higher relative risk of developing HZ in the future,[25] it is possible that both the efficacy and the safety of zoster vaccination may be reduced in such recipients, as compared with uninfected persons.

Vaccination with zoster vaccine is *not* recommended for persons with AIDS or symptomatic HIV infection (see 3.3 *Groups with special vaccination requirements*, Table 3.3.4 *Categories of immunocompromise in HIV-infected persons, based on age-specific CD4⁺ counts and percentage of total lymphocytes*), or significant immunocompromise due to other diseases and/or treatment (see 4.24.9 *Contraindications* below).

Persons anticipating future significant immunocompromise

Immunocompetent persons who anticipate alteration of their immunity because of their existing illness can be given zoster vaccine on a case-by-case basis after seeking appropriate specialist advice.[36] Persons with conditions such as chronic lymphocytic leukaemia, conditions requiring organ transplantation,[50]

solid tumours that will require future chemotherapy or radiation therapy, and inflammatory diseases (e.g. rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, psoriasis) may have minimal alteration to their immune system, but can anticipate significant immunocompromise in the future due to their disease and/or treatment. Since these persons are at higher risk of developing zoster than if they remained immunocompetent, vaccination at least 1 month prior to the onset of immunocompromise may be appropriate (after seeking specialist advice).[36] Serological confirmation of previous VZV infection must be obtained prior to vaccination (see 'Serological testing before and after zoster vaccination' below).

Household contacts of persons who are immunocompromised

Vaccination is recommended for persons ≥50 years of age who are household contacts of a person who is immunocompromised. Based on evidence that the rate of VZV-like rashes after vaccination is extremely low, it is unlikely that transmission of vaccine-associated virus to a susceptible contact would occur.[23] If a vaccinated person develops a varicella- or zoster-like rash, they should cover the rash and avoid contact with persons who are immunocompromised for the duration of the rash. The efficacy of the HZ vaccine is less than 100%, and rashes in vaccinated persons may be due to reactivation of wild-type VZV. If household contacts (<50 years of age) of a person who is immunocompromised have not been previously infected with VZV or immunised with varicella vaccine, they should receive varicella vaccine (see 4.22 *Varicella*).

Serological testing before and after zoster vaccination

Neither history of previous varicella infection nor evidence of prior immunity to VZV is required prior to the routine administration of the zoster vaccine (with the exception of immunocompromised persons, see below). Most older people in Australia are seropositive to VZV due to previous primary varicella infection. Limited data from small studies of the administration of high-dose VZV-containing vaccine (comparable to Zostavax) to VZV seronegative adults, compared with previously infected adults, suggest that the vaccine was well tolerated and immunogenic in seronegative persons, although the incidence of self-limited injection site reactions may be slightly higher.[51,52] If an adult eligible for zoster vaccine has laboratory evidence of a lack of immunity to VZV, and does not have a history of age-appropriate varicella vaccination, they should be vaccinated with 2 doses of varicella vaccine, rather than zoster vaccine (see 4.22 *Varicella*).

Serological testing prior to zoster vaccination is recommended if vaccination is being considered for persons with asymptomatic HIV infection or persons anticipating significant immunocompromise (see 'Persons with immunocompromise due to HIV/AIDS' and 'Persons anticipating future significant immunocompromise' above).

Laboratory testing to check for an immune response after zoster vaccination is not recommended. Zoster vaccine boosts both humoral (IgG) and cellular immune responses; however, confirmation of such immune responses is neither necessary nor predictive of protection against the development of zoster.

4.24.8 Pregnancy and breastfeeding

VZV-containing vaccines are contraindicated in pregnant women, although women of child-bearing age are not eligible for zoster vaccination. Pregnancy should be avoided for 28 days after vaccination (see 4.22 *Varicella*).

A non-immune pregnant household contact is *not* a contraindication to zoster vaccination.

Refer to 3.3 *Groups with special vaccination requirements*, Table 3.3.1 *Recommendations for vaccination in pregnancy* for more information.

4.24.9 Contraindications

Anaphylaxis to vaccine components

Zoster vaccine is contraindicated in persons who have had:

- anaphylaxis following a previous dose of any VZV-containing vaccine
- anaphylaxis following any vaccine component.

Persons who are immunocompromised

Live attenuated zoster vaccine is contraindicated in persons with significant immunocompromise due to either a primary or acquired medical condition, or due to medical treatment. This includes persons receiving high-dose systemic immunosuppressive therapy, such as chemotherapy, radiation therapy or oral corticosteroids; persons suffering from malignant conditions of the reticuloendothelial system (such as lymphoma, leukaemia, Hodgkin's disease); and any person with similar immunocompromise due to a disease or treatment (see 3.3.3 *Vaccination of immunocompromised persons*).

Persons who have been receiving high-dose systemic steroids (or equivalent) and have ceased therapy may be vaccinated (see 3.3.3 *Vaccination of immunocompromised persons*). Persons on low-dose corticosteroids or less significantly immunocompromised than described above, may be considered for vaccination on a case-by-case basis. Studies of zoster vaccine in such persons are being conducted.

4.24.10 Precautions

Vaccination with other live attenuated parenteral vaccines

If zoster vaccine is to be given around the same time as another live viral parenteral vaccine (e.g. MMR, yellow fever), the vaccines should be given either at the same visit or at least 4 weeks apart.

Vaccination before or after immunoglobulin or blood product administration

Zoster vaccine can be given at any time before or after administration of immunoglobulin or any antibody-containing blood product. This is because zoster vaccine is indicated in persons who, because of their age, are assumed to have had a previous VZV infection and, therefore, already have serum antibody levels comparable to those found in blood products. (See also 3.3.4 *Vaccination of recent recipients of normal human immunoglobulin and other blood products*.)

Persons receiving long-term aspirin or salicylate therapy

Persons receiving long-term salicylate therapy (aspirin) can be vaccinated if indicated. There have been no reports of an association between Reye syndrome and varicella vaccination, and it is unlikely that vaccination of a previously VZV-infected older person with zoster vaccine carries any risk of Reye syndrome.

Persons receiving antiviral medication

It is possible that the use of antivirals with anti-VZV activity, such as acyclovir, famciclovir or valaciclovir, may interfere with the replication of the Zostavax live attenuated virus. Persons on such antiviral medication should cease treatment no less than 24 hours prior to vaccination and for at least 14 days after vaccination.[36,53]

4.24.11 Adverse events

Injection site reactions (including erythema, pain, swelling and/or itch at the injection site) occurred in approximately half of clinical trial participants given Zostavax, irrespective of a previous history of HZ (see also 4.24.4 *Vaccine* above).

Varicella-like rashes at the injection site occurred rarely, in 0.1% of recipients; however, they were more common than in placebo recipients. Varicella-like rashes that were not localised to the injection site were also rare, and did not occur more often in vaccine compared with placebo recipients (0.1% in both groups). In the clinical trials in which rashes were analysed by PCR for VZV, the majority were due to wild-type virus; only 2 subjects were found to have rashes due to the Oka/Merck VZV vaccine strain (see also 4.24.4 *Vaccine* above).

Fever >38.3°C was not seen more commonly in vaccine recipients, and occurred in <0.1% of subjects overall.

Systemic symptoms were reported in vaccine recipients more commonly than in placebo recipients (Zostavax 6.3% versus placebo 4.9%), with the most frequently reported systemic symptoms being headache[38] and fatigue.[23]

Post-marketing surveillance in the United States in a cohort of almost 200 000 adults who received the zoster vaccine found no increased risk for a number of potential adverse events occurring after vaccination (such as cerebrovascular events, encephalitis, etc.), but did find a 2-fold increased risk in the 1st week after vaccination for events coded as 'allergic reactions', of which the majority were injection site reactions.[54]

4.24.12 Variations from product information

The product information for Zostavax states that the vaccine can be administered concurrently with inactivated influenza vaccine but not with 23vPPV. The ATAGI instead recommends that Zostavax may be administered concurrently with other vaccines as indicated. The ATAGI also recommends that if inadvertent concomitant administration of Zostavax and pneumococcal polysaccharide vaccine occurs, there is no need to revaccinate.

The product information for Zostavax states that the safety and efficacy of Zostavax have not been established in adults with known HIV infection, with or without evidence of immunocompromise. The ATAGI recommends instead that Zostavax may be administered to HIV-infected persons without immunocompromise on a case-by-case basis, after seeking appropriate specialist advice, and following confirmation of pre-existing immunity to VZV.

References

A full reference list is available on the electronic *Handbook* or website www.immunise.health.gov.au

PART 5 PASSIVE IMMUNISATION

5.1 PASSIVE IMMUNISATION USING IMMUNOGLOBULIN PREPARATIONS

Immunoglobulin preparations are used to provide passive immunisation, that is, the direct administration of antibodies to a non-immune person to provide immediate protection against infection or disease.

Immunoglobulin infusions are also indicated for some immunocompromised persons who are antibody-deficient. In addition, immunoglobulins are also used in the treatment of a number of specific immune-mediated conditions in order to modulate the disease course. For further information regarding the use of intravenous immunoglobulins, refer to *Criteria for the clinical use of intravenous immunoglobulin in Australia*[1] (www.nba.gov.au/ivig/index.html).

It is important to recognise that separate immunoglobulin preparations are provided for intramuscular (IM) use and for intravenous (IV) use. These have different properties, and the preparations should be given only by the recommended route. Administration of IM immunoglobulin by the IV route will lead to severe reactions. For more information on intravenous immunoglobulin, refer to *Criteria for the clinical use of intravenous immunoglobulin in Australia*.[1]

There are two types of immunoglobulin:

- normal human immunoglobulin
- specific immunoglobulins.

Normal human immunoglobulin (NHIG) is derived from the pooled plasma of blood donors. It contains antibody to microbial agents that are prevalent in the general population.

Specific immunoglobulin preparations are obtained from pooled blood donations from patients convalescing from the relevant infection, donors recently vaccinated with the relevant vaccine, or those who, on screening, have been found to have sufficiently high antibody concentrations. These blood-derived specific immunoglobulins therefore contain concentrations of antibody to an individual organism or toxin at a higher titre than would be present in normal immunoglobulin.

Donors of blood used for the production of NHIG and specific immunoglobulin products are screened, and the products are treated to minimise the risk of

the immunoglobulin preparations containing HIV, hepatitis A, hepatitis B or hepatitis C viruses, or parvovirus. Two dedicated pathogen inactivation steps are incorporated into the manufacturing process. A pasteurisation step is usually used during manufacture. The risk of prion transmission remains theoretical (see www.transfusion.com.au/adverse_events/risks/estimates for further details).

5.1.1 Availability of immunoglobulins

CSL Limited supplies NHIG for IM use both directly to hospitals and to the Australian Red Cross Blood Service. Rabies immunoglobulin, tetanus immunoglobulin and botulism antitoxin can only be obtained by application to state/territory health authorities. Respiratory syncytial virus (RSV) monoclonal antibody (Synagis; Abbott Australia) is available commercially.

Other specific immunoglobulins (for hepatitis B, cytomegalovirus, tetanus and varicella-zoster), which are derived from Australian donated plasma, can be obtained only from the Australian Red Cross Blood Service with permission from an Australian Red Cross Blood Service medical officer. The Australian Red Cross Blood Service supplies these products free of charge.

The Blood Service can be contacted by telephone nationally on 13 14 95; callers will then be connected to the relevant state or territory Australian Red Cross Blood Service branch.

Individual state or territory contact numbers:

- Australian Capital Territory 02 6206 6024
- New South Wales 1300 478 348
- Northern Territory 08 8928 5116
- Queensland 07 3838 9010
- South Australia 08 8422 1201
- Tasmania 03 6230 6209
- Victoria 03 9694 0200
- Western Australia 08 9421 2869

5.1.2 Transport, storage and handling

Store all immunoglobulins at +2°C to +8°C. Do not freeze. Protect from light.

5.1.3 Normal human immunoglobulin for intramuscular use

Normal human immunoglobulin (NHIG) is prepared by plasma fractionation of blood collected from volunteer donors by the Australian Red Cross Blood Service. It is a sterile solution of immunoglobulin, mainly IgG, and contains those antibodies commonly present in adult human blood. In Australia, NHIG is supplied as a 16% solution and made available through the Australian Red Cross Blood Service.

- ***Normal Immunoglobulin-VF (human)*** (NHIG; for intramuscular use) – CSL Limited. 160 mg/mL immunoglobulin (mainly IgG) prepared from Australian blood donations. Supplied in 2 mL and 5 mL vials. Also contains glycine.

Administration

NHIG should be given by deep IM injection, using an appropriately sized needle. The NHIG should be introduced slowly into the muscle, to reduce pain. This product *must not* be administered intravenously because of possible severe adverse events, and hence an attempt to draw back on the syringe after IM insertion of the needle should be made in order to ensure that the needle is not in a small vessel. A special product for IV use (NHIG [intravenous]) has been developed for patients requiring large doses of immunoglobulin. For further information regarding the use of intravenous immunoglobulins, refer to *Criteria for the clinical use of intravenous immunoglobulin in Australia*.[1]

Recommendations

Immunoglobulin preparations may be given to susceptible persons, as either pre-exposure or post-exposure prophylaxis, against specific infections. Normal pooled immunoglobulin contains sufficiently high antibody concentrations to be effective against hepatitis A and measles. Both hepatitis A and measles are notifiable diseases and further instructions about their management and the need for immunoglobulin can be found in national guidelines (www.health.gov.au/cdnasongs) and obtained from state/territory public health authorities (see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*).

The duration of effect of NHIG is dose-related. It is estimated that protection is maintained for 3 to 4 weeks with standard recommended doses of NHIG.

Prevention of hepatitis A

Hepatitis A vaccination (see 4.4 *Hepatitis A*) is recommended in preference to NHIG for post-exposure hepatitis A prophylaxis in persons ≥12 months of age who are immunocompetent.

NHIG can be used when hepatitis A vaccine administration is contraindicated, in infants <12 months of age, or in persons who are immunocompromised and who might not mount a sufficient response following vaccination.[2] NHIG contains sufficiently high levels of antibody against hepatitis A to be able to prevent or ameliorate infection in susceptible persons, if administered within 2 weeks of exposure.[2]

Prevention of measles

Measles vaccination (see 4.9 *Measles*) within 72 hours of case contact is recommended in preference to NHIG for post-exposure measles prophylaxis in many instances (see Table 4.9.2 in 4.9 *Measles*).

NHIG contains a sufficiently high concentration of antibody against measles to be able to prevent or ameliorate infection in susceptible persons. NHIG should be given as soon as possible and within 7 days of exposure.[3] Passive protection, against measles particularly, may be required if the exposed person has an underlying immunological disorder (HIV/AIDS, immunosuppressive therapy), or to control an outbreak of measles among non-immunised persons, for example, in a childcare centre. The use of NHIG should be considered in HIV-positive persons exposed to a patient with measles.

Immune deficiency

Patients with abnormal antibody production (primary hypogammaglobulinaemia, multiple myeloma, chronic lymphoblastic leukaemia) usually receive therapy with the IV preparation of normal human immunoglobulin (NHIG [intravenous]). However, in some cases, NHIG is given by IM injection. The aim of therapy is to maintain serum IgG levels above 6 g/L. Some patients may receive the IM (160 mg/mL) preparation subcutaneously. For further information regarding the use of intravenous immunoglobulins, refer to *Criteria for the clinical use of intravenous immunoglobulin in Australia*.[1]

Note: Skin tests with NHIG should not be undertaken. The intradermal injection of concentrated immunoglobulin causes a localised area of inflammation, which can be misinterpreted as a positive allergic reaction. True allergic responses to NHIG given by IM injection are extremely rare.

5.1.4 Specific immunoglobulins

Specific immunoglobulins are used to protect against specific microbial agents such as hepatitis B, rabies and varicella-zoster viruses, and tetanus. Further instructions about the management of these diseases and the need for immunoglobulin should be obtained from state/territory public health authorities (see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*), and the national guidelines for management of disease from rabies and other lyssaviruses, including Australian bat lyssavirus (www.health.gov.au/cdnasongs).

Specific immunoglobulins for botulism and cytomegalovirus (CMV) and a monoclonal antibody preparation for respiratory syncytial virus (RSV) are available as described below. Potential interactions, adverse events and storage requirements for these specific immunoglobulins are similar to those for NHIG (IM).

Hepatitis B specific immunoglobulin

Hepatitis B specific immunoglobulin (HBIG) is prepared from plasma donated through routine blood bank collection. Stocks of HBIG are very limited, and use should be strictly reserved for those who are at high risk, such as babies born to mothers with chronic hepatitis B infection and non-immune persons who are exposed through occupational exposure to the blood of unidentified persons, or to persons who are chronically infected with hepatitis B or whose hepatitis status cannot be ascertained in time.[4] Requests for HBIG should be directed to the Australian Red Cross Blood Service in your state/territory (see 5.1.1 *Availability of immunoglobulins* above).

See 4.5 *Hepatitis B*, 'Management of infants born to mothers who are HBsAg-positive' in 4.5.7 *Recommendations* and 4.5.11 *Public health management of hepatitis B*, for more information.

Rabies specific immunoglobulin

Rabies specific immunoglobulin (HRIG) is prepared from the plasma of hyperimmunised human donors. HRIG is only administered in persons who have not received a previous course of rabies vaccine. HRIG is also administered as part of the post-exposure prophylaxis used following potential Australian bat lyssavirus or other lyssavirus exposures in previously unvaccinated persons.[5]

A single dose of HRIG is given to provide localised anti-rabies antibody protection while the patient responds to the rabies vaccine. It should be given at the same time as the 1st post-exposure dose of vaccine (day 0). If not given with the 1st vaccine dose, it may be given up to day 7. From day 8 onwards, an antibody response to rabies vaccine is presumed to have occurred.

The dose of HRIG is based on body mass and should be infiltrated in and around all wounds, using as much of the calculated HRIG dose as possible. The remainder of the HRIG dose should be administered intramuscularly at a site away from the injection site of rabies vaccine.

See 4.16 *Rabies and other lyssaviruses (including Australian bat lyssavirus)* for more information.

Varicella-zoster specific immunoglobulin

Zoster immunoglobulin (ZIG) is highly efficacious, but is often in short supply. Normal high-titre zoster immunoglobulin is available from the Australian Red Cross Blood Service on a restricted basis for the prevention of varicella in high-risk subjects who report a significant exposure to varicella or herpes zoster. If ZIG is unavailable, large doses of NHIG can be given intramuscularly. This does not necessarily prevent varicella, but it lessens the severity of the disease. ZIG has no proven use in the treatment of established varicella or zoster infection. ZIG must be given early in the incubation period (within 96 hours of exposure), but may have some efficacy if administered out to as late as 10 days post exposure. ZIG is able to prevent or ameliorate varicella in infants <1 month of age, in children

who are being treated with immunosuppressive therapy, and in pregnant women.[6,7] Patients suffering from primary or acquired diseases associated with cellular immune deficiency and those receiving immunosuppressive therapy should be tested for varicella-zoster antibodies following contact with a person with confirmed varicella. However, this should not delay ZIG administration, preferably within 96 hours and up to 10 days after initial exposure.[7]

See 4.22 *Varicella* for more information.

Botulism antitoxin

An equine antitoxin (derived from horses) has long been used in the treatment of adult botulism, but has not been shown to be effective in infant botulism.[8] Equine antitoxin is manufactured by pharmaceutical companies such as Chiron. Use in Australia is governed by the Therapeutic Goods Administration's Special Access Scheme and physicians wishing to access this product should initially contact the relevant state/territory health authority (see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*). Hypersensitivity, presenting as fever, serum sickness or anaphylaxis, may follow the use of equine antitoxin. Skin testing followed by appropriate dosing should be administered according to the manufacturer's instructions.

An intravenous botulinum antitoxin, produced in the United States (BabyBIG; its sponsor is the Californian Department of Health Services), significantly reduces the duration of mechanical ventilation and hospitalisation in infant's with botulism.[9] This product has been administered to Australian children with infant botulism.[10] It is not currently registered in Australia, but is registered by the United States Food and Drug Authority. Access to this product should be sought through the TGA's Special Access Scheme.

Cytomegalovirus immunoglobulin

Cytomegalovirus (CMV) immunoglobulin is indicated for the prevention of CMV infection in immunocompromised persons at high risk of severe CMV disease, such as after bone marrow and renal transplants.[11-13] The treatment of established CMV infection and disease is primarily with antivirals, such as ganciclovir or vanciclovir, and there is contradictory evidence whether the addition of CMV immunoglobulin improves outcome.[11,13]

The product contains no antibacterial agent, and so it must be used immediately after opening. Any unused portion must be discarded. If the solution has been frozen, it must not be used. If the use of CMV immunoglobulin is contemplated, detailed protocols for administration and management of adverse events should be consulted, in addition to the product information.

- ***CMV Immunoglobulin-VF (human)*** – CSL Limited. 55–65 mg/mL immunoglobulin (mainly IgG) prepared from human plasma with high levels of antibody to CMV. Single vials contain 1.5 million units of CMV immunoglobulin activity. Contains maltose.

Respiratory syncytial virus monoclonal antibodies

A humanised mouse monoclonal antibody to respiratory syncytial virus (RSV) produced by cultured cells, palivizumab, is registered in Australia for prevention of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease. There is no consensus regarding the use of palivizumab in Australia.[14] This product is given by IM injection each month to children at high risk of severe RSV disease, during the seasonal period of exposure to RSV. Palivizumab has been found to reduce the absolute risk of hospitalisation from about 10% to about 5% for babies born prematurely, for babies with chronic neonatal lung disease, and also for babies with haemodynamically significant congenital heart disease, particularly when complicated by large left-to-right shunts leading to pulmonary hypertension.[14-22] It has not been shown to reduce the incidence of more severe outcomes, such as the need for ventilation, nor has it been shown to reduce mortality.[20,21] There are currently a number of clinical trials assessing a recombinant humanised antibody, motavizumab.[23]

- ***Synagis*** – Abbott Australia (palivizumab). Supplied in single-use vials of powder, to be reconstituted with sterile water for injection; 50 mg in 4 mL vial; 100 mg in 10 mL vial.

The dose of palivizumab is 15 mg/kg once a month, to be given by IM injection, preferably in the anterolateral thigh. Where possible, the 1st dose should be administered before commencement of the RSV season.

Tetanus immunoglobulin

Tetanus immunoglobulin (human) for intramuscular use

Tetanus immunoglobulin (TIG) should be used for passive protection of persons who have sustained a tetanus-prone wound, where the person has not previously received 3 or more doses of a tetanus toxoid-containing vaccine or where there is doubt about their tetanus vaccination status. In persons who have a humoral immune deficiency, TIG should be provided after a tetanus-prone injury, regardless of the time since their last dose of tetanus-containing vaccine. TIG provides immediate protection that lasts for a period of 3 to 4 weeks.[24] For wounds not categorised as tetanus-prone, such as clean cuts, TIG is unnecessary. Detailed information on appropriate tetanus prophylaxis measures in wound management, including use of TIG, are outlined in Table 4.19.1 in 4.19 *Tetanus*.

The recommended dose for TIG is 250 IU, to be given by IM injection as soon as practicable after the injury. If more than 24 hours have elapsed, 500 IU should be given. Because of its viscosity, TIG should be given to adults using a 21 gauge needle. For children, it can be given slowly using a 23 gauge needle. A tetanus toxoid-containing vaccine should be given at the same time in the opposite

limb with a separate syringe, and arrangements should be made to complete the full course of tetanus toxoid-containing vaccinations. Details for accessing TIG should be obtained from the Australian Red Cross Blood Service (see 5.1.1 *Availability of immunoglobulins* above).

Tetanus immunoglobulin (human) for intravenous use

- ***Tetanus Immunoglobulin-VF (human, for intravenous use)*** – CSL Limited. 55–65 mg/mL immunoglobulin (mainly IgG) prepared from human plasma containing high levels of antibody to the toxin of *Clostridium tetani*. Single vials containing 4000 IU human tetanus antitoxin. Contains maltose.

Tetanus immunoglobulin for IV use (TIVG) is used in the management of clinical tetanus.[24] The recommended dose is 4000 IU, to be given by slow intravenous infusion. Detailed protocols for administration of this product and management of adverse events should be consulted if its use is contemplated. Requests for TIVG should be directed to the Australian Red Cross Blood Service in your state/territory (see 5.1.1 *Availability of immunoglobulins* above).

Diphtheria antitoxin

Diphtheria antitoxin is prepared by immunising horses against the toxin produced by *Corynebacterium diphtheriae*.

Advice should be sought with respect to diphtheria antitoxin access and dosage, and special arrangements made if hypersensitivity is suspected; this can be coordinated through the relevant state/territory health authority (see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*).

5.1.5 Potential interaction with vaccines

Live attenuated viral vaccines

Immunoglobulin preparations can interfere with the response to certain live attenuated viral vaccines by preventing vaccine virus replication after administration. Therefore, administration of live attenuated viral vaccines, such as measles and varicella vaccines (but not rotavirus, zoster or yellow fever vaccines), should be deferred, dependent on the clinical status of the patient, for at least 3 months after the IM administration of NHIG, and for at least 8 months after the administration of intravenous NHIG.[25] For detailed information on recommended intervals, see 3.3 *Groups with special vaccination requirements*, Table 3.3.6 *Recommended intervals between either immunoglobulins or blood products and MMR, MMRV or varicella vaccination*. For the same reason, if vaccination has occurred, administration of immunoglobulin products should be

deferred if possible until at least 3 weeks after a measles-containing or varicella-containing vaccine has been given, unless it is essential that immunoglobulin be administered. However, Rh (D) immunoglobulin (anti-D) does not interfere with the antibody response to MMR- or varicella-containing vaccines and the two may be given at the same time in different sites with separate syringes or at any time in relation to each other (see 3.3 *Groups with special vaccination requirements*, Table 3.3.6 *Recommended intervals between either immunoglobulins or blood products and MMR, MMRV or varicella vaccination*).

Inactivated vaccines

Inactivated vaccines, such as tetanus, hepatitis B or rabies, may be administered concurrently with immunoglobulin preparations, or at any time before or after receipt of immunoglobulin, using separate syringes and separate injection sites. This usually would occur when there has been actual or possible acute exposure to one of these infectious agents.

5.1.6 Use in pregnancy

Refer to 3.3 *Groups with special vaccination requirements*, Table 3.3.1 *Recommendations for vaccination in pregnancy* for more information.

5.1.7 Contraindications

Hypersensitivity reactions to immunoglobulin preparations occur rarely but may be more common in patients receiving repeated injections. Intramuscular immunoglobulins should not be administered to persons who have severe thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injections.

5.1.8 Adverse events and precautions

Local tenderness, erythema and muscle stiffness at the site of injection occur very commonly (in over 10% of recipients) and may persist for several hours after injection. Systemic adverse events such as mild pyrexia, malaise, drowsiness, urticaria and angioedema are uncommon, occurring in fewer than 1% of recipients). Skin lesions, headache, dizziness, nausea, general hypersensitivity reactions and convulsions may occur rarely.

Anaphylaxis following an injection of NHIG is very rare, but has been reported. Anaphylaxis is more likely to occur if NHIG for IM use is inadvertently given intravenously.

References

A full reference list is available on the electronic *Handbook* or website www.immunise.health.gov.au

APPENDIX 1: CONTACT DETAILS FOR AUSTRALIAN, STATE AND TERRITORY GOVERNMENT HEALTH AUTHORITIES AND COMMUNICABLE DISEASE CONTROL*

Australian Government health authorities	
Australian Government Department of Health	***02 6289 1555*** Freecall: ***1800 671 811*** www.immunise.health.gov.au
Australian Childhood Immunisation Register enquiries (ACIR)†	***1800 653 809*** ACIR email: acir@humanservices.gov.au ACIR Internet site: www.humanservices.gov.au/customer/services/medicare/australian-childhood-immunisation-register
State and territory government health authorities	
Australian Capital Territory	***02 6205 2300*** Immunisation Enquiry Line
New South Wales	***1300 066 055*** (to connect to your local Public Health Unit)
Northern Territory	***08 8922 8044*** Centre for Disease Control
Queensland	***13 HEALTH*** (13 4325 84) Contact your local Public Health Unit, details at www.health.qld.gov.au/cdcg/contacts.asp
South Australia	***1300 232 272*** (8.30 am to 5.00 pm) Email: CDCB@health.sa.gov.au www.sahealth.sa.gov.au
Tasmania	***03 6222 7666*** or ***1800 671 738***
Victoria	***1300 882 008*** Email: immunisation@health.vic.gov.au www.health.vic.gov.au/immunisation
Western Australia	***08 9388 4868*** ***08 9328 0553*** (after hours Infectious Diseases Emergency) Email: cdc@health.wa.gov.au
Contact details for communicable disease control	
Australian Capital Territory	24-hour Communicable Disease Control Section: ***02 6205 2155***
New South Wales	***1300 066 055*** (for connection to Public Health Unit)

Northern Territory	8.30 am to 5.00 pm: ***08 8922 8044*** Centre for Disease Control (After hours Royal Darwin Hospital ***08 8922 8888*** for CDC on-call doctor)
Queensland	***Contact your local Public/Population Health Unit***, phone number listed in the White Pages
South Australia	24 hour general enquiries line: ***1300 232 272***
Tasmania	24 hour hotline: ***1800 671 738***
Victoria	24 hour contact number: ***1300 651 160***
Western Australia	Perth Metropolitan area: ***08 9388 4852*** After hours/Emergency: ***08 9328 0533*** Outside Perth Metropolitan area: Contact regional Population Health Unit

* See also state/territory and Therapeutic Goods Administration (TGA) contact details for reporting AEFI in Table 2.3.3 *Contact information for notification of adverse events following immunisation* in 2.3.2 *Adverse events following immunisation*.

† For more information on other registers, see 2.3.4 *Immunisation registers*.

APPENDIX 2: LITERATURE SEARCH STRATEGY FOR THE 10TH EDITION OF THE *HANDBOOK*

For each *Handbook* chapter, broad literature searches were conducted for the years since the last *Handbook* searches were performed, using up to 24 databases, listed in Table A2.1. The purpose of these searches was to ensure that NCIRS technical writers and ATAGI members had access to all relevant information from the latest medical literature to allow identification of important issues related to the updating of all *Handbook* chapters. In addition, since writing of the 9th edition of the *Handbook*, Selected Dissemination Information (SDI) searches were established to enable the ongoing collection of new relevant items on the search topics. This process used the same search strategies as previously described, which allowed consideration and inclusion of papers published since publication of the 9th edition *Handbook*.

Table A2.1: Electronic databases searched for the 10th edition

Electronic database	Time period
MEDLINE	2006–2011
Cochrane Library – including Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), Methods Studies, the Health Technology Assessment Database, the NHS Economic Evaluation Database	2006–2011
Cumulated Index Nursing & Allied Health Literature (CINAHL) (when required)	2006–2011
Clinical Evidence	2006–2011
EMBASE	2006–2011
Australian focused Informit databases (AMI, APA-FT, APAIS, APAIS - Health, ATSIhealth, Ausport Med, CINCH - Health, DRUG, Health and Society, HIVA, Health Collection, Indigenous Collection, RURAL, SAGE)	2006–2011

Searches were conducted using the electronic databases detailed in Table A2.1, with the search period from 2006 to October 2011, in order to retrieve items published since the searches completed for the 9th edition of the *Handbook*. The scope of the searches was broad, to ensure maximum retrieval and minimise the exclusion of items of interest. Previous *Handbook* searches were examined to determine the scope required for the new searches, and similar search strategies

were employed to ensure consistency of information retrieval, taking into account new terms added to the databases.

Various search methods were tested, including 'explode' and 'focus' options. 'Exploded' terms retrieve citations containing the term being searched and all the narrower related terms in the database. 'Focus' searches retrieve citations that have the search term as the major focus of the item. In the trial searches, some items of interest were missed using the 'focus' method, thus 'exploded' searches were utilised. All subheadings assigned to the subject headings were generally included. In general, the search strategy consisted of the disease topic and relevant vaccine terms, used in combination with the terms immunisation/immunisation programs. Boolean operators AND, OR and NOT were used as appropriate. To ensure relevant and accurate retrieval, thesaurus terms (the controlled vocabulary terms used in the database) were used whenever possible. Keyword searching was used in the absence of an appropriate thesaurus term or if the database did not have thesaurus terms. To facilitate relevant retrieval and to limit what, in some instances, are very large search result sets, the following limits were applied to the disease topic searches:

- Publication year – searches were generally limited to items published from 2006–2011.
- Language – searches were limited to items in English.
- Human – items discussing only animals were removed.
- In vitro – items discussing only in vitro studies were removed.
- Abstracts – search results restricted to items containing abstracts.

The search limits were slightly modified for some of the searches. For example, the Australian-specific searches did not have search results limited to abstract only, to ensure that all Australian items were retrieved.

The ATAGI and NCIRS technical writers also identified, where possible, focused clinical questions for each of the *Handbook* chapters, in advance of conducting literature searches. Specific searches were conducted for these questions, both using the databases and time periods above, but also using additional databases, longer time periods and other strategies, such as clinical trial registries and handsearching, as necessary.

APPENDIX 3: COMPONENTS OF VACCINES USED IN THE NATIONAL IMMUNISATION PROGRAM

Please note that vaccine manufacture is subject to ongoing refinement and change. Therefore, the information in Table A3.1 may change. This information was current as of mid-2012 and has been sourced from the product information (PI) of each vaccine listed. The Therapeutic Goods Administration provides the most current versions of the PI and Consumer Medicines Information (CMI) documents for vaccines (and other medicines) on its website at www.tga.gov.au.

For vaccines *not* listed in the National Immunisation Program, please refer to individual product information leaflet as supplied with the vaccine, or the *Handbook* chapter pertinent to that vaccine.

None of the vaccines listed on the National Immunisation Program contains thiomersal.

Table A3.1: Components of vaccines used in the National Immunisation Program

Vaccine component*	Vaccine brand†	Antigen
Albumin/serum	Avaxim	Hepatitis A (HAV)
	ProQuad	Measles-mumps-rubella-varicella (MMRV)
	Quadracel	Diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis (DTPa-IPV)
	Vaqta	Hepatitis A (HAV) paediatric/adolescent
	Varilrix	Varicella (VV)
	Varivax Refrigerated	Varicella (VV)
Aluminium hydroxide	Avaxim	Hepatitis A (HAV)
	Cervarix	Human papillomavirus (HPV)
	Engerix-B	Hepatitis B (HBV) adult and paediatric
	Havrix Junior	Hepatitis A (HAV) paediatric
	H-B-Vax II	Hepatitis B (HBV) adult and paediatric
	Infanrix IPV	Diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis (DTPa-IPV)
	Menjugate Syringe	Serogroup C meningococcal conjugate (MenCCV)
	NeisVac-C	Serogroup C meningococcal conjugate (MenCCV)
	Vaqta	Hepatitis A (HAV) paediatric/adolescent

Vaccine component*	Vaccine brand†	Antigen
Aluminium hydroxide/ phosphate	Boostrix	Diphtheria-tetanus-acellular pertussis (dTpa) reduced antigen
	Gardasil	Human papillomavirus (HPV)
	Infanrix hexa	Diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliomyelitis-*Haemophilus influenzae* type b (DTPa-hepB-IPV-Hib)
Aluminium phosphate	Adacel	Diphtheria-tetanus-acellular pertussis (dTpa) reduced antigen
	Meningitec	Serogroup C meningococcal conjugate (MenCCV)
	Prevenar 13	13-valent pneumococcal conjugate (13vPCV)
	Quadracel	Diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis (DTPa-IPV)
Borax/sodium borate	Gardasil	Human papillomavirus (HPV)
	Vaqta	Hepatitis A (HAV) paediatric/adolescent
Egg protein	***All influenza vaccines***	
	Agrippal	Influenza
	Fluarix	Influenza
	Fluvax	Influenza
	Influvac	Influenza
	Vaxigrip	Influenza
Formaldehyde	Adacel	Diphtheria-tetanus-acellular pertussis (dTpa) reduced antigen
	Agrippal	Influenza
	Avaxim	Hepatitis A (HAV)
	Boostrix	Diphtheria-tetanus-acellular pertussis (dTpa) reduced antigen
	Fluarix	Influenza
	Havrix Junior	Hepatitis A (HAV) paediatric
	Infanrix hexa	Diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliomyelitis-*Haemophilus influenzae* type b (DTPa-hepB-IPV-Hib)
	Infanrix IPV	Diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis (DTPa-IPV)
	Influvac	Influenza
	Quadracel	Diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis (DTPa-IPV)
	Vaqta	Hepatitis A (HAV) paediatric/adolescent
	Vaxigrip	Influenza

Vaccine component*	Vaccine brand†	Antigen
Gelatin	ProQuad	Measles-mumps-rubella-varicella (MMRV)
	Varivax Refrigerated	Varicella (VV)
Gentamicin	Fluarix	Influenza
	Influvac	Influenza
Glutaraldehyde	Adacel	Diphtheria-tetanus-acellular pertussis (dTpa) reduced antigen
	Quadracel	Diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis (DTPa-IPV)
Kanamycin	Agrippal	Influenza
Mannitol	Priorix	Measles-mumps-rubella (MMR)
	Priorix-tetra	Measles-mumps-rubella-varicella (MMRV)
Monosodium glutamate (MSG)	ProQuad	Measles-mumps-rubella-varicella (MMRV)
	Varivax Refrigerated	Varicella (VV)
Neomycin	Agrippal	Influenza
	Avaxim	Hepatitis A (HAV)
	Fluvax	Influenza
	Havrix Junior	Hepatitis A (HAV) paediatric
	Infanrix hexa	Diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliomyelitis-*Haemophilus influenzae* type b (DTPa-hepB-IPV-Hib)
	Infanrix IPV	Diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis (DTPa-IPV)
	Priorix	Measles-mumps-rubella (MMR)
	Priorix-tetra	Measles-mumps-rubella-varicella (MMRV)
	ProQuad	Measles-mumps-rubella-varicella (MMRV)
	Quadracel	Diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis (DTPa-IPV)
	Vaqta	Hepatitis A (HAV) paediatric/adolescent
	Varilrix	Varicella (VV)
	Varivax Refrigerated	Varicella (VV)
	Vaxigrip	Influenza
Phenol	Pneumovax 23	23-valent pneumococcal polysaccharide (23vPPV)
Phenoxyethanol	Adacel	Diphtheria-tetanus-acellular pertussis (dTpa) reduced antigen
	Avaxim	Hepatitis A (HAV)
	Quadracel	Diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis (DTPa-IPV)

Vaccine component*	Vaccine brand†	Antigen
Polymyxin	Fluvax	Influenza
	Infanrix hexa	Diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliomyelitis-*Haemophilus influenzae* type b (DTPa-hepB-IPV-Hib)
	Infanrix IPV	Diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis (DTPa-IPV)
	Quadracel	Diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis (DTPa-IPV)
Polysorbate or sorbitol	Agrippal	Influenza
	Boostrix	Diphtheria-tetanus-acellular pertussis (dTpa) reduced antigen
	Fluarix	Influenza
	Gardasil	Human papillomavirus (HPV)
	Havrix Junior	Hepatitis A (HAV) paediatric
	Infanrix hexa	Diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliomyelitis-*Haemophilus influenzae* type b (DTPa-hepB-IPV-Hib)
	Infanrix IPV	Diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis (DTPa-IPV)
	Influvac	Influenza
	Prevenar 13	13-valent pneumococcal conjugate (13vPCV)
	Priorix	Measles-mumps-rubella (MMR)
	Priorix-tetra	Measles-mumps-rubella-varicella (MMRV)
	ProQuad	Measles-mumps-rubella-varicella (MMRV)
	Quadracel	Diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis (DTPa-IPV)
	RotaTeq	Rotavirus
Yeast	Engerix-B	Hepatitis B (HBV) adult and paediatric
	Gardasil	Human papillomavirus (HPV)
	H-B-Vax II	Hepatitis B (HBV) adult and paediatric
	Infanrix hexa	Diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliomyelitis-*Haemophilus influenzae* type b (DTPa-hepB-IPV-Hib)

* If the person to be vaccinated has had an anaphylactic reaction to any of the vaccine components, administration of that vaccine may be contraindicated. Specialist advice should be sought to identify the component and to review if the person can be vaccinated in future.

† Please also refer to Appendix 4 *Commonly asked questions about vaccination* for more specific information about these various constituents.

APPENDIX 4: COMMONLY ASKED QUESTIONS ABOUT VACCINATION

This appendix contains information for providers to refer to when responding to questions and concerns about immunisation. It covers general questions on adult and childhood vaccination, including contraindications and precautions. In addition, a discussion on some of the more recent concerns about vaccination is included, covering issues relating to vaccine safety, vaccine content, immunisation as a possible cause of some illnesses of uncertain origin, and the need for vaccination.

This appendix is divided into six sections:

- General questions
- Questions about contraindication and precautions
- Questions about vaccine safety
- Questions about vaccine content
- Questions about the need for immunisation
- Further information about vaccination

A.4.1 General questions

How does vaccination work?

When a healthy person becomes infected with a virus or bacteria (also known as a pathogen), for example, the measles virus, the body recognises the virus as an invader, produces antibodies that eventually destroy the virus, and recovery occurs. If contact with the measles virus occurs again in the future, the body's immune system 'remembers' the measles virus and produces an increase in antibodies to destroy this pathogen.

Vaccination is the process that is used to stimulate the body's immune system in the same way as the real pathogen or disease would, but without causing the symptoms of the disease. Most vaccines provide the body with 'memory' so that an individual does not get the disease if exposed to it (see 1.5 *Fundamentals of immunisation*).

Vaccination conveys immunity to diseases by a process called active immunity, which can be achieved by administration of either inactivated (i.e. not live) or live attenuated pathogens or their products. Live vaccines are attenuated, or weakened, by growing the organism through serial culturing (or passaging) steps in various tissue culture media. Inactivation is usually done using heat or formalin (sometimes both). Inactivated vaccines may include the whole pathogen (such as oral cholera vaccine), the toxin produced by the pathogen (such as tetanus and diphtheria vaccines), or specific antigens (such as *Haemophilus influenzae* type b [Hib], meningococcal and pneumococcal

vaccines). In some cases, the antigen is conjugated (i.e. chemically linked) with proteins to facilitate the immune response. Inactivated viral vaccines may include whole viruses (such as inactivated poliomyelitis vaccine [IPV] and hepatitis A vaccines) or specific antigens (such as influenza and hepatitis B vaccines). Live attenuated viral vaccines include measles-mumps-rubella (MMR), varicella and yellow fever vaccines.

Immunity can also be acquired passively by the administration of immunoglobulins, which are the same as antibodies (see 1.5 *Fundamentals of immunisation*). Such immunity is immediate and is dose-related and transient. For example, measles or hepatitis B immunoglobulin can be used promptly after exposure in an unimmunised person to help reduce the chance of getting measles or hepatitis B disease from the exposure.

What is the correct site for vaccination?

The top, outer part of the thigh (the vastus lateralis muscle) is the recommended site for injections for infants <12 months of age. The deltoid region of the upper arm is the recommended site for vaccination of all persons aged ≥12 months, because it is associated with fewer local reactions and, in younger children, has sufficient muscle bulk to facilitate the injection. However, the vastus lateralis muscle can also be used in both young children and, where absolutely necessary, adults.

The ventrogluteal area is an alternative site in children. (See 2.2.6 *Recommended injection sites* and 2.2.8 *Identifying the injection site*).

Rotavirus vaccines are administered by the oral route and must *never* be injected.

How many injections can be given into the same limb, particularly in a child aged <12 months?

More than one vaccine can be safely administered into a limb at the same immunisation visit in either children or adults (See 2.2.9 *Administering multiple vaccine injections at the same visit*).

Where more than one injection is required into the one limb, the injections should be given at least 25 mm (2.5 cm) apart. Use separate sterile injection equipment for each vaccine administered. The accompanying documentation should indicate clearly which vaccines were given into which site (e.g. left arm upper/ left arm lower).

Most Australian states and territories have routine immunisation schedules that include at least two injections during the primary course for children <12 months of age. In this case, injections can be given into either the same leg, into the vastus lateralis muscle, or the second injection can be given into the other vastus lateralis muscle; an alternative is the ventrogluteal site.

When should preterm infants be vaccinated?

Babies born at <32 weeks gestation or <2000 g birth weight should receive their 1st dose of hepatitis B vaccine either at birth (within the first few days of life) or at 2 months of age. The routine 2-month vaccines containing the antigens diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus-*Haemophilus influenzae* type b (DTPa-hepB-IPV-Hib), *Streptococcus pneumoniae* (13vPCV) and rotavirus should be given 2 months after birth as normal, unless an infant is very unwell. 'Very unwell' can be interpreted in many ways, but, in general, reflects that the premature neonate is particularly medically unstable. Delaying the 2-month vaccines is rarely required. If any preterm infant has the *2-month vaccines* delayed, it should be remembered that the subsequent infant doses can be given 1 month apart rather than 2 months. Hence, if an infant receives the 2-month vaccines at 3 months of age then the 4-month vaccines should still be given at 4 months of age. However, the 3rd dose of DTPa-hepB-IPV-Hib should not be given before 6 months of age. Further explanation of the special immunisation needs of premature babies is provided in 3.3.2 *Vaccination of women who are planning pregnancy, pregnant or breastfeeding, and preterm infants.*

Do elderly people (>65 years) who have no chronic illnesses need the influenza vaccine?

Yes. Age is an independent risk factor for severe influenza. Vaccination of those aged >65 years, regardless of the presence or absence of chronic illness, reduces mortality during the winter period in this age group (see 4.7 *Influenza*). The healthy elderly should also receive the 23-valent pneumococcal polysaccharide vaccine (see 4.13 *Pneumococcal disease).*

Should adults receive pertussis (whooping cough) vaccine boosters?

Yes. Two brands of acellular pertussis vaccines, both combined with tetanus and diphtheria antigens, are now available for adolescents and adults. dTpa vaccines are recommended in Australia for booster vaccination of individuals ≥10 years of age who have previously had a primary course of diphtheria-tetanus-pertussis vaccine. dTpa vaccines have a lower content of diphtheria and pertussis antigens than DTPa formulations for young children.

A recent study showed that adults can be protected against pertussis after a single dose of dTpa. No recommendations about the need for further boosters using reduced antigen content formulation dTpa have been made at this time.

A single dose of dTpa is recommended for the following groups, unless contraindicated or if they have already received a previous dose of dTpa in the last 10 years (or 5 years when specifically indicated, see 4.12 *Pertussis*):

- adults working with young children; vaccination is especially recommended for those working in early childhood education and care
- all healthcare workers

- adults planning a pregnancy, or both parents as soon as possible after delivery of an infant (preferably before hospital discharge)

  Pregnant women can also be vaccinated during the last trimester of pregnancy, as an alternative to getting vaccinated straight after delivery. This allows for antibodies to be transferred to the infant during the pregnancy – this particularly helps to protect the infant against pertussis. Other adult household members, grandparents and carers of young children should also be vaccinated. This recommendation is based on evidence from several studies of infant pertussis cases, in which family members, particularly parents, were identified as the source of infection in more than 50% of cases, and were the presumed source in a higher proportion.
- any adult expressing an interest in receiving a booster dose of dTpa.

Adults ≥50 years of age who have not previously received dTpa vaccine should also be offered vaccination (see 4.2 *Diphtheria*, 4.12 *Pertussis* or 4.19 *Tetanus* in this *Handbook*).

Contraindications to the reduced antigen content formulation dTpa are discussed in 4.2 *Diphtheria*, 4.12 *Pertussis* and 4.19 *Tetanus* in this *Handbook* and include previous anaphylactic reaction to any vaccine component.

If the patient has never received a primary course of dT, see 4.2 *Diphtheria*, 4.12 *Pertussis* or 4.19 *Tetanus* in this *Handbook*.

A person wants to receive his/her vaccines separately. Why can't they do this?

There is no scientific evidence or data to suggest that there are any benefits in receiving vaccines such as MMR as separate monovalent vaccines. Using the example of MMR vaccine, there is no individual mumps, measles or rubella vaccine approved for use in Australia. If these vaccines were to be administered individually, it would require three separate vaccines, which would unnecessarily increase discomfort for the child. In addition, if these monovalent vaccines were not given on the same day, they would need to be spaced 1 month or more apart, which would increase the risk of that person being exposed to serious vaccine-preventable diseases. A policy of providing separate vaccines would cause some people to not receive the entire course. Combination vaccines can offer a reduced amount of vaccine preparation to be injected overall, compared to three individual vaccine doses.

Is vaccination compulsory? What happens if children do not get vaccinated?

Vaccination is not compulsory in Australia.

Eligibility for the Family Tax Benefit Part A supplement will require either that children are assessed as fully immunised or that the parent has obtained an appropriate medical or philosophical exemption. This replaced the Maternity Immunisation Allowance on 1 July 2012.

If a parent decides not to have a child vaccinated and, if cases of certain vaccine-preventable diseases occur at that child's day-care centre or school, the parent may, in some circumstances, be required to keep the unvaccinated child at home until the incubation period for that particular disease has passed or no further cases have occurred in that setting.

A4.2 Questions about contraindications and precautions

If a person has any concerns about whether to proceed with vaccination, they should be provided with appropriate information and encouraged to obtain expert advice from their usual immunisation provider or an immunisation specialist, if necessary. See Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control* for contact details.

What are the absolute contraindications to childhood vaccination?

True contraindications to vaccines are extremely rare (see relevant chapters), and include only anaphylaxis to any of the particular vaccine's components, and anaphylaxis following a previous dose of that vaccine. Follow-up specialist medical advice should always be sought if any severe reaction or anaphylaxis has occurred following the administration of any vaccine(s).

Note: Anaphylaxis following ingestion of eggs does not contraindicate MMR vaccine, as the vaccine viruses are not grown in eggs and the vaccine does not contain any egg protein (see 4.9 *Measles*). Many persons who have a history of a severe allergic reaction to eggs can also be vaccinated with influenza vaccine (see 4.7 *Influenza*).

Can someone who has had whooping cough (pertussis) still be vaccinated?

Vaccination with pertussis vaccine in children, adolescents or adults who have had laboratory-confirmed pertussis infection is safe and is necessary, as natural immunity does not confer life-long protection. In particular, incompletely vaccinated infants <6 months of age who develop pertussis may not mount an adequate immune response following infection and should receive all routinely scheduled vaccines, including pertussis-containing vaccines (see 4.12 *Pertussis*).

What are the precautions to vaccination?

In general, persons with impaired immunity or on immunosuppressive therapy, or pregnant women, should not be given live vaccines. However, any general concerns that the person to be vaccinated or the parent/carer holds should always be fully discussed prior to the administration of any vaccine.

Should a person with an intercurrent illness be vaccinated?

A child or adult with a minor illness (without systemic illness and with a temperature <38.5°C) may be safely vaccinated. People, including infants, toddlers and teenagers with minor coughs and colds without fever, or those receiving antibiotics in the recovery phase of an acute illness, can be vaccinated safely and effectively. In a person with a major illness or high fever ≥38.5°C, vaccination should be postponed until they are well. If vaccination were to be carried out during such an illness, the fever might be confused with vaccine side effects and might also increase discomfort to the person. In such cases, it is advisable to defer vaccination and arrange for the person to return for vaccination when well again (see Table 2.1.2 *Responses to relevant conditions or circumstances identified by the pre-vaccination screening checklist*).

Should persons with epilepsy be vaccinated?

Yes. Stable neurological conditions (such as epilepsy) are not a reason to avoid giving any vaccines, including pertussis (whooping cough). Children and adults who are prone to fits should have paracetamol before and for 48 hours after vaccination to reduce the chance of a fever after vaccination bringing on a convulsion. A family history of fits or epilepsy is not a reason to avoid vaccination.

Should persons with a neurological disease or conditions receive the normal vaccination schedule?

Yes. Persons with a neurological disease are often at increased risk of complications from diseases like measles, influenza and whooping cough, as they can be more prone to respiratory infections and chest problems. It is important that these children be immunised, on time, as recommended in the National Immunisation Program schedule.

Are steroids a contraindication to vaccination?

Live vaccines, such as MMR, measles-mumps-rubella-varicella (MMRV), bacille Calmette-Guérin (BCG) and varicella-zoster vaccines, should *not* be given to children or adults receiving high-dose oral or parenteral corticosteroid therapy for more than 1 week. High-dose oral corticosteroid therapy is defined as more than 2 mg/kg per day prednisolone for more than 1 week in children, or more than 60 mg per day for more than 1 week in adults. This is because steroids, in large doses, greatly suppress the immune system, which means that, not only is the vaccine unlikely to be effective, but there is an increased chance of an adverse event occurring as a result of the immunosuppression (see 3.3.3 *Vaccination of immunocompromised persons*).

Inactivated vaccines, for example, DTPa-hepB-IPV-Hib or hepatitis B, may be less effective in this group, but are not contraindicated. Therapy with inhaled steroids is not a contraindication to vaccination.

Should vaccines be given to persons who have problems with their immune systems?

Persons who are immunocompromised (from either a disease or medical treatment) should generally *not* be given live viral vaccines such as MMR, MMRV, varicella, zoster or rotavirus vaccines (see 4.9 *Measles*, 4.22 *Varicella*, 4.24 *Zoster* and 4.17 *Rotavirus*).

HIV-infected persons may be given MMR, varicella and zoster vaccines, provided they do not have severe immunocompromise (see 3.3 *Groups with special vaccination requirements* and Table 3.3.4 *Categories of immunocompromise in HIV-infected persons, based on age-specific CD4⁺ counts and percentage of total lymphocytes*). The close contacts of persons who are immunocompromised can be given live viral vaccines, except oral polio vaccine, which is no longer used in Australia.

The rash seen in a small percentage of MMR vaccine recipients, usually between 5 and 12 days after vaccination, is not infectious. Non-immune household contacts of persons who are immunocompromised should receive varicella vaccine. There is an almost negligible risk of transmitting varicella vaccine virus from a vaccine-related vesicular rash to contacts. However, vaccine-related rash occurs in 3 to 5% of vaccinated persons, either locally at the injection site or generalised, with a median of only 25 lesions. This small infection risk of the less virulent attenuated vaccine strain is far outweighed by the high risk of non-immune contacts catching wild varicella infection and transmitting the virus to the immunocompromised household member via respiratory droplets or from the large number of skin lesions that occur with wild varicella infection (a median of 300 to 500 lesions).

Live viral vaccines can be given to persons with leukaemia and other malignancies at least 3 months after they have completed chemotherapy, provided there are no concerns about their immune status. Such measures would normally be carried out under the supervision of the person's oncologist (see 3.3.3 *Vaccination of immunocompromised persons*).

What vaccines should someone with HIV infection receive?

Persons with HIV (human immunodeficiency virus) infection, especially children, should have all routine *inactivated* vaccines on the National Immunisation Program schedule. Varicella vaccine is contraindicated in persons with HIV who are significantly immunocompromised, as it can cause disseminated varicella infection. However, it may be considered for asymptomatic or mildly symptomatic HIV-infected children, after weighing up the potential risks and benefits. This should be discussed with the child's specialist. MMR vaccine can be given to children with HIV, depending on their CD4⁺ counts (see 'Should vaccines be given to persons who have problems with their immune systems?' above). Persons with HIV infection should also be vaccinated against pneumococcal disease (see 4.13 *Pneumococcal disease*). Influenza vaccine is also recommended for HIV-infected persons. They should

not be given BCG, due to the risk of disseminated infection. More detailed information on the use of vaccines in persons with HIV is included in 3.3.3 *Vaccination of immunocompromised persons*.

Should chronically ill persons be vaccinated?

In general, persons with chronic diseases should be vaccinated as a matter of priority, because they are often more at risk from complications from vaccine-preventable diseases. Annual influenza vaccine is highly recommended for chronically ill persons and their household contacts.

Care is needed with the use of live attenuated viral vaccines in situations where the person's illness, or its treatment, may result in impaired immunity. Advice may need to be sought on these patients to clarify the safety of live viral vaccine doses.

Should children or household contacts be vaccinated while the child's mother is pregnant?

There is no problem with giving routine vaccinations to a child, or others, living in the same household with a pregnant woman. MMR vaccine viruses are not transmissible. Administration of varicella vaccine to household contacts of non-immune pregnant women is safe. Transmission of varicella vaccine virus is very rare. There is an almost negligible risk of transmitting varicella vaccine virus from a vaccine-related vesicular rash to contacts. However, vaccine-related rash occurs in 3 to 5% of vaccinated persons, either locally at the injection site or generalised, with a median of only 25 lesions. Furthermore, vaccinating the child of a pregnant mother will reduce the risk of her being infected by her offspring with the more virulent wild virus strain if she is not immune (see 3.3.2 *Vaccination of women who are planning pregnancy, pregnant or breastfeeding, and preterm infants*).

Should persons with allergies be vaccinated? What precautions are required for atopic or egg-sensitive children or adults?

Depending on the allergy identified, there often may *not* be a contraindication to vaccination. Specialist medical advice should always be sought in order to determine which vaccinations can be safely given. For example, a history of an allergy to antibiotics most commonly relates to β-lactam, or related antibiotics, and is not a contraindication to vaccines that contain neomycin, polymyxin B or gentamicin. Previous reactions to neomycin that only involved the skin are not considered a risk factor for a severe allergic reaction or anaphylaxis to vaccines manufactured with neomycin, since there are only trace amounts of this antibiotic in the final product (see 3.3.1 *Vaccination of persons who have had an adverse event following immunisation*).

For other allergies, see Appendix 3, *Components of vaccines used in the National Immunisation Program*, and the relevant vaccine product information (PI) enclosed in the vaccine package. Unless the person being vaccinated has an allergy to a specific constituent of a vaccine (or has another contraindication), there is no

reason not to vaccinate. Asthma, eczema and hay fever are not contraindications to any vaccine, unless the child/adult is receiving high-dose oral steroid therapy.

Persons with egg allergies can receive MMR vaccines because the measles and mumps components of MMR vaccine do not contain sufficient amounts of egg ovalbumin to contraindicate MMR vaccination of people with egg allergy (even anaphylaxis) (see 3.3.1 *Vaccination of persons who have had an adverse event following immunisation* and 4.9 *Measles*). A simple dislike of eggs, or having diarrhoea or stomach pains after eating eggs, are not reasons to avoid MMR vaccination, and no special precautions are required in these circumstances. These persons can also have all other routine vaccines without special precautions.

A history of anaphylaxis or allergy to egg had previously been considered an absolute contraindication to influenza vaccination, but there have now been a number of studies indicating that the majority of such persons can be safely vaccinated.[1,2] Given that there is still a small risk of anaphylaxis, it is essential that such persons are vaccinated in facilities with staff able to recognise and treat anaphylaxis. (See also 4.7 *Influenza*.)

Yellow fever, Q fever and one of the available rabies vaccines contain a higher amount of egg albumin than is present in the currently available influenza vaccines. Persons with egg allergy requiring vaccination with either yellow fever, rabies or Q fever vaccines, should seek specialist immunisation advice from their state or territory health department. See also relevant chapters of this *Handbook*.

Families with questions about allergies and vaccines are encouraged to discuss this with their immunisation service provider and, where necessary, seek referral to an immunologist to have any questions promptly answered to avoid unnecessary delays of vaccine doses or referral to a specialist immunisation clinic. Information on specialist immunisation clinics is available from your local state or territory health department. (See Appendix 1 for further details.)

A4.3 Questions about vaccine safety

Some people have concerns about immunisation. These mostly relate to whether the vaccine is safe and whether vaccines weaken the immune system. Providers should always listen to and acknowledge people's concerns. Providers should discuss the risks and benefits of immunisation with parents/carers honestly and in a non-defensive manner. Parents/carers and adult vaccine recipients should receive accurate information on the risks from vaccine-preventable diseases and information about vaccine side effects and adverse events (see table *Comparison of the effects of diseases and the side effects of NIP vaccines* inside the back cover of this *Handbook*). The following section responds to some concerns raised about the safety of immunisation, and examines the scientific evidence in order to assist providers and parents in making an informed choice about the risks and benefits of vaccination.

How safe are vaccines?

Before vaccines are made available for general use they are tested for safety and efficacy in clinical trials and then in large trials, otherwise known as phase II (2) and III (3) trials. All vaccines marketed in Australia are manufactured according to strict safety guidelines and are evaluated by the Therapeutic Goods Administration, to ensure they are efficacious and are of adequate quality and safety, before marketing approval is granted.

After vaccines are introduced into vaccination schedules, they are subjected to continuing surveillance of efficacy and safety through trials and post-marketing surveillance. In Australia, there are regional and national surveillance systems actively seeking any adverse events following immunisation. This is necessary, as sometimes unexpected side effects occur after vaccines are registered for use. Australian reports on adverse events that occur following immunisation are published on a 6-monthly basis in the journal *Communicable Diseases Intelligence* (www.health.gov.au/internet/main/publishing.nsf/content/cda-pubs-cdi-cdiintro.htm).

Can too many vaccines overload or suppress the natural immune system?

No. Although the increase in the number of vaccines and vaccine doses given to children has led to concerns about the possibility of adverse effects of the aggregate vaccine exposure, especially on the developing immune system, there is not a problem. In day-to-day life, all children and adults confront enormous numbers of antigens, and the immune system responds to each of these in various ways to protect the body. Studies of the diversity of antigen receptors indicate that the immune system can respond to an extremely large number of antigens. In addition, the number of antigens received by children during routine childhood vaccination has actually decreased compared with several decades ago. This has occurred in spite of the increase in the total number of vaccines given, and can be accounted for by the removal of two vaccines – smallpox vaccine (which contained about 200 different proteins), and whole-cell pertussis vaccine (about 3000 distinct antigenic components) from routine vaccination schedules. In comparison, the acellular pertussis vaccine currently used in Australia has only 3 to 5 pertussis antigens.[3]

Do vaccines cause disease?

Some studies have suggested a temporal link between vaccinations and certain medical conditions, such as asthma, multiple sclerosis and diabetes. The questions of a link are often made for a disease of unknown cause. The appearance of a certain medical condition after vaccination does not necessarily imply that they are causally related. Importantly, however, once an issue is raised it needs prompt research, discussion and then education to avoid creating a myth. In many cases, subsequent epidemiological studies have indicated that the association is due to chance alone. The following is a list of concerns that have been raised.

Does MMR vaccine cause inflammatory bowel disease or autistic spectrum disorder?

No.

In 1998, Wakefield et al. (Royal Free Hospital, London) published a case-series study with 12 children suggesting that MMR vaccine caused inflammatory bowel disease (IBD), which then resulted in decreased absorption of essential vitamins and nutrients through the intestinal tract. They proposed that this could result in developmental disorders such as autism. *The Lancet* retracted this publication in 2010 and the British Medical Council struck off the lead author in 2010, following the British General Medical Council's Fitness to Practice Panel finding the author 'guilty of serious professional misconduct'.

An extensive review published in 2004 by the Institute of Medicine (IOM), an independent expert body in the United States, concluded that there is no association between the MMR vaccine and the development of autism. A 2011 update by the IOM continues to reject any causal association between MMR vaccine and autism (see www.iom.edu/vaccineadverseeffects).

See 4.9 *Measles* for further information. There is also an MMR vaccine decision aid designed for parents available at www.ncirs.edu.au/decisionaid/index.html.

Do childhood immunisations cause asthma?

There is no evidence that vaccination causes or worsens asthma. It is especially important that children with asthma be vaccinated like other children, as catching a disease like whooping cough can make an asthma attack worse. Although influenza vaccine is not routinely recommended for all asthmatics, it is recommended for severe asthmatics, such as those requiring frequent hospitalisation (see 4.7 *Influenza*).

Does influenza vaccine cause flu?

No. It is not possible for influenza vaccine to cause 'flu' as it is not a live viral vaccine. (*Note*: a live attenuated influenza vaccine is used in some countries, but not in Australia.) As some people experience side effects such as a mild fever after the vaccine, it is understandable that they may confuse these symptoms with actually having the flu. In addition, the influenza vaccine is recommended to be given at the commencement of the flu season. Hence, it is possible that a person who has contracted, and is incubating, influenza during vaccination will mistakenly believe the vaccine to be causal. In addition, influenza vaccine is given at the very time of year when there are a lot of upper respiratory tract infections (URTIs) around. It is not uncommon for someone to attribute an URTI within a week of an influenza vaccine to the vaccine dose. Importantly, URTI symptoms occurring after influenza vaccine should not put people off having the vaccine the following year.

A4.4 Questions about vaccine content[4]

See also Table A3.1 *Components of vaccines used in the National Immunisation Program* in Appendix 3. Refer also to the product information (PI) or the consumer medicines information (CMI) for individual vaccines; both are available from the TGA website (www.tga.gov.au).

Preservatives

Preservatives are used to prevent fungal and or bacterial contamination of the vaccine. They include thiomersal, phenoxyethanol and phenol.

Thiomersal

Thiomersal (or thimerosal) is a compound that is partly composed of a form of mercury called ethylmercury. It has been used in very small amounts in vaccines for about 60 years to prevent bacterial and fungal contamination of vaccines. In the past, the small amount of thiomersal in vaccines was one of several potential sources of mercury. Diet (such as some seafood) and other environmental sources are also possible sources of mercury. Vaccines used in the past, such as DTP, contained only 25 µg of thiomersal per dose.

Mercury causes a toxic effect after it reaches a certain level in the body. Whether or not it reaches a toxic level depends on the amount of mercury consumed and the person's body weight; individuals with very low body weight are usually more susceptible to toxic effects from a certain intake of mercury. Thus, the possibility existed that vaccination of newborn babies, particularly those of very low birth weight, with repeated doses of thiomersal-containing vaccines might have resulted in levels of mercury above the recommended guidelines.

Thiomersal was removed from vaccines in response to the above theoretical concern and to reduce total exposure to mercury in babies and young children in a world where other environmental sources may be more difficult to eliminate.[5-7]

Currently, all vaccines on the NIP for children and adolescents are free of thiomersal.

Phenoxyethanol

The aromatic ether alcohol, 2-phenoxyethanol, is used as a preservative in many vaccines, and also as a preservative in cosmetics. It is used in vaccines as an alternative preservative to thiomersal.

Phenol

Phenol is an aromatic alcohol used as a preservative in a few vaccines.

Adjuvants

Adjuvants are compounds used to enhance the immune response to vaccination and include various aluminium salts, such as aluminium hydroxide, aluminium phosphate and potassium aluminium sulphate (alum). A review of all available studies of aluminium-containing diphtheria, tetanus and pertussis vaccines

(either alone or in combination) found no evidence that aluminium salts in vaccines cause any serious or long-term adverse events.[8]

Aluminium

A small amount of aluminium salts has been added to some vaccines for about 60 years. Aluminium acts as an adjuvant, which improves the protective response to vaccination by keeping antigens near the injection site so they can be readily accessed by cells responsible for inducing an immune response. The use of aluminium in vaccines means that, for a given immune response, less antigen is needed per dose of vaccine, and a lower number of total doses are required. Although aluminium-containing vaccines have been associated with local reactions and, less often, with the development of subcutaneous nodules at the injection site, other studies have reported fewer reactions with aluminium-adsorbed vaccines than with unadsorbed vaccines. Concerns about the longer-term effects of aluminium in vaccines arose after some studies suggested a link between aluminium in the water supply and Alzheimer's disease, but this link has never been substantiated. The amount of aluminium in vaccines is very small and the intake from vaccines is far less than that received from diet or medications such as some antacids.[9,10]

Additives

Additives are used to stabilise vaccines in adverse conditions (temperature extremes of heat and freeze drying) and to prevent the vaccine components adhering to the side of the vial.

Examples of additives include:

- lactose and sucrose (both sugars)
- sorbitol and mannitol (both sugar alcohols)
- polysorbate 80, made from sorbitol and oleic acid (an omega fatty acid)
- glycine and monosodium glutamate or MSG (both are amino acids or salts of amino acids)
- gelatin, which is partially hydrolysed collagen, usually of bovine or porcine origin, although information on the source of gelatin is not routinely provided in the product information for all vaccines.

  Some members of the Islamic and Jewish faiths may object to vaccination, arguing that vaccines can contain pork products. However, scholars of the Islamic Organization for Medical Sciences have determined that the transformation of pork products into gelatin will sufficiently alter them, thus making it permissible for observant Muslims to receive vaccines, even if the vaccines contain porcine gelatin. Likewise, leaders of the Jewish faith have also indicated that pork-derived additives to medicines are permitted. Further information may be obtained from the following websites

www.vaccinesafety.edu/Porcine-vaccineapproval.htm and www.immunize.org/concerns/porcine.pdf

- human serum albumin (protein).

Manufacturing residuals

Manufacturing residuals are residual quantities of reagents used in the manufacturing process of individual vaccines. They include antibiotics (such as neomycin or polymyxin), inactivating agents (e.g. formaldehyde) as well as cellular residuals (egg and yeast proteins), traces of which may be present in the final vaccine. Antibiotics are used during the manufacturing process to ensure that bacterial contamination does not occur; traces of these antibiotics may remain in the final vaccine. Inactivating agents are used to ensure that the bacterial toxin or viral components of the vaccine are not harmful, but will result in an immune response. Cellular residuals are minimised by extensive filtering. However, trace amounts may be present in the final product. The most commonly found residual is formaldehyde.

Formaldehyde

Formaldehyde is used during the manufacture of many vaccines. For example, with tetanus vaccines, formaldehyde is used to detoxify the tetanus toxin protein produced. The non-toxic protein, which becomes the active ingredient of the vaccine, is further purified to remove contaminants and any excess (unreacted or unbound) formaldehyde. The current standard applicable to vaccines for human use in Australia is less than 0.02% w/v of free formaldehyde. The maximum amount of free formaldehyde detected by the Therapeutic Goods Administration during testing of vaccines registered in Australia has been 0.004% w/v, which is well below the standard limit.

Other ingredients and information about manufacturing

Vaccines also may be made up in sterile water or sterile saline (salt-water).

Some viruses used in vaccines require the use of 'cell lines' in which to grow the vaccine virus. The cell lines are not included as a component of the vaccine. Some of these cell lines (called human diploid cell lines – WI-38 and MRC-5) were originally derived from human fetal tissue in the 1960s. These cell lines have been growing under laboratory conditions for more than 40 years, and there has been no further fetal tissue obtained since the 1960s. The vaccines manufactured using viruses that were grown in these cell lines include rubella vaccine and MMR vaccine, hepatitis A vaccines, varicella vaccines, rabies vaccine and oral polio (Sabin) vaccine (no longer available in Australia). Many of these vaccines prevent severe disease in unborn babies and infants, including, most notably, rubella, which causes congenital rubella syndrome.

A4.5 Questions about the need for immunisation

Isn't natural immunity better than immunity from vaccination?

While vaccine-induced immunity may diminish with time without boosters (vaccine or contact with wild-type infection), 'natural' immunity, acquired by catching the disease, is usually life-long, with the exception of pertussis. The problem is that the wild or 'natural' disease has a higher risk of serious illness and occasionally death. Children or adults can be revaccinated (with some, but not all, vaccines) if their immunity from the vaccines falls to a low level or if previous research has shown that a booster vaccination is required for long-term protection. It is important to remember that vaccines are many times safer than the diseases they prevent.

Diseases like measles, polio and diphtheria have already disappeared from most parts of Australia. Why do we need to keep vaccinating children against these diseases?

Although these diseases are much less common now, they still exist. The potential problem of disease escalation is kept in check by routine vaccination programs. In countries where vaccination rates have declined, vaccine-preventable diseases have sometimes reappeared. For example, Holland has one of the highest rates of fully vaccinated people in the world. However, in the early 1990s, there was a large outbreak of polio among a group of Dutch people who belonged to a religious group that objected to vaccination. While many of these people suffered severe complications like paralysis, polio did not spread into the rest of the Dutch community. This was due to the high rate of vaccination against polio, which protected the rest of the Dutch community.

There have been recent outbreaks of whooping cough, measles and rubella in Australia, and a number of children have died. Cases of tetanus and diphtheria, although rare, still occur. Thus, even though these diseases are much less common now than in the past, it is necessary to continue to protect Australian children, so that the diseases cannot re-emerge to cause large epidemics and deaths.

Also, many of the diseases against which we vaccinate our children are still common in other areas of the world. For example, measles still occurs in many Asian countries, where many people take holidays or travel for business. Therefore, it is possible for non-immune individuals to acquire measles overseas, and, with the speed of air travel, arrive home and be able to pass measles onto those around them if they are unprotected. Measles is highly infectious and can infect others for several hours after an infected person has left a room. Vaccination, while not 100% effective, can considerably minimise a person's chance of catching a disease. The more people who are vaccinated, the less chance there is that a disease, such as measles, will spread widely in the community. This is referred to as 'herd immunity'.

Why do some children get the disease despite being vaccinated?

This is possible because a small proportion of those who are vaccinated will remain susceptible to the disease. However, in the cases in which illness does occur in vaccinated individuals, the illness is usually much less severe than in those who were not vaccinated. The protection provided by the same vaccine to different individuals can differ. For example, if 100 children are vaccinated with MMR, 5 to 10 of the 100 fully vaccinated children might still catch measles, mumps or rubella (although the disease will often be less severe in vaccinated children). If 100 children are vaccinated with a full schedule of pertussis-containing vaccines, 20 of the children might still get whooping cough, but, once again, the disease is often less severe in these vaccinated children. To put it another way, if you do not vaccinate 100 children with MMR vaccine, and the children are exposed to measles, all of them will catch the disease with a risk of high rates of complications like pneumonia or encephalitis. The reason why fewer children become infected than these figures suggest is due to the high vaccine coverage rates in the community. If there are high coverage rates, there is less chance of contact with the infection and, although some children may be susceptible, they have a low chance of contact with the infection (this situation is also called 'herd immunity').

What about homeopathic 'immunisation'?

Homeopathic 'immunisation' has not been proved to give protection against infectious diseases; only conventional vaccination produces a measurable immune response. The Council of the Faculty of Homeopathy, London, issued a statement in 1993, which reads: 'The Faculty of Homeopathy, London, strongly supports the conventional vaccination program and has stated that vaccination should be carried out in the normal way, using the conventional tested and proved vaccines, in the absence of medical contraindications'.[11]

A4.6 Further information about vaccination

More information about vaccination can be found in the following publications produced by the Australian Government Department of Health:

- *Understanding childhood immunisation*
- *Immunisation myths and realities – responding to arguments against immunisation: a guide for providers.*

The following two websites include further publications, fact sheets, etc. and are recommended for both immunisation service providers and the general public:

- Immunise Australia website www.immunise.health.gov.au
- The National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases (NCIRS) website www.ncirs.edu.au.

Also, check with your local state or territory Public Health Unit or local council, maternal child health nurse or public health vaccination clinic for more information (see Appendix 1 *Contact details for Australian, state and territory government health authorities and communicable disease control*).

References

A full reference list is available on the electronic *Handbook* or website www.immunise.health.gov.au

APPENDIX 5: GLOSSARY OF TECHNICAL TERMS

Adjuvant
a preparation added to a vaccine to improve the immune response to that vaccine

Adverse event following immunisation (AEFI)
an unwanted reaction following administration of a vaccine, which may or may not be caused by the vaccine; adverse events may be at the site of injection, or may be a general illness or a general allergic reaction

Anaphylaxis
a sudden and severe allergic reaction, which results in a serious fall in blood pressure and/or respiratory obstruction and may cause unconsciousness and death if not treated immediately

Attenuation
the process of modifying a virus or bacteria to reduce its virulence (disease-inducing ability) while retaining its ability to induce a strong immune response (immunogenicity)

Bacteria
microorganisms that are smaller than a blood cell, but bigger than a virus; examples of bacterial infections are diphtheria, tetanus, pertussis, Hib and tuberculosis

Brachial neuritis
pain in the arm, causing persisting weakness of the limb on the side of vaccination

Chronically infected
formerly referred to as a 'carrier'; a person who has an infection that, although not necessarily causing symptoms, may still be active and may spread to others; chronic infection may last for years; examples of infections that can result in chronically infected states are hepatitis B and typhoid

Conjugate
some bacterial vaccines (e.g. Hib, meningococcal and pneumococcal conjugate vaccines) are made from the chemical linking (conjugation) of a tiny amount of the 'sugar' (correctly known as the polysaccharide) that makes up the cell coat of the bacteria with a protein molecule, in order to improve the immune response to the vaccine

Contraindication
a reason why a vaccine or drug *must* not be given

Corticosteroid
a drug used to reduce inflammation and other immune responses

DT
a vaccine that protects against diphtheria and tetanus. The acronym DT, using capital letters, signifies the child formulation of diphtheria and tetanus-containing vaccine, and denotes the substantially larger amounts of diphtheria toxoid in this formulation than in the adolescent/adult formulation.

dT
reduced antigen content formulation of diphtheria-tetanus vaccine, which contains substantially lower concentrations of diphtheria toxoid, and approximately half the tetanus antigen content, than the child formulation (which is signified by using capital letters DT). This vaccine is most commonly administered to adolescents/adults.

DTP/DTPa/DTPw
a vaccine that protects against diphtheria, tetanus and pertussis (whooping cough). The DTP used in Australia and many other industrialised countries is DTPa, which contains an acellular pertussis component made of refined pertussis extracts instead of inactivated whole pertussis bacteria (DTPw). The acronym DTPa, using capital letters, signifies child formulations of diphtheria, tetanus and acellular pertussis-containing vaccines, and denotes the substantially larger amounts of diphtheria toxoid and pertussis antigens in these formulations than in the adolescent/adult formulations.

dTpa
reduced antigen content formulation of diphtheria-tetanus-acellular pertussis vaccine, which contains substantially lower concentrations of diphtheria toxoid and pertussis antigens, and approximately half the tetanus antigen content, than the child formulations (which are signified by using all capital letters [DTPa]). This vaccine is most commonly administered to adolescents/adults.

Effectiveness
the extent to which a vaccine produces a benefit in a defined population in uncontrolled or routine circumstances

Efficacy
the extent to which a vaccine produces a benefit in a defined population in controlled or ideal circumstances, for example, in a randomised controlled trial

Encephalitis
inflammation of the brain

Encephalopathy
a general term to describe a variety of illnesses that affect the brain, including encephalitis

Endemic
endemic infections are present all the time in a community

Enzootic

enzootic infections are present all the time in animals of a specific geographic area

Epidemic

epidemic infections are those that spread rapidly in a community; measles and influenza viruses are common causes of epidemics in Australia; small epidemics are often called outbreaks

Extensive limb swelling

swelling of the limb, with or without redness, which:

- » extends from the joint above to the joint below the injection site, or beyond a joint (above or below the injection site), or
- » results in the circumference of the limb being twice the normal size.

Febrile

related to a fever, as in febrile illness and febrile convulsions

Hepatitis

an inflammation of the liver; can be caused by viral infections

Hypotonic-hyporesponsive episode (shock, collapse)

the sudden onset of pallor or cyanosis, limpness (muscle hypotonia), and reduced responsiveness or unresponsiveness occurring after vaccination, where no other cause is evident, such as a vasovagal episode or anaphylaxis. The episode usually occurs 1 to 48 hours after vaccination and resolves spontaneously.

Immunisation

the process of inducing immunity to an infectious agent by administering a vaccine

Immunity

the ability of the body to fight off certain infections; immunity can result from natural ('wild') infections or from vaccination

Immunogenicity

the ability (or the degree) to which a particular substance, in this context a vaccine, may provoke an immune response

Immunoglobulin

a protein extract from blood, sometimes called 'antibody', that fights off infection; injection of immunoglobulins provides temporary immunity against certain infections

Incubation period
after a person is infected with bacteria or viruses, it often takes days or weeks for the infection to cause an obvious illness; the time between exposure to the infectious agent and development of the disease is called the incubation period

Infection
an infection occurs when bacteria or viruses invade the body; if the body cannot fight the infection, it may cause an illness

Intradermal (ID) injection
an injection into the surface layers of the skin; this is used for the administration of bacille Calmette-Guérin (BCG), the tuberculosis vaccine

Intramuscular (IM) injection
an injection into the muscle; vaccines are usually injected into a muscle of the upper outer thigh, or a muscle in the upper arm

Intussusception
when one portion of the bowel telescopes into the next portion of bowel, resulting in a blockage

Invasive disease
this term is often used when talking about pneumococcal or meningococcal disease. This term means that the bacteria (or germs) have been found in the blood, spinal fluid or another part of the body that would normally be sterile (or germ free).

Jaundice
yellow skin colour that may result from severe hepatitis

Pandemic influenza

a global epidemic that results when a new strain of influenza virus appears in the human population. It causes more severe disease in the population because there is little immunity to this new strain.

Paracetamol
a medicine that helps reduce fever; it may be given to minimise fevers following vaccination

Pertussis
whooping cough, an illness caused by a bacterium, *Bordetella pertussis*

Polysaccharide
a group of complex carbohydrates (sugars), which make up the cell coating present in some bacteria

Polyvalent vaccine
a combination vaccine that protects against more than one disease; examples are DTPa and MMR

Rotavirus
a virus that is a common cause of diarrhoea (and often vomiting as well) in young children. The diarrhoea can be severe in very young children, such that they may need intravenous fluids (i.e. through a vein in the arm) in hospital.

Rubella
a viral illness, sometimes also known as German measles

Seizure
a witnessed sudden loss of consciousness and generalised, tonic, clonic, tonic–clonic, or atonic motor manifestations.

Types of seizures include:

- febrile seizures; with fever >38.5°C
- afebrile seizures; without fever
- syncopal seizures; a syncope/vasovagal episode followed by seizure(s).

Subcutaneous (SC) injection
an injection into the tissue between the skin and the underlying muscle

Syncope
see vasovagal episode

Thrombocytopenia
platelet count <50 x 10^9/L

Transverse myelitis
a brief but intense attack of inflammation (swelling) in the spinal cord that damages myelin

Vaccination
the administration of a vaccine; if vaccination is successful, it results in immunity

Vaccine
a product often made from extracts of killed viruses or bacteria, or from live weakened strains of viruses or bacteria; the vaccine is capable of stimulating an immune response that protects against natural ('wild') infection

Varicella
chickenpox, an infection caused by the varicella-zoster virus

Vasovagal episode (syncope, faint)
episode of pallor and unresponsiveness or reduced responsiveness or feeling light-headed AND occurring while vaccine is being administered or shortly after (usually within 5 minutes) AND bradycardia AND resolution of symptoms with a change in position (supine position or head between knees or limbs elevated)

Virus
a tiny living organism, smaller than a bacterium, that can cause infections; measles, rubella, mumps, polio, influenza and hepatitis B are examples of viruses

Zoster
an abbreviation for herpes zoster infection (also known as shingles); a painful rash and illness, caused by the varicella-zoster (chickenpox) virus

APPENDIX 6: COMMONLY USED ABBREVIATIONS

ABLV	Australian bat lyssavirus
ACIR	Australian Childhood Immunisation Register
ACT	Australian Capital Territory
ADRS	Adverse Drug Reactions System
AEFI	adverse event following immunisation
AIDS	acquired immunodeficiency syndrome
anti-HBe	antibody to hepatitis B e antigen
anti-HBc	antibody to hepatitis B core antigen
anti-HBs	antibody to hepatitis B surface antigen
AOM	acute otitis media
ASCIA	Australasian Society of Clinical Immunology and Allergy
ATAGI	Australian Technical Advisory Group on Immunisation
BCG	bacille Calmette-Guérin
$CCID_{50}$	cell culture infectious dose 50%
CDNA	Communicable Diseases Network Australia
CI	confidence interval
CIN	cervical intraepithelial neoplasia
CRS	congenital rubella syndrome
CSF	cerebrospinal fluid
DNA	deoxyribonucleic acid
DT	diphtheria-tetanus vaccine for use in children (for further explanation of this term, see Appendix 5 *Glossary of technical terms*)
dT	diphtheria-tetanus vaccine for use in adults (for further explanation of this term, see Appendix 5 *Glossary of technical terms*)
DTPa	diphtheria-tetanus-acellular pertussis vaccine (for further explanation of this term, see Appendix 5 *Glossary of technical terms*)
dTpa	diphtheria-tetanus-acellular pertussis vaccine, reduced antigen content formulation (for further explanation of this term, see Appendix 5 *Glossary of technical terms*)
DTPw	diphtheria-tetanus-whole-cell pertussis vaccine (for further explanation of this term, see Appendix 5 *Glossary of technical terms*)
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
FHA	filamentous haemagglutinin
FIM	fimbriae (pertussis)
GBS	Guillain-Barré syndrome
GP	general practitioner
GVHD	graft-versus-host disease
HAV	hepatitis A virus
HBcAg	hepatitis B core antigen
HBeAg	hepatitis B e antigen

HBIG	hepatitis B immunoglobulin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCW	healthcare worker
HDCV	human diploid cell vaccine (rabies)
HepA	hepatitis A vaccine
HepB	hepatitis B vaccine
HHE	hypotonic-hyporesponsive episode
Hib	*Haemophilus influenzae* type b
Hib-MenCCV	*Haemophilus influenzae* type b-meningococcal C conjugate vaccine
HIV	human immunodeficiency virus
HPV	human papillomavirus
2vHPV	bivalent HPV vaccine
4vHPV	quadrivalent HPV vaccine
HRIG	human rabies immunoglobulin
HSCT	haematopoietic stem cell transplant
HZ	herpes zoster
ID	intradermal
IgA/G/M	immunoglobulin A/G/M
IM	intramuscular
IPD	invasive pneumococcal disease
IPV	inactivated poliomyelitis vaccine
IS	intussusception
ITP	idiopathic thrombocytopenia purpura
IU	international units
IV	intravenous
JE	Japanese encephalitis
LT-ETEC	heat-labile toxin producing enterotoxigenic *Escherichia coli*
MenCCV	meningococcal serogroup C conjugate vaccine
4vMenCV	quadrivalent meningococcal conjugate vaccine
4vMenPV	quadrivalent meningococcal polysaccharide vaccine
MMR	measles-mumps-rubella
MMRV	measles-mumps-rubella-varicella
NCIRS	National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases
NHIG	normal human immunoglobulin
NHMRC	National Health and Medical Research Council
NHVPR	National HPV Vaccination Program Register
NIP	National Immunisation Program
NSW	New South Wales
NT	Northern Territory
NTHi	non-typeable *Haemophilus influenzae*
OMP	outer membrane protein

OPV	oral poliomyelitis vaccine
PCECV	purified chick embryo cell vaccine (rabies)
PCR	polymerase chain reaction
7vPCV	7-valent pneumococcal conjugate vaccine
10vPCV	10-valent pneumococcal conjugate vaccine
13vPCV	13-valent pneumococcal conjugate vaccine
PEP	post-exposure prophylaxis
pH1N1	pandemic influenza A(H1N1)pdm09
PHN	post-herpetic neuralgia
PI	product information
PreP	pre-exposure prophylaxis
23vPPV	23-valent pneumococcal polysaccharide vaccine
PRN	pertactin
PRP	polyribosylribitol phosphate
PRP-OMP	PRP conjugated to the outer membrane protein of *Neisseria meningitidis*
PRP-T	PRP conjugated to tetanus toxoid
PT	pertussis toxoid
Qld	Queensland
RCT	randomised controlled trial
RIG	rabies immunoglobulin
RNA	ribonucleic acid
SA	South Australia
SC	subcutaneous
SCID	severe combined immunodeficiency
SIDS	sudden infant death syndrome
SOT	solid organ transplant
SSPE	subacute sclerosing panencephalitis
Tas	Tasmania
TB	tuberculosis
$TCID_{50}$	tissue culture infectious dose 50%
TGA	Therapeutic Goods Administration
TIG	tetanus immunoglobulin
TST	tuberculin skin test
Vic	Victoria
VLP	virus-like particle
VNAb	(rabies) virus neutralising antibody
VPD	vaccine-preventable disease
VV	varicella vaccine
VZV	varicella-zoster virus
WA	Western Australia
WHO	World Health Organization
ZIG	zoster immunoglobulin

APPENDIX 7: OVERVIEW OF VACCINE AVAILABILITY IN AUSTRALIA

Table A7.1 provides an overview of key dates when vaccines first came into widespread use in Australia. This table provides only some dates; for specific details on vaccine registration, funding, recommendations and program use, please see complete information in the 'NCIRS Vaccination History Tables' available from the NCIRS website (www.ncirs.edu.au/immunisation/history/index.php). These tables, listed by vaccine type, provide a summary of the significant events in vaccination practice in Australia, particularly for vaccines used in population-based immunisation programs. Additional information regarding vaccines available in each jurisdiction can also be sought from your local state or territory Immunisation Department.

Table A7.1: Key dates when vaccines first came into widespread use in Australia

Year	Vaccine
1945	Tetanus toxoid
1953	Diphtheria-tetanus-pertussis, whole-cell (DTPw)
1956	Poliomyelitis (Salk) (inactivated poliomyelitis vaccine [IPV])
1966	Poliomyelitis (Sabin) (live attenuated oral poliomyelitis vaccine [OPV])
1970	Measles
1971	Rubella
1975	Child diphtheria-tetanus (CDT)
1982	Adult diphtheria-tetanus (ADT)
1982	Measles-mumps
1982	Hepatitis B (hepB) (serum-derived vaccine)
1987	Hepatitis B (recombinant vaccine)
1989	Measles-mumps-rubella (MMR)
1993	*Haemophilus influenzae* type b (Hib)
1994	Hepatitis A
1997	Diphtheria-tetanus-pertussis, acellular (DTPa)
1999	Influenza
1999	23-valent pneumococcal polysaccharide (23vPPV)
2000	DTPa-hepB
2000	Hib(PRP-OMP)-hepB
2001	7-valent pneumococcal conjugate (7vPCV)

Year	Vaccine
2003	Varicella
2003	Meningococcal C conjugate
2004	Diphtheria-tetanus-pertussis, acellular; reduced antigen content formulations (dTpa and dTpa-IPV)
2005	Pentavalent and hexavalent combination DTPa vaccines (DTPa-hepB-IPV-Hib; DTPa-IPV; DTPa-hepB-IPV; DTPa-IPV-Hib)
2007	Human papillomavirus (HPV)
2007	Rotavirus
2009	10-valent pneumococcal conjugate (10vPCV)
2011	13-valent pneumococcal conjugate (13vPCV)
2013	Measles-mumps-rubella-varicella (MMRV)

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INFORMATION SHEET – COMPARISON OF THE EFFECTS OF DISEASES AND THE SIDE EFFECTS OF NIP VACCINES

From *The Australian Immunisation Handbook* 10th Edition (see *Handbook* contents for more details)

DISEASE	EFFECT OF DISEASE	SIDE EFFECT OF VACCINE
Diphtheria – bacteria spread by respiratory droplets; causes severe throat and breathing difficulties.	Up to 1 in 7 patients die. The bacteria release a toxin, which can produce nerve paralysis and heart failure.	About 1 in 10 has local swelling, redness or pain at the injection site, or fever (DTPa/dTpa vaccine). Booster doses of DTPa may occasionally be associated with extensive swelling of the limb, but this resolves completely within a few days. Serious adverse events are very rare.
Hepatitis A – virus spread by contact or ingestion of faecally contaminated water/food or through contact with the faecal material of a person infected with hepatitis A.	At least 7 in 10 adult patients develop jaundice (yellowing of the skin and eyes), fever, anorexia (decreased appetite), nausea, vomiting, hepatic (liver) pain and malaise (tiredness).	About 1 in 5 will have local swelling, redness or pain at the injection site. Serious adverse events are very rare.
Hepatitis B – virus spread mainly by blood, sexual contact or from mother to newborn baby; causes acute hepatitis (liver infection) or chronic infection ('carrier').	About 1 in 4 chronic carriers will develop cirrhosis or liver cancer.	About 1 in 20 will have local swelling, redness or pain at the injection site and 2 in 100 will have fever. Anaphylaxis occurs in about 1 in 1 million. Serious adverse events are very rare.
Hib – bacteria spread by respiratory droplets; causes meningitis (infection of the tissues surrounding the brain), epiglottitis (respiratory obstruction), septicaemia (infection of the blood stream) and septic arthritis (infection in the joints).	About 1 in 20 meningitis patients dies and about 1 in 4 survivors has permanent brain or nerve damage. Epiglottitis is rapidly and invariably fatal without treatment.	About 1 in 20 has local swelling, redness or pain at the injection site. About 1 in 50 has fever. Serious adverse events are very rare.
Human papillomavirus – virus spread mainly via sexual contact; up to 80% of the population will be infected with HPV at some time in their lives. Some HPV types are associated with the development of cancer.	About 7 in 10 cervical cancers worldwide have been associated with HPV-16 and 1 in 6 with HPV-18.	About 8 in 10 will have pain and 2 in 10 will have local swelling, redness or pain at the injection site. Headache, fever, muscle aches and tiredness may occur in up to 3 in 10 people. Serious adverse events are very rare.
Influenza – virus spread by respiratory droplets; causes fever, muscle and joint pains, pneumonia. About 1 in 10 to 1 in 5 persons will get influenza every year.	There are an estimated 3000 deaths in people older than 50 years of age each year in Australia. Causes increased hospitalisation in the very young (under 5 years of age) and the elderly. Other high-risk groups include pregnant women, people who are obese, diabetics and others with certain chronic medical conditions.	About 1 in 10 has local swelling, redness or pain at the injection site. Fever occurs in about 1 in 10 children aged 6 months to 3 years. Guillain-Barré syndrome occurs in about 1 in 1 million. Serious adverse events are very rare.
Measles – highly infectious virus spread by respiratory droplets; causes fever, cough and rash.	About 1 in 15 children with measles develops pneumonia and 1 in 1000 develops encephalitis (brain inflammation). For every 10 children who develop measles encephalitis, 1 dies and many have permanent brain damage. About 1 in 100 000 develops SSPE (brain degeneration), which is always fatal.	About 1 in 10 has local swelling, redness or pain at the injection site, or fever. About 1 in 20 develops a rash, which is non-infectious. Low platelet count (causing bruising or bleeding) occurs after the 1st dose of MMR vaccine at a rate of about 1 in 20 000 to 30 000. Serious adverse events are very rare.
Meningococcal infection – bacteria spread by respiratory droplets; causes septicaemia (infection of the blood stream) and meningitis (infection of the tissues surrounding the brain).	About 1 in 10 patients dies. Of those that survive, 1 to 2 in 10 have permanent long-term problems, such as loss of limbs and brain damage.	About 1 in 10 has local swelling, redness or pain at the injection site, fever, irritability, loss of appetite or headaches (conjugate vaccines). About 1 in 2 has a local reaction (polysaccharide vaccine). Serious adverse events are very rare.
Mumps – virus spread by saliva; causes swollen neck and salivary glands, and fever.	One in 5000 children develops encephalitis (brain inflammation). One in 5 males (adolescent/adult) develop inflammation of the testes. Occasionally, mumps causes infertility or permanent deafness.	About 1 in 100 may develop swelling of the salivary glands. Serious adverse events are very rare.
Pertussis – bacteria spread by respiratory droplets; causes 'whooping cough', with prolonged cough lasting up to 3 months.	About 1 in 125 babies under the age of 6 months with whooping cough dies from pneumonia or brain damage.	About 1 in 10 has local swelling, redness or pain at the injection site, or fever (DTPa/dTpa vaccine). Booster doses of DTPa may occasionally be associated with extensive swelling of the limb, but this resolves completely within a few days. Serious adverse events are very rare.
Pneumococcal infection – bacteria spread by respiratory droplets; causes septicaemia (infection of the blood stream), meningitis (infection of the tissues surrounding the brain) and occasionally other infections.	About 3 in 10 people with meningitis die. One-third of all pneumonia cases and up to half of pneumonia hospitalisations in adults is caused by pneumococcal infection.	About 1 in 5 has local swelling, redness or pain at the injection site, or fever (conjugate vaccine). Up to 1 in 2 has local swelling, redness or pain at the injection site (polysaccharide vaccine). Serious adverse events are very rare.
Polio – virus spread in faeces and saliva; causes fever, headache and vomiting and may progress to paralysis.	While many infections cause no symptoms, up to 3 in 10 patients with paralytic polio die, and many patients who survive are permanently paralysed.	Local redness, pain and swelling at the injection site are common. Up to 1 in 10 has fever, crying and decreased appetite. Serious adverse events are very rare.
Rotavirus – virus spread by faecal–oral route; causes gastroenteritis, which can be severe.	Illness may range from mild diarrhoea to severe dehydrating diarrhoea and fever, which can result in death. Of children under 5 years of age, before vaccine introduction, approximately 10 000 children were hospitalised, 115 000 needed GP visits and 22 000 required an Emergency Department visit each year in Australia.	Up to 3 in 100 may develop diarrhoea or vomiting in the week after receiving the vaccine. About 1 in 17 000 babies may develop intussusception in the first few weeks after the 1st or 2nd vaccine doses. Serious adverse events are very rare.
Rubella – virus spread by respiratory droplets; causes fever, rash and swollen glands, but causes severe malformations in babies of infected pregnant women.	Patients typically develop a rash, painful swollen glands and painful joints. One in 3000 develops low platelet count (causing bruising or bleeding); 1 in 6000 develops encephalitis (brain inflammation). Up to 9 in 10 babies infected during the first trimester of pregnancy will have a major congenital abnormality (including deafness, blindness or heart defects).	About 1 in 10 has local swelling, redness or pain at the injection site. About 1 in 20 has swollen glands, stiff neck or joint pains. About 1 in 20 has a rash, which is non-infectious. Low platelet count (causing bruising or bleeding) occurs after the1st dose of MMR vaccine, at a rate of about 1 in 20 000 to 30 000. Serious adverse events are very rare.
Tetanus – caused by toxin of bacteria in soil; causes painful muscle spasms, convulsions, lockjaw.	About 2 in 100 patients die. The risk is greatest for the very young or old.	About 1 in 10 has local swelling, redness or pain at the injection site, or fever (DTPa/dTpa vaccine). Booster doses of DTPa may occasionally be associated with extensive swelling of the limb, but this resolves completely within a few days. Serious adverse events are very rare.
Varicella (chickenpox) – highly contagious virus; causes low-grade fever and vesicular rash (fluid-filled spots). Reactivation of the virus later in life causes herpes zoster (shingles).	One in 100 000 patients develops encephalitis (brain inflammation). Infection during pregnancy can result in congenital malformations in the baby. Infection in the mother around delivery time results in severe infection in the newborn baby in up to one-third of cases.	About 1 in 5 has a local reaction or fever. About 3 to 5 in 100 may develop a mild varicella-like rash. Serious adverse events are very rare.

NOTES

www.health.gov.au

All information in this publication is correct as at January 2014

RECOGNITION AND TREATMENT OF ANAPHYLAXIS

Signs of anaphylaxis

Anaphylaxis causes respiratory and/or cardiovascular signs or symptoms AND involves other organ systems, such as the skin or gastrointestinal tract, with:

- signs of airway obstruction, such as cough, wheeze, hoarseness, stridor or signs of respiratory distress (e.g. tachypnoea, cyanosis, rib recession)
- upper airway swelling (lip, tongue, throat, uvula or larynx)
- tachycardia, weak/absent carotid pulse
- hypotension that is sustained and with no improvement without specific treatment (*Note*: in infants and young children limpness and pallor are signs of hypotension)
- loss of consciousness with no improvement once supine or in head-down position
- skin signs, such as pruritus (itchiness), generalised erythema (redness), urticaria (weals) or angioedema (localised or general swelling of the deeper layers of the skin or subcutaneous tissue)
- abdominal cramps, diarrhoea, nausea and/or vomiting
- sense of severe anxiety and distress.

Management of anaphylaxis

- If the patient is unconscious, lie him/her on the left side and position to keep the airway clear. If the patient is conscious, lie supine in 'head-down and feet-up' position (unless this results in breathing difficulties).
- Give adrenaline by intramuscular injection (see below for dosage) if there are any signs of anaphylaxis with respiratory and/or cardiovascular symptoms or signs. Although adrenaline is not required for generalised non-anaphylactic reactions (such as skin rash without other signs or symptoms), administration of intramuscular adrenaline is safe.
- Call for assistance. Never leave the patient alone.
- If oxygen is available, administer by facemask at a high flow rate.
- If there is no improvement in the patient's condition within 5 minutes, repeat doses of adrenaline every 5 minutes, until improvement occurs.
- Check breathing; if absent, commence basic life support or appropriate cardiopulmonary resuscitation (CPR) as per the Australian Resuscitation Council guideline (www.resus.org.au/policy/guidelines).
- Transfer all cases to hospital for further observation and treatment.
- Complete full documentation of the event, including the time and dose(s) of adrenaline given.

Experienced practitioners may choose to use an oral airway, if the appropriate size is available, but its use is not routinely recommended, unless the patient is unconscious.

Antihistamines and/or hydrocortisone are not recommended for the emergency management of anaphylaxis.

Adrenaline dosage

The recommended dose of 1:1000 adrenaline is 0.01 mL/kg body weight (equivalent to 0.01 mg/kg), up to a maximum of 0.5 mL or 0.5 mg, given by deep intramuscular injection into the anterolateral thigh. Adrenaline 1:1000 *must not* be administered intravenously.

The use of 1:1000 adrenaline is recommended because it is universally available. Adrenaline 1:1000 contains 1 mg of adrenaline per mL of solution in a 1 mL glass vial. Use a 1 mL syringe to improve the accuracy of measurement when drawing up small doses.

The following table lists the doses of 1:1000 adrenaline to be used if the exact weight of the person is not known (based on the person's age).

Doses of 1:1000 (one in one thousand) adrenaline:

<1 year (approx. 5–10 kg)	0.05–0.1 mL	7–10 years (approx. 30 kg)	0.3 mL
1–2 years (approx. 10 kg)	0.1 mL	10–12 years (approx. 40 kg)	0.4 mL
2–3 years (approx. 15 kg)	0.15 mL	>12 years and adult (over 50 kg)	0.5 mL
4–6 years (approx. 20 kg)	0.2 mL		

For more detailed information, see 2.3.2 *Adverse events following immunisation*.

* Modified from The Brighton Collaboration Case Definition Criteria for Anaphylaxis, and an insert published in *Australian Prescriber* in August 2011 (available at www.australianprescriber.com/magazine/34/4/article/1210.pdf).

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