# PART 3: VACCINES LISTED BY DISEASE

## 3.1 ANTHRAX

### Bacteriology

Anthrax is a zoonotic disease of both wild and domestic animals, primarily herbivores. Animals generally ingest spores of the causative organism, *Bacillus anthracis,* while grazing on contaminated land or as a result of eating contaminated meat. Virulent bacteria then rapidly cause fulminant clinical disease in infected animals. Extremely durable spores are produced when organisms in the carcass are exposed to air.

### Clinical features[1-2]

The cutaneous form of the disease starts as a small papule, which develops into a characteristic painless skin ulcer (eschar) surrounded by significant oedema. Patients are generally toxic and there may be local lymphadenitis. Without appropriate treatment 10 to 20% percent of persons contracting cutaneous anthrax will die, but with treatment mortality should be less than 1%. High mortality rates are associated with the less common pulmonary, meningeal or gastrointestinal forms of anthrax infection in man. The incubation period for inhalational anthrax is thought to range from 1 to 43 days after exposure. The initial phase consists of flu-like symptoms such as sore throat, mild fever, chest pain, cough and myalgia. Within 2 to 3 days, a second phase begins with the abrupt onset of high fever, dyspnoea and hypoxia, rapidly progressing to shock and death within 24 to 36 hours. Chest X-ray may show lobulated mediastinal widening consistent with lympadenopathy, pulmonary infiltrates or pleural effusions. Blood cultures yield *B. anthracis.*

### Epidemiology[1-2]

*B. anthracis* spores are found throughout the world but most human disease is reported from the Middle East, parts of Europe, Africa and Asia as a result of contact with infected domestic animals or infected animal products. Occupational anthrax, once seen amongst European and American agricultural workers and tanners who contracted the disease after exposure to hides of animals contaminated by the spores, is now extremely rare. Bovine anthrax occurs sporadically in Australia, notably in Victoria in the summer of 1997[3] and more recently in Queensland. The most recent Australian human cases of anthrax, both cutaneous, occurred in a Victorian knackery worker in 1997 and a Brisbane warehouse fork-lift driver in 1998.

The biggest epidemic of human inhalational anthrax this century occurred in 1979 after the accidental release of spores from a Russian military research facility.[4] In October 2001, US case studies of pulmonary and cutaneous anthrax resulting from the delivery of letters containing readily dispersible *B. anthracis* spores revealed the ease with which such transmission can be achieved. The CDC web site provides regular updates on the public health measures adopted in response to this threat to the public (http://www.bt.cdc.gov/Agent/Anthrax/Anthrax.asp).

### Vaccines

While anthrax vaccines are not currently registered in Australia, their use may be authorised by the Therapeutic Goods Administration. The only licensed US vaccine, 'AVA', produced by Bioport Corporation in Lansing, Michigan, has been well described. It is prepared from a cell-free filtrate of a cultured toxigenic strain of *B. anthracis* adsorbed on to aluminium hydroxide as an adjuvant.[5,6]

### Dosage and administration

The Bioport vaccine is administered subcutaneously in 0.5 mL doses at 0, 2 and 4 weeks followed by boosters at 6, 12 and 18 months. Thereafter annual booster doses are recommended for at-risk individuals. A number of studies suggest greater than 90% production of protective antibodies after the third dose of anthrax vaccine.[5]

### Recommendations

Anthrax vaccine should be administered to persons exposed to a high risk of the disease. These include workers handling infected animals or exposed to imported, infected animal products.

Recommendations for the management of civilian US populations exposed to *B. anthracis* have recently been revised by the Working Group on Civilian Biodefense.[1] Although there are no FDA-approved post-exposure prophylactic antibiotic regimens, a 60-day course of oral ciprofloxacin is recommended. If the isolate of *B. anthracis* is shown to be susceptible to tetracyclines, doxycyline may be used. The Working Group[1] believes that vaccination should accompany antibiotic use, but most people exposed to anthrax in the recent US outbreak were not given the vaccine, partly because of its unavailability.

## Adverse events[7]

- Local reactions including induration, erythema larger than 5 cm in diameter, oedema, pruritus and tenderness may occur 1 to 2 days after vaccination and generally disappear by day 3.
- Very rare adverse events include oedema extending from the vaccination site to the elbow or forearm, and a small, painless nodule that may persist for weeks.
- Systemic adverse events are characterised by mild myalgia, headache, and mild to moderate malaise, which last 1 to 2 days.
- There are no reported long-term sequelae of local or systemic adverse events following anthrax vaccination.
- Although anthrax vaccination has been linked to the so-called 'Gulf War syndrome', there are no objective data to support this contention.[7]

## Contraindications

People who have recovered from a cutaneous infection with anthrax may have severe local reactions if vaccinated with anthrax vaccine.

## Use in pregnancy

Information not available.

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# 3.2 AUSTRALIAN BAT LYSSAVIRUS INFECTION AND RABIES

## Virology

Australian bat lyssavirus (ABL) and rabies virus are members of the family Rhabdoviridae, genus Lyssavirus. There are 7 known genotypes within the genus *Lyssavirus*; ABL (genotype 7) is more closely related to rabies virus (genotype 1) than any of the other 6 genotypes.

## Clinical features

Based on the two recognised human cases of ABL infection, it has to be assumed that ABL has the same clinical features as rabies. 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.[1] 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.[1] 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.[1] 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. Rabies is almost invariably fatal.

## Epidemiology

Rabies is endemic throughout much of Africa, Asia, the Americas and Europe, where the virus is maintained in certain species of mammals.[1] Australia, New Zealand and Papua New Guinea are free of endemic rabies. Human rabies characteristically follows a bite from a rabid animal, most frequently a dog, but in some parts of the world other animals, such as jackals and bats, are important sources of exposure. In countries where rabies vaccination of domestic animals is widespread (North America and Europe), wild animals such as raccoons and foxes are important reservoirs.[1]

Cases of rabies after animal scratches or the licking of open wounds are extremely rare. Cases have been recorded after exposure to aerosols in a laboratory and in caves infested with rabid bats, and cases have been reported following corneal transplants from donors who died with undiagnosed rabies.[1]

In Australia, 2 cases of a fatal rabies-like illness caused by ABL have been reported, one in 1996 and the other in 1998.[2] Both patients had been bitten by bats. Evidence of ABL infection has since been identified in all 4 species of Australian fruit bats (flying foxes) and in at least 3 species of Australian insectivorous bats. It should therefore be assumed that all Australian bats have the potential to be infected with ABL.

### Rabies vaccine

- **Mérieux Inactivated Rabies Vaccine** – Aventis Pasteur. Each 1.0 mL dose contains at least 2.5 IU viral antigens, neomycin 100-150 µg, and up to 70 mg of human serum albumin. Presentation is a 1.0 mL single dose vial of lyophilised vaccine with 1.0 mL distilled water as diluent.

The vaccine is a lyophilised, stabilised suspension of inactivated Wistar rabies virus (strain PM/W1381503-3M) that has been cultured on human diploid cells and then inactivated by beta-propiolactone. The dry vaccine 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.

## Rabies immunoglobulin

- **Imogam Rabies** – Aventis Pasteur (Human rabies immunoglobulin). Each 1.0 mL contains IgG class human rabies antibodies with a minimum titre of 150 IU, glycine 22.5 mg and sodium chloride 1 mg.

Human rabies immunoglobulin (HRIG) is prepared by cold ethanol fractionation from the plasma of hyperimmunised human donors. It is supplied in 2 mL and 10 mL vials.

## Transport, storage and handling

The vaccine, diluent and HRIG should be transported and stored at 2°C to 8°C. They must not be frozen; do not use either the vaccine or HRIG if either has been exposed to a temperature of less than 0°C. Do not freeze or store either the vaccine or HRIG in direct contact with ice packs. The reconstituted vaccine should be used immediately after reconstituting; the HRIG should be used immediately once the vial is opened.

## Dosage and administration

**(i) Pre-exposure prophylaxis**

The dose of rabies vaccine for pre-exposure prophylaxis is 1.0 mL by IM or SC injection, on days 0, 7 and 28.

**(ii) Post-exposure treatment**

The dose of rabies vaccine for post-exposure treatment is 1.0 mL by IM or deep SC injection on days 0, 3, 7, 14 and 30. Also administer HRIG (human rabies immunoglobulin) 20 IU/kg body mass, by infiltration around wounds (may give remainder of dose by IM injection).

## Recommendations

**(i) Pre-exposure prophylaxis for Australian bat lyssavirus infection and rabies**

Rabies vaccine is effective and safe when used for pre-exposure prophylaxis for either ABL[3] or rabies[1] *(level IV evidence).* The rationale for pre-exposure prophylaxis is that: (i) vaccination may provide protection to people with inapparent exposure to either ABL infection or rabies; (ii) it may protect people whose post-exposure treatment may be delayed or inadequate; and (iii) it simplifies post-exposure treatment. Patients should be advised that the main reason for pre-exposure prophylaxis is to prime the immune system for a secondary response, and that if a possible ABL or rabies exposure occurs, booster doses of vaccine may still be required.

Pre-exposure prophylaxis with rabies vaccine is strongly recommended for people in Australia liable to receive bites or scratches from bats (this includes bat handlers, veterinarians, wildlife officers and others who come into direct contact with bats).

Pre-exposure prophylaxis is strongly recommended for expatriates and travellers who will be spending prolonged periods (ie. more than a month) in rural parts of rabies endemic areas.[4] The World Health Organization (WHO) maintains data on rabies infected countries, the most recent of which can be accessed at the following web site – http://www.who.int/emc/diseases/zoo/rabies.html

Pre-exposure prophylaxis for both ABL infection and rabies, for all ages, consists of a total of 3 IM or deep SC injections of 1 mL of rabies vaccine, the second given 7 days after the first, and the third given 28 days after the first. For pre-exposure prophylaxis, the vaccine can be obtained from CSL Vaccines. Costs of pre-exposure prophylaxis have to be met by the individual or the employer.

Inadvertent prolongation of the intervals does not impair the response. Doses should be given in the deltoid area, as rabies neutralising antibody 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.

Because the antibody response is reported as satisfactory after the pre-exposure prophylaxis regimen, routine serological testing to confirm seroconversion is not necessary. However, immunosuppressed people who are at risk of exposure to ABL or rabies should have their antibody titres determined 2 to 3 weeks after the third dose of vaccine.

Booster doses of rabies vaccine should be considered for immunised people who have ongoing exposure to either ABL or rabies. People who work with live lyssaviruses in research laboratories are at risk of inapparent exposures, and should have rabies antibody titres measured every 6 months. If the titre is reported as inadequate, they should have a booster dose. Other laboratory workers who perform ABL or rabies diagnostic tests, those with occupational exposures to bats in Australia, and those who are likely to be exposed to potentially rabid animals in endemic countries should have rabies antibody titres measured every 2 years. If the titre is reported as inadequate, they should have a booster dose. Alternatively a booster dose may be offered every 2 years without determining the antibody titre.

**Intradermal pre-exposure prophylaxis:** There are no data on the protection provided by intradermal rabies vaccination for ABL exposures. Therefore ***intradermal pre-exposure administration of rabies vaccine should not be used for pre-exposure prophylaxis of ABL.***

Antibody titres are lower after intradermal compared to either IM or SC administration of rabies vaccine,[1] and there may be an impaired anamnestic response following exposure to rabies virus in those given intradermal rabies vaccine.[5,6] For these two reasons ***it is strongly recommended that either the IM or SC route be used for pre-exposure prophylaxis for potential future exposures to rabies virus.***

However, the cost of either IM or SC rabies vaccination may be prohibitive for some travellers. In this circumstance intradermal rabies vaccination, using a dose of 0.1 mL on days 0, 7 and 28, may be considered provided that:

- it is given by those with not only expertise in, but also regular practice of, the intradermal technique (because intradermal vaccination is reliable only if the whole of the 0.1 mL dose is properly given into the dermis);
- it must not be administered to anyone known to be immunocompromised in any way;
- it must not be administered to those taking either chloroquine or other antimalarials structurally related to chloroquine (eg. mefloquine) at either the time of, or within a month following vaccination;
- any remaining vaccine is discarded at the end of the session during which the vial is opened; and
- the rabies antibody level should be checked 2 to 3 weeks following completion of the pre-exposure course of intradermal vaccine.[1]

The use of the intradermal route for rabies vaccination is the practitioner's own responsibility as the vaccine is not licensed for use via this route in Australia. The intradermal route should never be used to administer rabies vaccine by practitioners who only occasionally provide travel medicine services.

**(ii) Post-exposure treatment for Australian bat lyssavirus and rabies exposures**

Rabies vaccine and HRIG are effective and safe when used for post-exposure treatment following either ABL[3] or rabies exposures[1] *(level IV evidence).* The essential components of post-exposure treatment for either ABL or rabies exposures are prompt local wound management and, for people who have not previously been vaccinated, administration of HRIG and rabies vaccine. Both HRIG and rabies vaccine are available for post-exposure treatment, without charge, from the relevant State/Territory health authorities (see Appendix 1 for contact phone numbers).

Post-exposure treatment should be considered whenever a bite, scratch or mucous membrane exposure to saliva from any Australian bat has occurred, regardless of:

- the extent of the bite or scratch – even very minor bites overseas have been known to transmit rabies;[1]
- the time lapsed since the bite or scratch – although treatment should begin as soon as practicable after a bite or scratch, incubation periods of several years have been recorded for both ABL and rabies;[2]
- the species of bat – ABL has been detected in all 4 species of flying fox, and in at least 3 species of Australian insectivorous bats; and
- the bat being apparently normal in appearance and behaviour – although ABL is more likely to be found in bats that either appear unwell or are behaving abnormally[7] it has to be assumed that any bat is potentially infected with ABL.

However, exposure to bat blood, urine or faeces, or to a bat that has been dead for more than 4 hours does not warrant post-exposure treatment.

Where post-exposure treatment for a potential exposure to ABL is indicated the bat should, if possible without placing other persons at risk of exposure, be kept and arrangements made immediately for testing by the relevant State/Territory veterinary or health authority. Following the wound management, the administration of HRIG and rabies vaccine can be withheld if the result (concerning

the bat's ABL status) will be available within 48 hours of the exposure; if the result will not be available within 48 hours full post-exposure treatment should be commenced as soon as practically possible.

An assessment must be made of the potential risk of transmission of rabies as soon as possible after exposure to a possibly infected animal. Dogs and monkeys comprise the usual exposures in Asia, Africa and Central and South America, but exposures to other animals must also be assessed for potential rabies transmission. Advice should be sought from the relevant State/Territory health authority before advising against rabies post-exposure treatment.

Post-exposure treatment of a patient presenting after possible rabies exposure should be commenced as soon as possible; treatment should not be withheld even if there has been a considerable delay in recognising the exposure. Unless the animal has been tested and found to be negative for rabies, the course should be completed irrespective of the clinical outcome in the animal.

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, is an important measure in the prevention of ABL infection and rabies.[1] Consideration should be given at this stage of wound management 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 well infiltrated with HRIG (see below). Secondary suture, if necessary, should be performed after 1 to 2 weeks, when it can be assumed that the patient has circulating neutralising antibodies.

The treatment subsequent to the wound management is the same for both ABL and rabies exposures, except that consideration may be given to omitting the HRIG if it is more than one year after an exposure to ABL. This is because the risk of infection at this time is considered to be low. Advice should be sought from the relevant State/Territory health authorities.

**a) Use of rabies vaccine in post-exposure treatment**

Following the local wound management, the subsequent post-exposure treatment for either ABL or rabies exposures consists of: (i) a total of 5 doses of 1.0 mL of rabies vaccine given by IM or SC injection; and (ii) HRIG (see below). The volume of vaccine administered to infants and children is the same as that given to adults (ie. 1.0 mL). The first dose of vaccine is given immediately (day 0), and subsequent doses are given on days 3, 7, 14 and 28. In adults and children the vaccine should be administered into the deltoid area, as administration in other sites may result in reduced neutralising antibody titres. In infants less than 12 months of age, administration into the anterolateral aspect of the thigh is recommended.

Serological testing to measure response is unnecessary except in unusual circumstances, such as when the patient is known to be immunocompromised. In such cases, the antibody titre should be measured 2 to 3 weeks after the dose given at 28 days and a further dose given if the titre is reported as inadequate.

**b) Use of rabies immunoglobulin in post-exposure treatment**

Rabies has occurred in people who have received post-exposure rabies vaccine without rabies immunoglobulin being infiltrated in and around the wound.[8,9] Therefore ***post-exposure treatment should always include the infiltration of HRIG in and around wounds at the same time as the first dose of rabies vaccine***, the only exceptions being people with documented evidence of either completion of the pre-exposure prophylaxis regimen or adequate rabies antibody titres. These people should receive vaccine only.

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 first post-exposure dose of vaccine (day 0). If not given with the first vaccine dose, it may be given up to day 7, but should not be given any later in the course of the vaccination program. From day 8 onwards, an antibody response to rabies vaccine is presumed to have occurred.

The dose of HRIG for all age groups is 20 IU per kg body mass. HRIG should be infiltrated in and around all wounds using as much of the calculated dose as possible, and the remainder administered intramuscularly at a site away from the injection site of rabies vaccine. Although the value of administering the remaining HRIG intramuscularly is uncertain,[10] it must not be omitted. Rather, it

must be emphasised that as much as possible of the HRIG be infiltrated in and around the wounds, so that as little HRIG as possible needs to be given intramuscularly.

If the wound has healed, the HRIG should be administered in the vicinity of the healed wound (eg. around a scar). If the wounds are severe and the calculated volume of HRIG is inadequate for complete infiltration (eg. 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.

However, many bat bites occur as small puncture wounds on the fingers;[11] such exposures are probably high-risk exposures because of the extensive nerve supply to the fingers and hand.[1] Therefore, although infiltration of HRIG into finger wounds is likely not only to be technically difficult but also to be painful for the recipient, it must be undertaken. As much of the calculated dose of HRIG as possible should be infiltrated into finger and hand wounds using either a 25 or a 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. If necessary a ring-block using a local anaesthetic may be required.

There is a theoretical risk that HRIG may suppress the patient's response to rabies vaccine, and no more than the recommended dose should be given.

**Table 3.2.1: Summary of Australian bat lyssavirus and rabies post-exposure treatment for non-immune individuals**

| Treatment | Immediate (Day 0) | Follow-up |
|---|---|---|
| Local treatment | Wound cleansing is vital | |
| Rabies vaccine | 1.0 mL | 1.0 mL on days 3, 7, 14, 30 |
| Human rabies immunoglobulin (150 IU / mL) | 20 IU/kg – no later than 7 days after rabies vaccine started | Do not give later than 7 days after rabies vaccine started |

**c) Post-exposure treatment of previously vaccinated people**
People who have either completed a recommended course of pre-exposure prophylaxis, or previous post-exposure treatment, or who have documented adequate rabies neutralising antibodies, require a modified post-exposure treatment regimen if potentially exposed to either rabies virus or ABL. Local wound management as described above must be carried out, and a total of 2 doses of rabies vaccine (1.0 mL each) should be given by IM injection on day 0 and day 3. HRIG is not necessary in these cases.

In cases where the vaccination status is uncertain because the documentation of a full course of rabies vaccine is not available, the standard post-exposure treatment regimen (HRIG plus 5 doses of rabies vaccine) should be administered.

**d) Post-exposure treatment commenced overseas**
Australians who are exposed to a potentially rabid animal while travelling abroad may be given post-exposure treatment whilst abroad with vaccines that are not available in Australia.

The Thai Red Cross Rabies Committee considers that the following 'first' and 'second' generation tissue culture vaccines are interchangeable:[12]

- human diploid cell vaccines (eg. Imovax Rabies),
- purified chick embryo cell vaccines (eg. Rabipur),
- purified Vero cell vaccine (Verorab),
- purified duck embryo vaccine (Lyssavac N), and
- rhesus lung cell vaccine (Rabies Vaccine Adsorbed).

Therefore, if a person has received one of the above vaccines abroad, the standard post-exposure treatment regimen should be continued in Australia with the locally available human diploid cell rabies vaccine. If the post-exposure treatment was started overseas with one of the above vaccines but HRIG

was not given, and the person presents in Australia within 7 days of commencing post-exposure treatment, HRIG should be given immediately. If the person presents in Australia after 8 days then HRIG should be withheld.

If post-exposure treatment was started abroad using either a primary hamster kidney cell culture vaccine (in widespread use in China) or a nerve tissue vaccine (eg. sheep brain vaccine), the standard post-exposure treatment regimen (HRIG plus 5 doses of human diploid cell rabies vaccine) should be commenced in Australia as soon as possible. The full regimen of 5 doses of vaccine should be administered, regardless of how many doses of the (suboptimal) hamster kidney or nerve tissue vaccines were received overseas.

## Adverse events and precautions

In a large (1770 volunteers) study the following adverse events were reported after administration of human diploid cell culture rabies vaccines: sore arm (15 to 25%), headache (5 to 8%), malaise, nausea or both (2 to 5%); and allergic oedema (0.1%).[1] In another study of post-exposure vaccination, 21% had local reactions, 3.6% had fever, 7% had headache and 5% had nausea. These reactions are not more frequent in children.[1]

Anaphylactic reactions are rare (approximately 1 per 10 000 vaccinations) following administration of human diploid cell culture rabies vaccines. However, allergic reactions occur in approximately 6% of people receiving booster doses of some of the human diploid cell vaccines.[1] 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. These reactions are not life-threatening; they have been attributed to the presence of beta-propiolactone-altered human albumin in the implicated vaccines.[1] NB: Mérieux Inactivated Rabies Vaccine contains human albumin.

### Management of adverse events

Once initiated, rabies prophylaxis should not be interrupted or discontinued because of local reactions or mild systemic reactions. Such reactions can usually be managed with either aspirin or paracetamol.

Because ABL infection and rabies are lethal diseases, the recommended vaccination regimens, in particular the post-exposure treatment 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 ABL infection or rabies must be carefully considered before deciding to discontinue vaccination.

## Contraindications

There are no contraindications to post-exposure treatment in a person with a presumed exposure to either ABL or rabies.

### Use of steroids and immunosuppressive agents

Corticosteroids and immunosuppressive agents can interfere with the development of active immunity, and therefore if possible should not be administered during post-exposure treatment. A person who either has an immunosuppressing illness or is taking immunosuppressant medications should have his/her rabies antibody titres checked 2 to 4 weeks after completion of the vaccination regimen (see above).

## Pregnancy

Pregnancy is never a contraindication to rabies vaccination. Follow-up of 202 Thai women vaccinated during pregnancy did not indicate either increased medical complications or birth defects.[13]

## Conflicts with product information

The product information does not mention that the rabies vaccine should be used for both pre-exposure prophylaxis and post-exposure treatment for ABL exposures.

The product information recommends a routine sixth dose at 90 days in the post-exposure treatment regimen. This dose is not considered necessary on a routine basis but should be offered to an immunosuppressed person without adequate antibodies following the standard regimen. It also

recommends a pre-exposure booster after a year; boosters are usually recommended in Australia after 2 years (see above).

The product information for rabies vaccine recommends administration by 'deep subcutaneous injection, preferably into the infraspinous fossa'. However, NHMRC recommends that it be given by either IM or SC injection into the usual sites. The vaccine is not licensed for adminstration by the intradermal route in Australia.

## Rabies-free countries

The WHO maintains data on rabies-infected countries, the most recent of which can be accessed at the following web site: http://www.who.int/emc/diseases/zoo/rabies.html.

As of March 2003 the Department of Agriculture, Fisheries & Forestry – Australia advised that Bali continued to be rabies free. Furthermore, no cases of Bali-acquired rabies have ever been reported in the medical literature despite many people being bitten and scratched by animals in Bali every year. Although post-exposure treatment following animal bites sustained in Bali is therefore not warranted, it must be emphasised that this situation could change at any time.

However, rabies still exists in other parts of Indonesia including the islands of Flores, Sulawesi, Sumatra and parts of Java and Kalimantan. Post-exposure treatment is necessary for any animal bite sustained in any of these locations. Any doubts or concerns about the need for post-exposure treatment following animal bites in any part of Indonesia should be discussed with the State/Territory public health authority.

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# 3.3 BOTULISM

## Bacteriology

Botulism is the paralytic disease which follows ingestion or absorption of one of the 8 neurotoxins produced by the soil organism, *Clostridium botulinum*. Cases occur singly or in small clusters following consumption of home-canned or prepared foods in which the heat-resistant spores of *C. botulinum* have germinated under anaerobic conditions. Typically, after an interval of 12 to 36 hours, patients develop weakness and dry mouth followed by cranial nerve palsies, initially involving the external ocular muscles. Paralysis may progress over a period of hours or days to involve many muscle groups and the patient may require respiratory support. Recovery occurs over a period of weeks to months.

## Epidemiology

Two recent Australian cases of infant botulism, presenting with lethargy, hypotonia, constipation and poor feeding, followed consumption of honey.[1,2] Wound botulism is a rare condition following infection in traumatic soil-contaminated wounds.

## Botulism antitoxin (Botulism Immune Globulin, BIG)

Botulism antitoxin harvested from hyperimmune adults (hBIG) and available only to investigators in the USA, halves the mean time to resolution of symptoms.[3] Antitoxin made in horses (eBIG) has long been used in the treatment of botulism and, although controlled trials are lacking, it is accepted as being effective for disease induced by toxins A and E.[4]

Equine botulism immune globulin is manufactured by major vaccine producing companies such as Aventis and Chiron. Use in Australia is governed by the TGA's Special Access Scheme and physicians wishing to access this stock should initially contact their State/Territory health department. Hyper-sensitivity, presenting as fever, serum sickness or anaphylaxis, may follow its use. Skin testing followed by appropriate dosing should be administered according to the manufacturer's instructions.

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# 3.4 CHOLERA

< Click to see handbook changes P 2-7

**What's new in this chapter:**
A new vaccine, "Dukoral", has been added, and information about its administration, safety and effectiveness has been included.

## Bacteriology

Cholera is caused by enterotoxin producing *Vibrio cholerae* of serogroups 01 and 0139. Serogroup 01 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]

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## 3.5 CYTOMEGALOVIRUS

### Virology

Cytomegalovirus (CMV) is a double-stranded DNA herpes virus, which causes characteristic intranuclear and cytoplasmic inclusion bodies.

### Clinical features

CMV infection is usually asymptomatic in normal hosts. It may occasionally cause a mononucleosis syndrome. It can cause congenital abnormalities following primary infection or reactivation in mothers. Congenital CMV is characterised by petechiae, hepatosplenomegaly and jaundice. Microcephaly, cerebral calcification and prematurity may also occur. In adults, severe CMV infection, including retinitis, colitis and pneumonitis, is seen in immunocompromised hosts, particularly those with HIV infection or following organ transplantation.

### Epidemiology

CMV has a world-wide distribution, and is spread by repeated or prolonged intimate exposure. The virus is present in milk, saliva, faeces and urine. Once infected, an individual probably carries the infection for life, most commonly in latent form.

### Vaccine

There is no CMV vaccine registered in Australia.

### CMV immunoglobulin

CMV immunoglobulin is indicated for the prevention and treatment of CMV infection in immunodeficient people at high risk of severe CMV infection.[1,2] 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 (human) – CSL Bioplasma. A sterile solution of immunoglobulin prepared from human plasma containing high levels of antibody to CMV. The plasma protein content is 60 mg/mL. Maltose is added to achieve isotonicity. Each bottle contains 1.5 million units of CMV antibody activity.

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# 3.6 DIPHTHERIA

## 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 to produce an adherent pseudomembrane. Systemically, the toxin acts on cells of the myocardium, nervous system and adrenals.

## 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 droplets or by direct contact with sores or with articles soiled by infected persons. The disease primarily affects the upper respiratory tract, but the skin can be involved. It is characterised by an inflammatory exudate which forms a greyish or green membrane in the upper respiratory tract and which can cause acute severe respiratory obstruction. Diphtheria toxin can cause neuropathy and cardiomyopathy, which may be fatal. The introduction of diphtheria antitoxin in the 1890s reduced the death rate to about 10%, but the mortality has not been further reduced by the use of antibiotics and other modern treatments. Effective protection against diphtheria is achieved by active immunisation with diphtheria vaccine.

## 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.[1] Diphtheria has been almost eradicated from Australia, but sporadic cases continue to occur in unvaccinated individuals.[2] There is now little possibility of acquiring natural immunity, and no opportunity to boost declining immunity with subclinical infection. A high vaccination rate must therefore be maintained to protect the population from resurgence of the disease. An increase in the incidence of infections from toxigenic strains could follow introduction of cases or carriers from overseas, or from local emergence of a virulent strain.

The re-emergence of diphtheria in an inadequately immunised population is demonstrated by the epidemic of diphtheria in the newly independent States of the former Soviet Union. In 1995 alone, there were over 50 000 cases reported, and from 1991 to 1996 there were over 140 000 cases and over 4000 deaths.[3] Cases also occurred in neighbouring European countries and in visitors to the area. The major cause of the epidemic was decreasing vaccination rates.

## Vaccines

A variety of formulations of diphtheria vaccine are available in Australia, that are commonly presented as the combinations CDT, dT (ADT), DTPa or adult/adolescent formulation dTpa. It is likely that additional vaccines containing diphtheria toxoid in combination with other antigens will become available in the near future.

**Adsorbed diphtheria-tetanus vaccines**

- **CDT Vaccine** – CSL Vaccines (paediatric formulation diphtheria-tetanus vaccine); diphtheria toxoid 30 IU and tetanus toxoid 40 IU per 0.5 mL adsorbed on to aluminium phosphate; thiomersal 0.01% w/v.

- **ADT Vaccine –** CSL Vaccines (adult formulation diphtheria-tetanus vaccine); diphtheria toxoid 2 IU and tetanus toxoid 40 IU per 0.5 mL adsorbed on to aluminium phosphate; thiomersal 0.01% w/v.

**Combination vaccines that include both diphtheria and pertussis antigens –** see Part 3.16, 'Pertussis'.

Diphtheria vaccination stimulates the production of antitoxin, which protects against the toxin. The immunogen is prepared by treating a cell-free purified preparation of toxin with formaldehyde, thereby converting it into the innocuous diphtheria toxoid. The toxoid is usually adsorbed on to an adjuvant, either aluminium phosphate or aluminium hydroxide, to increase its immunogenicity. Antigens from *Bordetella pertussis,* present in the combined vaccines, also act as an effective adjuvant.

Circulating levels of antitoxin are closely related to immunity to diphtheria. Antitoxin levels of less than 0.01 IU are poorly protective, 0.01 to 0.1 IU are usually protective, and titres of >0.1 IU are associated with more certain and prolonged protection.[4] Complete immunisation induces protective levels of antitoxin lasting throughout childhood but by middle age about 50% of vaccinees have levels less than 0.01 IU.[5-7] Single low doses of toxoid in previously immunised adults induce protective levels within 6 weeks.[8]

## Transport, storage and handling

Transport according to general guidelines (see Part 1.10, 'Transport, storage and handling of vaccines'). Store in refrigerator between 2°C and 8°C. Do not freeze.

## Dosage and administration

The dose of diphtheria vaccine is 0.5 mL by IM injection.

Note that the adult formulations of diphtheria-containing vaccines provide a much smaller dose of diphtheria toxoid than the children's formulation (2 IU versus 30 IU).

## Recommendations

**(i)** Diphtheria vaccination is part of the standard vaccination schedule. Diphtheria toxoid is given in combination with tetanus toxoid and acellular pertussis vaccine as DTPa in a primary course of vaccination at 2, 4 and 6 months of age and in boosting doses given as DTPa at 4 years of age and as adult/adolescent formulation dTpa at 15 to 17 years of age. Before the eighth birthday, DTP-containing vaccines should be given, as they contain a larger dose of diphtheria toxoid. After the eighth birthday, smaller doses of toxoid (adult/adolescent formulation dTpa or dT-containing vaccines) should be given. Dose reduction is necessary because of the reduced tolerance of older children and adults to diphtheria toxoid. For details on the management of children who have missed some doses of the standard childhood vaccination schedule, see Part 1.9, 'Catch-up vaccination'.

**(ii)** Older individuals who have not received diphtheria vaccination are also likely to have missed tetanus vaccination. Those individuals who have passed their eighth birthday should receive 3 doses of dT at minimum intervals of 4 weeks, followed by 2 booster doses at 10-yearly intervals.

**(iii)** Diphtheria can be a significant risk for travellers to some countries (particularly southeast Asia, the Russian Federation of Independent States, the Ukraine, Baltic countries or Eastern European countries), so all international travellers should ensure that they are up to date with routine vaccinations, including diphtheria.

**(iv) Booster doses**

The removal from the ASVS of triple antigen (DTPa) at age 18 months means that the first booster dose of diphtheria toxoid will now be given at age 4 years. Immunity to diphtheria in early childhood will not be compromised because the serological response to the primary course of vaccination is sufficient for those years. The second (smaller) booster dose of diphtheria toxoid, given in combination with tetanus toxoid and an adult dose of acellular pertussis vaccine (adult/adolescent formulation dTpa) at age 15–17 years is an important component of the new ASVS, maintaining immunity to diphtheria in adults. A booster dose of either dT or adult/adolescent formulation dTpa should be given to adults at 50 years of age.

## Diphtheria cases

A case of diphtheria is of considerable public health importance. A doctor treating a suspected case should ensure that the case is officially notified and should seek advice from the State/Territory public health authorities on further management. In general terms, contacts of a diphtheria case will require vaccination (either primary or booster, depending on vaccination status), and appropriate prophylactic antibiotics.[9]

In cases of suspected clinical diphtheria, diphtheria antitoxin should be given immediately, without waiting for bacteriological confirmation of the disease. Penicillin should also be given at this stage. Diphtheria antitoxin from horse serum is used because sera of sufficient titre are not available from humans. Due to the presence of foreign protein, diphtheria antitoxin may provoke acute severe allergic reactions or serum sickness. Consequently, a test dose should be administered to exclude hypersensitivity. If there is evidence of hypersensitivity, it may be necessary to administer diphtheria antitoxin under corticosteroid, adrenaline, and antihistamine cover. The therapeutic dose of antitoxin will depend on the clinical condition of the patient, and may be given either intramuscularly or diluted for administration in an intravenous infusion. Seek expert advice.

- **Diphtheria antitoxin** – CSL Vaccines (diphtheria antitoxin 10 000 U); phenol 0.22% as preservative.

## Adverse events and precautions

Diphtheria vaccine is most commonly given in combination with tetanus and pertussis vaccines (DTPa), and adverse events may be due to any of the components. Rarely, diphtheria vaccine may cause transient fever, headache, malaise, and local reactions at the injection site.

Extensive limb swelling is reported in about 2% of children after booster doses of DTPa vaccines when DTPa has been also been given in the 3-dose primary series.[10] Less frequent reactions have been described in subjects given DT vaccines.[11] The swelling resolves without sequelae and is not a contraindication to further doses of the vaccine (see also Appendix 5, 'Definitions of adverse events following immunisation').

## Contraindications

The only true contraindication is previous anaphylactic reaction to the vaccine or any of the vaccine components.

## Use in pregnancy

Diphtheria toxoid is safe during pregnancy and breastfeeding.

## Conflicts with product information

Product information states that booster injections should be given every 10 years. This is no longer recommended because a full primary course of 3 diphtheria-containing vaccine and at least 2 booster doses produce long-lasting immunity.

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## 3.7 *HAEMOPHILUS INFLUENZAE* TYPE B (HIB)

### Bacteriology

*Haemophilus influenzae* is a Gram-negative coccobacillus that is a normal part of upper respiratory tract flora. Strains isolated from respiratory tract specimens such as sputum and middle ear or sinus fluid usually do not have a capsule, and are also known as non-typable (NT). Although 6 capsular types (a to f) have been described, 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.

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 less than 2 years of age are usually unable to mount an antibody response to the type b capsular polysaccharide, even after invasive disease.[1]

### 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. 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. There are no specific clinical features of any of the focal infections due to Hib which 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.[2]

### Epidemiology

**(i) Before Hib vaccination**

Before the introduction of routine Hib vaccination in 1993, there were at least 500 cases of Hib disease in Australian children under 6 years of age every year.[3] Hib meningitis accounted for approximately

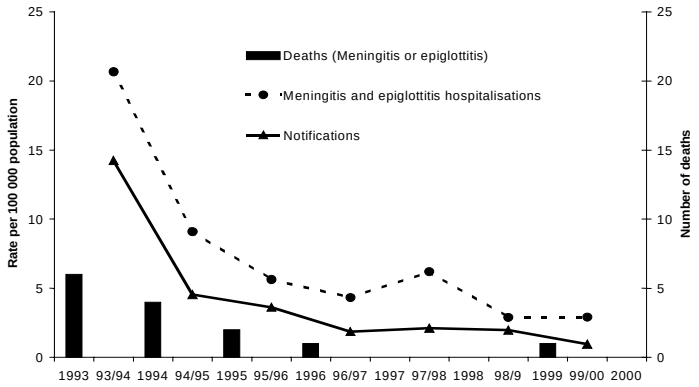
60% of all invasive Hib disease, with most cases occurring in children under the age of 18 months. Hib epiglottitis usually occurred in children over the age of 18 months. Other manifestations such as cellulitis, septic arthritis and pneumonia occurred at a similar age to meningitis.[4]

The incidence of Hib disease in Aboriginal and Torres Strait Islander children, especially those in remote rural areas, was considerably higher than in non-Indigenous children.[5] Most importantly, the onset of Hib disease in Aboriginal and Torres Strait Islander children was at a much younger age, manifesting mostly as meningitis, with epiglottitis being rare. In both Aboriginal and Torres Strait Islander children and non-Indigenous children, the case fatality rate for Hib meningitis was approximately 5%, and up to 40% of the survivors had neurological sequelae such as deafness and intellectual impairment.[5,6] In Australia, there were about 10 to 15 deaths each year from Hib infection,[3] and 20 to 40% of the survivors were left with permanent neurological damage.

**(ii) After Hib vaccination**

Since Hib vaccines were included in the routine vaccination schedule in 1993, there has been a reduction of >90% in notified cases of Hib disease from 502 in 1992 to 31 in the 2 years 1999 to 2000. (see Figure 3.7.1).[7] This reduction has been particularly marked in Indigenous children in Australia.[8] Similar impressive reductions in Hib disease have been seen in other countries with routine childhood vaccination.[9] 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.[10-12]

**Figure 3.7.1: *H. influenzae* type b (Hib) notifications, presumed Hib hospitalisations* and deaths of children aged 0 to 4 years from Hib, Australia 1993 to 2000†**




* Hospitalisations for *H. influenzae* meningitis and acute epiglottitis.

† Notifications with onset dates between July 1993 and June 2000; hospitalisations with separation between July 1993 and June 2000; deaths reported between 1993 and 2000.[7]

## Vaccines

The first generation Hib vaccines, consisting of purified polysaccharide (PRP) from the Hib capsule, were not effective in children under the age of 18 months. However, the second generation Hib vaccines, which consist of PRP chemically linked ('conjugated') to a variety of carrier proteins, have been shown to be not only immunogenic but also highly effective (over 95%) in protecting young children from invasive Hib disease. There are 2 main groups of carrier proteins associated with a different temporal pattern of PRP antibody response. The vaccine using the outer membrane protein of *Neisseria meningitidis* as a carrier protein (PRP-OMP) gives protective PRP antibody responses after the first dose, and requires only 2 doses to complete the primary course. Vaccines using other protein carriers do not achieve protective PRP antibody levels until after at least a second dose has been given and require 3 doses to complete primary immunisation.

- **ActHib** – Aventis Pasteur – PRP-T; purified *Haemophilus influenzae* type b capsular polysaccharide (PRP) 10 µg conjugated to 18-30 µg tetanus toxoid; lyophilised powder for reconstitution with 0.5 mL diluent; contains buffer and sucrose.

- **Comvax** – CSL Vaccines/Merck Sharp & Dohme – Hib (PRP-OMP)-hepatitis B; PRP 7.5 µg conjugated to meningococcal protein 125 µg; hepatitis B surface antigen 5 µg; aluminium hydroxide containing 225 µg aluminium; 35 µg borax as a pH stabiliser in 0.9% sodium chloride.

- **HibTITER –** Wyeth – HbOC; purified capsular derivative of the Eagan *Haemophilus influenzae* type b strain 10 µg conjugated to non-toxic diphtheria $CRM_{197}$ protein 25 µg in 0.9% sodium chloride.

- **Hiberix** – GlaxoSmithKline – PRP-T; PRP 10 µg conjugated to 30 µg tetanus toxoid as a white lyophilised pellet for reconstitution with 0.9% saline.

- **Liquid PedvaxHIB** – CSL Vaccines/Merck Sharpe & Dohme – PRP-OMP; PRP 7.5 µg conjugated to meningococcal protein 125 µg; (liquid formulation with borax 35 µg; aluminium hydroxide containing 225 µg aluminium; 0.9% sodium chloride).

**Combination vaccines that include both DTPa and Hib (Infanrix Hexa, Infanrix-Hib, Pediacel and Poliacel)** – see Part 3.16, 'Pertussis').

## Transport, storage and handling

Transport according to general guidelines (see Part 1.10, 'Transport, storage and handling of vaccines'). Store conjugate Hib vaccines at 2°C to 8°C. With the exceptions of the two lypholised PRP-T monovalent Hib vaccines (ActHib and Hiberix), Hib containing vaccines must not be frozen. If vaccine has been exposed to temperature less than 0°C, do not use.

## Dosage and administration

The dose of Hib vaccine is 0.5 mL to be given by IM injection. Conjugate Hib vaccines may be administered on the same day as any of the other childhood vaccines in the ASVS.

## Recommendations

**(i)** Hib vaccine is recommended for all infants from 2 months of age.

**(ii)** In Indigenous populations, where high attack rates associated with early peak disease onset were known to occur prior to the introduction of Hib immunisation,[5] it is important that PRP-OMP be used because of the early antibody response seen with this vaccine. Re-emergence of Hib disease has been observed in Alaska, a population with a pattern of high incidence early onset disease, when the Hib vaccine in use was changed from PRP-OMP to HbOC.[13] As the detailed epidemiology of Hib disease before vaccination in Aboriginal and Torres Strait Islander children throughout Australia is not known, and for simplicity of implementation, PRP-OMP is recommended for all Aboriginal and Torres Strait Islander children. Immunisation using PRP-OMP requires 2 doses, at 2 and 4 months, followed by a booster at 12 months of age.

**(iii)** In non-Indigenous children, any licensed Hib vaccine may be used, as the period of disease risk does not begin until after 6 months of age. Immunisation using PRP-OMP requires 2 doses at 2 and 4 months, followed by a booster at 12 months of age. If either PRP-T or HbOC is used, 3 doses at 2, 4 and 6 months are needed, with a booster at 12 months of age.

**(iv) Interchangeability of Hib vaccines**

It is recommended that the same conjugate vaccine be used for all doses. However, if necessary, after the first dose any Hib vaccine may be used to complete the primary course.[14] For primary vaccination, only 2 doses of PRP-OMP are required, but if any other Hib vaccine is given, a total of 3 doses is required to complete the primary course.[15] This means that if the previous Hib vaccine type is unknown for any doses or the same vaccine type is unavailable, the primary course can be completed with a total of 3 doses of any combination of registered Hib vaccines. For booster doses and in children over 15 months of age, regardless of previous Hib vaccinations, a single dose of any registered Hib vaccine is sufficient for protection. Details of catch-up vaccination schedules are given in Part 1.9, 'Catch-up vaccination'.

**(v) Vaccine failures**

Children who have developed confirmed Hib disease after 2 or more doses of PRP-OMP or 3 or more doses of either PRP-T or HbOC warrant investigation of their immune response, including PRP antibody levels before and after a booster dose of Hib vaccine. Consultation with an immunologist with paediatric expertise is recommended.

**(vi) Preterm babies**
Extremely preterm babies (<28 weeks or <1500 g) who are vaccinated with PRP-OMP should be given an extra dose at 6 months, resulting in a 4-dose schedule at 2, 4, 6 and 12 months.[16] When other Hib vaccines are used, no change in the usual schedule is required.

**(vii) Splenectomy**
Hib is an uncommon cause of post-splenectomy sepsis in adults and children. Children over 2 years of age who have received all scheduled doses of Hib vaccine do not require a booster dose following splenectomy. A single dose of Hib vaccine is recommended for other splenectomised individuals (unvaccinated or incompletely vaccinated for age) of any age who have close contact with children less than 5 years of age. The vaccine should be given 2 weeks before a planned splenectomy. Subsequent booster doses of Hib vaccine are not required.[17] For other immunisations recommended for asplenic or splenectomised persons, see Part 2.3, 'Groups with special vaccination requirements'.

**(viii) Management of contacts of a child with invasive Hib disease**
Health-care workers should be guided by public health authorities in the public health management of cases of invasive Hib disease.

As the incidence of invasive Hib disease is low, rifampicin chemoprophylaxis is no longer routinely indicated unless the household contains one or more infants under 7 months of age (regardless of vaccination status), or a child aged 7 months to 5 years who is inadequately vaccinated according to the Hib schedule. In this case, all persons in the household should receive rifampicin prophylaxis following a case of invasive Hib disease in any household member, with the exception of pregnant women for whom ceftriaxone may be used. The recommended dose of rifampicin is 20 mg/kg as a single daily dose (maximum daily dose 600 mg) for 4 days. Neonates (<1 month of age) should receive 10 mg/kg daily for 4 days. "*Similarly, if the index case attends a child day-care facility for more than 18 hours a week, rifampicin should be given to all children and staff who were in the same room group (as the case) in the 7 days preceding the case's onset, provided that at least one of these close contacts is a child under 24 months of age who is inadequately vaccinated. Although there may have been some intermingling of all the children at the facility at the beginning and end of the day, this is usually of a short duration only and not enough to justify extending the use of rifampicin*." Rifampicin prophylaxis is of no value more than 30 days after initial contact with case

## Adverse events and precautions
Swelling and redness at the injection site following the first dose have been reported in up to 5% of cases. These adverse events usually appear within 3 to 4 hours and resolve completely within 24 hours. The incidence of these reactions declines with subsequent doses, so it is recommended that the course of vaccination be completed despite the occurrence of such events.

## Contraindications
The only contraindication to Hib vaccine are a previous anaphylactic reaction to the vaccine or any vaccine components.

## Conflicts with product information
The product information for Hib vaccines recommends the vaccine for children aged 2 months to 5 years. NHMRC recommends administration of Hib vaccine to older persons with asplenia who are in contact with children under the age of 5 years.

With the exception of PRP-OMP, the product information for Hib vaccines recommends use as a booster at 18 months, but the NHMRC regards use at 12 months of age as likely to result in an equivalent immune response.

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## 3.8 HEPATITIS A

## Virology

Hepatitis A is an acute infection of the liver caused by the hepatitis A virus (HAV), which is now classified as a hepatovirus.[1] The virus survives well in the environment – 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.[2,3]

## Clinical features

The incubation period of hepatitis A is 15 to 50 days, with a mean of about 30 days.[1] HAV is excreted in faeces for up to 2 weeks before the onset of illness and for at least one week afterwards.[1] Therefore patients with hepatitis A should be considered as being infectious for a week after the onset of jaundice.

In young children HAV usually causes either an asymptomatic infection or a very mild illness without jaundice. 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, followed a day or two later by jaundice and pale faeces. 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. Complications of hepatitis A are uncommon but include, on rare occasion, fulminant hepatitis.[4] Hepatitis A does not cause chronic liver disease.

The diagnosis 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] False-negative IgM results are extremely rare but there are occasional false positives in patients with rheumatoid arthritis. Serum anti-HAV IgG indicates past infection and therefore immunity; it probably persists for life.

## Epidemiology

HAV is predominantly transmitted by the faecal-oral route. The infecting dose is unknown, but because HAV is transmitted so readily by person to person contact, it is presumed to be low.

The epidemiology of hepatitis A is closely linked to social and environmental circumstances. Globally, 3 patterns of hepatitis A are recognised.[5]

- In regions with poor environmental sanitation and hygiene, HAV infection is 'highly' endemic. It is virtually a universal infection early in life (<5 years of age), at an age when most of the infections are asymptomatic. Consequently hepatitis A is an 'invisible' public health issue with few reported cases.
- A pattern of 'intermediate' endemicity is seen in regions with transitional economies and recent improvements in environmental circumstances. Many children escape infection in early childhood, but nevertheless still become infected later in childhood or during adolescence when symptomatic disease is likely. Therefore paradoxically, whereas the rate of infection is declining the 'visibility' of hepatitis A, and therefore the public health concern, is increasing.
- In industrialised countries with high standards of hygiene and sanitation the pattern is of 'low' endemicity. Because they have not been previously exposed to HAV many adults are susceptible,[6] and they can readily acquire hepatitis A when, for example, they travel to regions of high endemicity.

Within Australia, 3 main patterns of hepatitis A transmission occur.

- Large, slowly evolving community-wide outbreaks.[7] These occur at intervals of 5 or more years and are particularly difficult to control. They tend to affect low socioeconomic areas, and young children play a substantial role in their propagation.[8,9] Certain gatherings or groups of people are prone to be affected by HAV; they are susceptible to intense transmission among themselves, and are able to serve as a potential source for further transmission back to the broader community. The intensifying effect of these settings is particularly evident during community-wide outbreaks. These settings include: child day-care centres and pre-schools;[10] communities of men who have sex with men;[11] schools and residential facilities for the intellectually disabled;[12] and communities of injecting drug users.[11]

- Sporadic cases of hepatitis A. Although some of these cases are acquired during travel to developing countries, many do not have either an obvious risk factor or an apparent link to other cases. It is probable that unrecognised infection in young children contributes to a substantial proportion of these cases.
- Point-source outbreaks from either a contaminated food item[13]or contaminated water or an infected food-handler. Although HAV is readily transferred from hands to food if personal hygiene is suboptimal,[14] point-source outbreaks of hepatitis A are nevertheless very uncommon in Australia.

## Vaccines

Five monovalent hepatitis A vaccines, 2 combined hepatitis A/hepatitis B vaccines and a combined hepatitis A/typhoid vaccine are currently available in Australia.

- **Avaxim** – Aventis Pasteur (formaldehyde inactivated hepatitis A virus (GBM strain)) adsorbed on to aluminium hydroxide; each 0.5 mL dose contains 160 enzyme linked immunosorbent assay (ELISA) units of viral antigens; aluminium 0.3 mg as aluminium hydroxide, 2-phenoxyethanol 2.5 µL, formaldehyde 12.5 µg, and a trace amount of neomycin sulphate).

- **Havrix Junior** – GlaxoSmithKline (formaldehyde inactivated hepatitis A virus (HM175 strain)) adsorbed on to aluminium hydroxide; each 0.5 mL dose contains 720 ELISA units of viral antigens, aluminium 0.25 mg as aluminium hydroxide, 0.5% w/v 2-phenoxyethanol and a trace amount of neomycin sulphate.

- **Havrix 1440** – GlaxoSmithKline (formaldehyde inactivated hepatitis A virus (HM175 strain)) adsorbed on to aluminium hydroxide; each 1.0 mL dose contains 1440 ELISA units of viral antigens, aluminium 0.5 mg as aluminium hydroxide, 0.5% w/v 2-phenoxyethanol and a trace amount of neomycin sulphate.

- **Twinrix Junior (360/10)** – GlaxoSmithKline (formaldehyde inactivated hepatitis A virus (HM175 strain) and recombinant hepatitis B vaccine) adsorbed on to aluminium adjuvant; each 0.5 mL dose contains 360 ELISA units of HAV antigens, 10 µg recombinant DNA hepatitis B surface antigen protein, aluminium 0.225 mg as aluminium phosphate and aluminium hydroxide, 0.5% w/v 2-phenoxyethanol and a trace amount of neomycin sulphate.

- **Twinrix (720/20)** (previously known as **Twinrix Adult**) – GlaxoSmithKline (formaldehyde inactivated hepatitis A virus (HM175 strain) and recombinant hepatitis B vaccine) adsorbed on to aluminium adjuvant; each 1.0 mL dose contains 720 ELISA units of HAV antigens, 20 µg recombinant DNA hepatitis B surface antigen protein, aluminium 0.45 mg as aluminium phosphate and aluminium hydroxide, 0.5% w/v 2-phenoxyethanol and a trace amount of neomycin sulphate).

- **VAQTA Paediatric/Adolescent formulation** – CSL Vaccines/Merck Sharp & Dohme (formaldehyde inactivated hepatitis A virus (CR326F strain)) adsorbed on to aluminium hydroxide; each 0.5 mL dose contains approximately 25 units (U) of hepatitis A virus protein, aluminium 0.225 mg as aluminium hydroxide and borax 35 µg.

- **VAQTA Adult formulation** – CSL Vaccines/Merck Sharp & Dohme (formaldehyde inactivated hepatitis A virus (CR326F strain)) adsorbed on to aluminium hydroxide; each 1.0 mL dose contains approximately 50 units (U) of hepatitis A virus protein, aluminium 0.45 mg as aluminium hydroxide and borax 70 µg.

- **Vivaxim –** Aventis Pasteur (inactivated hepatitis A virus and typhoid Vi capsular polysaccharide); supplied in a unique dual-chamber syringe which enables the two vaccines to be mixed just prior to administration. Each 1.0 mL dose of mixed vaccine contains 160 ELISA units of inactivated hepatitis A virus antigens, 25 µg purified typhoid capsular polysaccharide, aluminium 0.3 mg as aluminium hydroxide, 2-phenoxyethanol 2.5 µL, formaldehyde 12.5µg, and trace amounts of neomycin sulphate and bovine serum albumin).

The 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 then adsorbed on to 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]

The Avaxim, Havrix, Twinrix and Vivaxim vaccines contain a preservative, 2-phenoxyethanol. All the vaccines contain minute amounts of residual formaldehyde. Although the manufacturers use slightly different production methods and quantify the HAV antigen content in their respective vaccines differently, several studies indicate that the 'equivalent' vaccines of the different manufacturers are, if necessary, interchangeable.[15-17]

The inactivated hepatitis A vaccines induce HAV antibodies (anti-HAV) at titres many fold greater than that provided by the recommended dose of normal human immunoglobulin. Although the vaccines are highly immunogenic (see below), the titres are usually below the detection limits of the routinely available commercial tests for anti-HAV.[1] *Therefore testing to assess immunity following vaccination against hepatitis A is neither necessary nor appropriate.*

The seroconversion and anti-HAV levels in adults appear to be 2 weeks less following administration of Havrix than following the other vaccines,[16,18] but this is unlikely to be of clinical significance. Nevertheless, ≥90% of adults have seroconverted by 4 weeks after vaccination with high anti-HAV titres regardless of the vaccine used.[16,18] The vaccines are also highly immunogenic in children, with virtually universal seroconversion by 4 weeks.[19,20]

Two randomised clinical trials conducted in the early 1990s documented the fact that the inactivated hepatitis A vaccines have a very high protective efficacy, approaching 100%.[21,22] This finding is supported by a vaccine effectiveness of 98% (95% confidence interval 86 to 100%) observed following routine hepatitis A vaccination of children in a community in the United States prone to recurrent epidemics of the disease.[23]

The duration of immunity and therefore protection following vaccination is not certain. However, vaccine-induced anti-HAV persists for at least 10 years,[24] and probably lasts for considerably longer.[25]

## Transport, storage and handling

Transport hepatitis A vaccines according to the general recommendations (see Part 1.10, 'Transport, storage and handling of vaccines'). Store in the refrigerator at 2° to 8°C; hepatitis A vaccine must not be frozen.

## Dosage and administration

The inactivated hepatitis A vaccines are administered by IM injection. The recommended dosages and schedules for use in Australia are given in Table 3.8.1.

**Table 3.8.1: Recommended dosages and schedules for use of the inactivated hepatitis A vaccines**

| Vaccine | Vaccinee's age (yr) | Dose (HAV antigen) | Volume per dose (mL) | Vaccination schedule (mo=months) |
|---|---|---|---|---|
| **Monovalent hepatitis A vaccines** | | | | |
| Avaxim | ≥2 | 160 EIA U | 0.5 | 0, 6 to 12 mo |
| Havrix Junior | 2–15 | 720 EIA U | 0.5 | 0, 6 to 12 mo |
| Havrix 1440 | >15 | 1440 EIA U | 1.0 | 0, 6 to 12 mo |
| VAQTA Paediatric/ Adolescent | 1–17 | 25 U | 0.5 | 0, 6 to 18 mo |
| VAQTA Adult | >17 | 50 U | 1.0 | 0, 6 to 18 mo |
| **Combination hepatitis A/B vaccines** | | | | |
| Twinrix Junior (360/10) | 1–15 | 360 EIA U | 0.5 | 0, 1, 6 mo |
| Twinrix (720/20) | >15 | 720 EIA U | 1.0 | 0, 1, 6 mo |
| Twinrix (720/20)* | 1–15 | 720 EIA U | 1.0 | 0, 6 to 12 mo |
| Twinrix (720/20)** | >15 | 720 EIA U | 1.0 | 0, 7, 21 days, 12 mo |
| **Combination hepatitis A/typhoid vaccine** | | | | |
| Vivaxim | ≥16 | 160 EIA U | 1.0 (mixed | 0; a single dose of adult |

| | | | | |
|---|---|---|---|---|
| | | | vaccine) | formulation hepatitis A vaccine should be given at 6- to 12 mo. |

*This schedule should not be used for those who require prompt protection against hepatitis B; for example if there is close contact with a known hepatitis B carrier.

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

## Recommendations

**(i)** To avoid unnecessary vaccination, it is recommended that the following groups be screened for pre-existing immunity to hepatitis A:

- those born before 1950;
- those who spent their early childhood in endemic areas, including in Indigenous Australian communities; and
- those with an unexplained previous episode of hepatitis or jaundice.

If, upon screening, a person has either total hepatitis A antibodies or anti-HAV IgG, he/she has presumably had prior, perhaps unrecognised, HAV infection, and can be assumed to be immune and therefore does not need hepatitis A vaccination.

**(ii) Hepatitis A vaccination is recommended for:**

- travellers to endemic areas;

  Hepatitis A vaccine is recommended for all travellers to 'moderate' and 'high' endemicity countries, which essentially means to all developing countries. 'Travellers' includes 'up-market' business travellers, particularly those undertaking regular visits to endemic countries, as well as backpackers undertaking prolonged travel 'on the cheap'. It also includes expatriates, diplomats, aid workers and missionaries living abroad, and military personnel who may have to be deployed overseas at very short notice.

  A single dose of vaccine provides protective levels of anti-HAV for at least a year,[1] but the second dose is recommended to increase the duration of protection. A single dose can be assumed to provide adequate protection if administered within 2 weeks of departure.

  Although a single dose of hepatitis A vaccine may not provide complete protection if administered within 2 weeks of departure, travellers departing at short notice must be advised on the need for care when choosing food and drinks in the 2 weeks following vaccination. Because normal human immunoglobulin is now in very short supply it should only be given (at the same time as a dose of hepatitis A vaccine[19]) to those, such as aid-workers about to be deployed in refugee camps, who will be living in inadequate circumstances.

  As they do not contain live viruses, the inactivated hepatitis A vaccines can be administered either simultaneously with or within a month of other vaccines relevant to international travel.[26]

- all Aboriginal and Torres Strait Islander children between 18 months and 6 years of age in north Queensland. This recommendation is a response to the high incidence of hepatitis A, with associated fatalities, documented in Aboriginal and Torres Strait Islander children in the region in the 1990s.[4] Routine hepatitis A vaccination of these children commenced in early 1999. The first dose is scheduled at 18 months of age, and the second dose 6 months later at the second birthday.
- those working in rural and remote Indigenous communities;
- child day-care and preschool personnel. Occupationally acquired hepatitis A is a not uncommon occurrence among day-care and preschool personnel.[10] Vaccination against hepatitis A is strongly recommended for these staff, and must be considered as a standard 'workplace health and safety' practice;
- the intellectually disabled and their carers;
- health-care workers – even though standard precautions should be utilised at all times, hepatitis A vaccination is recommended for nursing and medical staff in paediatric wards, intensive care units

and emergency departments that provide for substantial populations of Aboriginal and Torres Strait Islander children, and nursing and medical staff on rural and remote Indigenous communities;

- sewage workers;
- men who have sex with men;
- injecting drug users;
- patients with chronic liver disease. Hepatitis A vaccination is recommended for patients with chronic liver disease of any aetiology. Those with chronic liver diseases of mild to moderate severity mount a satisfactory immune response following vaccination,[27] but those with end-stage liver disease do not respond as well, and liver transplant recipients may not respond at all.[28] Nevertheless, all those with chronic liver disease should be vaccinated, preferably as early in the course of the disease as possible.
- patients with haemophilia who may receive pooled plasma concentrates.

**(iii) The combined hepatitis A/hepatitis B vaccines**
The immunogenicity and reactogenicity profiles of the combined hepatitis A/hepatitis B vaccines are similar to those when the vaccines are administered separately.[29] Virtually all recipients of the combination vaccines are immune to HAV, and at least 90% are immune to hepatitis B, after the first 2 doses of a 3-dose regimen.[29]

**Twinrix (720/20)** can be administered in a 2-dose regimen in people 1 to 15 years of age (Table 3.8.1).[30] 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 known hepatitis B carrier.

The combined hepatitis A/hepatitis B vaccines should be considered for those at risk of acquiring both infections including:

- expatriates and long-term visitors to developing countries. NB: Twinrix (720/20) can be administered according to a 'rapid' schedule if there is limited time before departure. This consists of a single dose on each of days 0, 7 and 21. A (fourth) booster should be given 12 months after the first dose to ensure longer-term protection;[31]
- medical, dental and nursing undergraduate students;
- men who have sex with men;
- injecting drug users;
- patients with chronic liver disease;
- the intellectually disabled and their carers;
- people with haemophilia who may receive pooled plasma concentrates.

**(iv) The combined hepatitis A/typhoid vaccine**
Combining the inactivated hepatitis A and typhoid capsular polysaccharide vaccines results in reactogenicity and immunogenicity profiles similar to those experienced when the vaccines are administered separately.[32]

The combined hepatitis A/typhoid vaccine is recommended for all those ≥16 years of age who intend travelling to developing countries. The vaccine can be administered simultaneously with or within a month of other vaccines relevant to international travel.

A single dose of a monovalent adult formulation hepatitis A vaccine 6–12 months later is required to provide longer term protection against hepatitis A. A booster dose of typhoid capsular polysaccharide vaccine is required after 3 years if there is a continued risk. The combined hepatitis A/typhoid vaccine may be used as a 'booster' vaccine if a person received a previous dose of an adult formulation hepatitis A.

**(v) Interchangeability of vaccines**
Several studies indicate that the 'equivalent' vaccines of the different manufacturers are, if necessary, interchangeable.[15-17]

## Adverse events and precautions

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 50% of adult recipients of either Havrix or VAQTA reported local soreness at the injection site, ~15% reported headache and ~5% malaise or fatigue.[19] Local adverse events, although usually mild, are less following administration of Avaxim[15,18] probably because of the smaller volume and lower aluminium content of this vaccine. Up to 20% of children who received either Havrix or VAQTA experienced 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.[19]

The hepatitis A vaccines do not affect liver enzyme levels. Although, upon rare occasions, serious adverse events such as Guillain-Barré syndrome and autoimmune haemolytic anaemia may follow hepatitis A vaccination, there is to date no evidence of a causal relationship.[33]

## Contraindications

Hepatitis A vaccines should not be administered to anyone with a previous anaphylactic reaction to either any of the vaccine components, or a previous dose of hepatitis A vaccine.

## Management of hepatitis A

**(i) Following all cases**

Normal human immunoglobulin (NHIG) should be administered to close contacts of all cases of hepatitis A. 'Close contacts' are those who have had contact with a case during the 2 weeks before, up until one week after the onset of jaundice, and usually includes only household and/or sexual contacts. The NHIG should be given within 2 weeks of the exposure in the doses given in Table 3.8.2; NHIG may not be effective if given >2 weeks after the exposure.[19]

**Table 3.8.2: Recommended doses of normal human immunoglobulin (NHIG) to be given as a single intramuscular injection for outbreak control**

| Weight | Dose NHIG |
|---|---|
| Under 25 kg | 0.5 mL |
| 25–50 kg | 1.0 mL |
| Over 50 kg | 2.0 mL |

If a person with hepatitis A is a food-handler by occupation, NHIG should be administered to the other food-handlers employed in the same food establishment.[19] A review of food-handling procedures in the establishment should be undertaken and the staff reminded of standard food and personal hygiene practices. A food-handler with hepatitis A should be excluded from work until one week after the onset of jaundice.

(Although a recent clinical trial in Italy demonstrated that hepatitis A vaccine was ~80% effective in preventing secondary infection among household contacts of sporadic cases of hepatitis A, the trial did not involve the use of NHIG.[34] Because only NHIG can offer immediate protection, the use of vaccine alone is not recommended for the management of close contacts of cases of hepatitis A in Australia unless there is a shortage of NHIG *and* the contact (with a case) took place less than one week previously.[35] As mentioned above in 'Recommendations', hepatitis A vaccine can be administered at the same time as NHIG.)

**(ii) Cases associated with either a child day-care centre or preschool**

Although a single case of hepatitis A probably does not justify the mass use of NHIG, two or more cases (associated with a day-care or preschool facility) that occur in different households is strongly suggestive that transmission of HAV is occurring within the facility.[10] NHIG should then be offered to all staff and children at the facility.

**(iii) Outbreaks of hepatitis A[35]**

The prompt and liberal administration of NHIG has been shown to interrupt outbreaks of hepatitis A in well-defined communities such as child day-care centres, and in closed communities such as religious communities. Provided that vaccination is started early in the course of an outbreak and provided that high vaccine coverage can be achieved, hepatitis A vaccination can also interrupt outbreaks in well-defined communities such as rural[36] and religious communities.[37] However, neither NHIG[7] nor hepatitis A vaccine[38] have been demonstrated to effectively interrupt transmission of HAV in large community-wide outbreaks. This may be because these interventions have been implemented too late and with inadequate coverage.

Therefore, as soon as an outbreak of hepatitis A is recognised in either a well-defined or closed community, NHIG should be administered to all those considered as being at risk. Hepatitis A vaccine should be considered as an alternative to NHIG in those communities that are likely to experience further outbreaks in the future.[23] During large community-wide outbreaks, the emphasis should be on ensuring that NHIG is administered to the close contacts (ie. household and sexual contacts) of cases, and to maintain surveillance for hepatitis A occurring within those settings capable of intensifying the transmission of HAV.

## Use in pregnancy

Pregnancy is not a contradiction to hepatitis A vaccination.

## Conflicts with product information

None.

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# 3.9 HEPATITIS B

## Virology

Hepatitis B virus (HBV) contains a partially double-stranded DNA. The outer surface of the virus is a glycolipid which contains the hepatitis B surface antigen (HBsAg); the other important antigenic components are the hepatitis B core antigen (HBcAg), and the hepatitis B e antigen (HBeAg). HBcAg is not detectable in serum, but can be detected in liver tissue in people with acute or chronic hepatitis B infection. Antibodies developed to HBsAg (anti-HBs) indicate immunity, whereas persistence of HBsAg denotes infectivity, which is greater if HBeAg is positive.[1]

## Clinical features

In adults, the infection frequently causes symptomatic acute hepatitis (approximately 50%), but in young children, particularly those under one year of age, infection is usually asymptomatic. The incubation period is 45 to 180 days and the period of communicability extends from several weeks before the onset of acute illness to usually the end of the period of acute illness. Acute illness is 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, arthralgia, skin rashes, arthritis and the passage of dark coloured urine and light coloured stools. During recovery, malaise and fatigue may persist for many weeks. Fulminant hepatitis occurs in approximately 1% of acute cases.[1,2]

Following acute infection, one to 12% of those infected as adults[2,3] and up to 90% of those infected as neonates[1,2] remain persistently infected for many years. Chronically infected carriers of HBV are identified by the long-term presence (longer than 6 months) of circulating HBsAg.[4]

**A**lthough they are capable of transmitting the disease, carriers of HBV often remain asymptomatic and may not be aware that they are infected. Most of the serious complications associated with hepatitis B infection occur in HBV carriers. Chronic active hepatitis develops in over 25% of carriers, and up to 25% die prematurely of cirrhosis or hepatocellular carcinoma.[1,2]

## Epidemiology

The prevalence of HBV carriage differs in different parts of the world, and may be quite variable within countries. Carrier rates vary from 0.1 to 0.2% among Caucasians in the United States, Northern Europe and Australia, 1 to 5% in the Mediterranean countries, parts of Eastern Europe, China, Africa, Central and South America, and greater than 10% in some Australian Aboriginal, Central African, and South-East Asian populations. First generation immigrants usually retain the carrier rate of their country of origin, but subsequent generations show a declining carrier rate irrespective of vaccination.

Transmission of hepatitis B may result from inoculation or mucosal contact with blood or sexual secretions from an HBsAg-positive individual. However, screening of blood and organ donors has virtually eliminated the risk of transmission of hepatitis B through blood transfusion and organ transplants.[5,6] Saliva may also contain levels of virus which are likely to be infective only if inoculated directly into tissue. Transmission by inadvertent parenteral inoculation such as by toothbrush, razor etc. through close personal contact in households in which a carrier resides is a low but significant risk.

Routes of transmission include:

- sharing injecting equipment, (such as occurs in injecting drug use);
- needlestick injury, and other types of parenteral inoculation;
- sexual intercourse (heterosexual or homosexual, although the latter has a higher risk);
- transmission from infected mother to neonate (vertical transmission), usually at or around the time of birth;
- child-to-child (horizontal) transmission, usually through contact between open sores or wounds;
- breastfeeding.

**Australian vaccination policy**

The initial strategy for the control of hepatitis B in Australia commenced in 1988, targeting groups at particular risk for vaccination at birth. In addition to vaccine, hepatitis B immunoglobulin (HBIG) was given if the mother was a hepatitis B carrier. In 1996, the NHMRC recommended a universal hepatitis B vaccination program for infants and adolescents. The adolescent program commenced in some States and Territories in 1997 and the universal infant program began nationally in 2000. The adolescent program will continue until those immunised for hepatitis B in the childhood program reach adolescence.

## Vaccines

- **Engerix-B –** GlaxoSmithKline (recombinant DNA hepatitis B vaccine). **Adult formulation** – each 1 mL monodose vial contains hepatitis B surface antigen protein 20 µg per mL, adsorbed on to 0.5 mg elemental aluminium as aluminium hydroxide. **Paediatric formulation** – each 0.5 mL monodose vial contains 10 µg of antigen protein adsorbed on 0.25 mg elemental aluminium as aluminium hydroxide. The paediatric formulation is registered for use in children and young adults up to the twentieth birthday. Both formulations contain a trace of thiomersal (< 3 µg).

- **H-B-Vax II** – CSL Vaccines/Merck Sharpe & Dohme (recombinant DNA hepatitis B vaccine). **Adult formulation preservative free** – each 1 mL dose of adult formulation contains hepatitis B surface antigen protein 10 µg adsorbed on to 0.5 mg aluminium hydroxide. The adult formulation is approved for use as an alternative 2-dose schedule in adolescents aged 11–15 years. **Paediatric formulation preservative free –** each 0.5 mL monodose vial contains 5 µg of antigen protein

adsorbed on to 0.25 mg aluminium hydroxide. The paediatric formulation is registered for use in children and adolescents up to the twentieth birthday. **Dialysis formulation preservative free –** each 1 mL vial contains hepatitis B surface antigen 40 µg adsorbed on to 0.5 mg aluminium hydroxide.

- **Combination vaccines that include both DTPa and hepatitis B (Infanrix HepB, Infanrix Penta and Infanrix Hexa)** – See Part 3.16, 'Pertussis'.

- **Comvax** – CSL Vaccines/Merck Sharp & Dohme (Hib (PRP-OMP) -hepatitis B); see Part 3.7, '*Haemophilus influenzae* type b'.

- **Twinrix (720/20)** (previously known as **Twinrix Adult)** and **Twinrix Junior (360/10)** – combined hepatitis A/hepatitis B vaccines: see Part 3.8, 'Hepatitis A'.

Hepatitis B vaccines are prepared using recombinant technology. Following purification, the HBsAg protein is adsorbed onto elemental aluminium (as hydroxide and/or phosphate). Preservatives, including thiomersal, may be added. Hepatitis B vaccines may contain up to 1% yeast proteins (but no yeast DNA).

Thiomersal-free vaccines, such as H-B-Vax II preservative-free paediatric formulation, are now available and are recommended for administration in newborns and infants.[7] Engerix-B paediatric formulation contains a trace amount of thiomersal (1:500 000) which is one-twentieth the previous thiomersal content. All other infant and childhood hepatitis B-containing combination vaccines, such as Infanrix-HepB, Infanrix Penta, Comvax and Twinrix Junior (360/10), are thiomersal-free.

## Transport, storage and handling

Store in refrigerator at 2°C to 8°C. Do not freeze. Transport and store in accordance with general guidelines (see Part 1.10, 'Transport, storage and handling of vaccines'). Monovalent hepatitis B vaccines are white, slightly opalescent liquids. Any visible change in the product, such as an amorphous flocculate or a granular precipitate, may indicate incorrect storage conditions and consequent reduction in vaccine immunogenicity. Do not use vaccine with these changes.

## Dosage and administration

**(i)** Administer by deep IM injection into the deltoid muscle in adults and older children, and into the anterolateral aspect of the thigh in neonates and infants under 12 months of age.

**(ii)** For children and young adults up to the twentieth birthday a total of 3 doses of 0.5 mL of paediatric formulation is recommended. The optimal interval is one month between the first and second doses and a third dose 5 months after the second dose. The use of longer time intervals between doses does not impair the immunogenicity of hepatitis B vaccine especially in adolescents and young children.[8,9] The minimum interval between the second and third doses is 2 months.

**(iii)** For adults over 20 years of age a full course of hepatitis B vaccine consists of 3 doses of 1 mL of adult formulation. There should be an interval of 1 to 2 months between the first and second doses with a third dose 2 to 5 months after the second dose (this schedule applies to both Engerix-B and H-B-Vax II). This induces protective levels of neutralising antibody against hepatitis B virus in over 90% of adults. The frequency of seroconversion increases progressively from approximately 35% after the first injection to over 90% after the third injection. There is evidence of immunity (anti-HBs) in most vaccinated subjects after administration of 2 doses of the 3-dose vaccine regimen. However, the third dose is necessary to increase the percentage of responders and to provide long-term protection.

**(iv) Alternative 2-dose regimens**

Adolescents (11 to 15 years of age), vaccinated with H-B-Vax II 10 µg (adult formulation) in a 2-dose regimen of 0 and 4-6 months, develop similar protective antibody levels to those with the 5 µg (paediatric) formulation in the standard 3-dose regimen administered at 0, 1 and 6-12 months[10,11] *(level II evidence)*. See Table 3.9.1.

When protection is required against both diseases in children 1 to 15 years of age, administration of Twinrix (720/20) in a 2-dose regimen at 0 and 6–12 months also results in protective antibody levels to both hepatitis A and B (Table 3.9.1).

**Table 3.9.1: Comparison of the standard and alternative hepatitis B and hepatitis A/B vaccination schedules for children and adolescents**

| Vaccine | Age | Dose (HBsAg protein) | Volume | Schedule (mo=months) |
|---|---|---|---|---|
| **Monovalent hepatitis B vaccines** | | | | |
| Engerix-B (paediatric) | up to 20 years | 10 µg | 0.5 mL | 0, 1, 6 mo (3-dose schedule) ***or*** 0, 1, 2, 12 mo (4 dose rapid schedule) |
| H-B-Vax II (paediatric) | up to 20 years | 5 µg | 0.5 mL | 0, 1, 6 mo (3-dose schedule) |
| H-B-Vax II (adult) | 11–15 years | 10 µg | 1.0 mL | 0, 4–6 mo (2-dose schedule) |
| **Combination hepatitis A/B vaccines** | | | | |
| Twinrix (720/20)* | 1–15 years | 20 µg | 1.0 mL | 0, 6–12 mo (2-dose schedule) |
| Twinrix Junior (360/10) | 1–15 years | 10 µg | 0.5 mL | 0, 1, 6 mo (3-dose schedule) |
| Twinrix (720/20) | >15 years | 20 µg | 1.0 mL | 0, 1, 6 mo (3-dose schedule) |
| Twinrix (720/20)** | >15 years | 20 µg | 1.0 mL | 0, 7, 21 days, 12 mo (rapid schedule) |

*This schedule should not be used for those who require prompt protection against hepatitis B; for example if there is close contact with a known hepatitis B carrier.

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

**(v) Accelerated schedule**
In circumstances where more rapid protection is required (eg. vaccination of travellers soon to depart to endemic regions), 2 products, Engerix-B (Adult) and Twinrix (720/20), are registered for use in an accelerated schedule of 0, 7 and 21 days, with a booster dose at 12 months. An alternative schedule using Engerix-B for children and adults is 0, 1, 2 and 12 months using the respective formulations.

## Recommendations

**Primary vaccination**

**(i) Infants and young children**

A birth dose of thiomersal free monovalent hepatitis B vaccine, followed by doses given in combination vaccines (such as DTPa-hepB, DTPa-hepB-IPV or Hib(PRP-OMP)-hepB) at 2, 4 and either 6 or 12 months, is now recommended for all children.

The rationale for the universal birth dose is not only to prevent vertical transmission from a carrier mother (recognising that there may be errors or delays in maternal testing or reporting), but also to prevent horizontal transmission in the first months of life from a carrier among the houshold contacts.[12] The birth dose should be given as soon as the baby is physiologically stable, and preferably within 24 hours of birth. Every effort should be made to administer the vaccine before discharge from the obstetric hospital.

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 or medical investigation for sepsis in the newborn.[13]

If an infant has missed the birth dose and is aged 8 days or older, a catch-up schedule is not required. A primary course of a hepatitis B-containing combination vaccine should be given at 2, 4 and either 6 or 12 months of age, (provided the mother is HBsAg negative).

**NB:** All babies of carrier mothers (preterm or term) must be given a birth dose of thiomersal free monovalent hepatitis B vaccine ***and*** HBIG (see (vi), 'Management of infants born to hepatitis B carrier mothers' below).

**(ii) Preterm babies**
Preterm babies do not respond as well to hepatitis B vaccine as term babies.[14-16] Thus, for babies under 32 weeks' gestation at birth, it is recommended to either:

(a) give vaccine at 0, 2, 4 and 6 months, measure anti-HBs at 7 months and give a booster at 12 months if antibody titre is low (less than 10 mIU/mL); or

(b) give vaccine at 0, 2, 4 and 12 months (if using Comvax), measure anti-HBs at 13 months and give a monovalent booster if antibody titre is less than 10 mIU/mL; or

(c) delay hepatitis B vaccination and use a 2, 4, 6 and 12 month 4-dose schedule. NB: This is only permissible if the mother is known to be hepatitis B seronegative.

**(iii) Booster doses**
Booster doses are not recommended in immunocompetent individuals after a primary course, as there is good evidence that a completed primary course of hepatitis B vaccination provides long-lasting protection. This applies to children *and* adults, *including* health-care workers and dentists.[17-20] However, booster doses are recommended for immunosuppressed individuals, in particular those with either HIV infection or renal failure. The time for boosting in such individuals should be decided by regular monitoring of anti-HBs levels at 6 to 12-monthly intervals.[17]

**(iv) Interchangeability of vaccines**
Although switching of brands is not recommended, in cases where the brand of vaccine used for previous doses is not known, any brand may be used as there is no reason to believe that use of a different brand will compromise immunogenicity or safety.

**(v) Serological confirmation of post-vaccination immunity**
Post-vaccination serological testing 4 weeks after the third dose of hepatitis B, is recommended for persons in the following categories:

- those at significant occupational risk (eg. health-care workers whose work involves frequent exposure to blood and body fluids);
- those at risk of severe or complicated disease (eg. the immunocompromised, and persons with pre-existing liver disease not related to hepatitis B);
- those in whom a poor response to hepatitis B vaccination is expected (eg. haemodialysis patients).

If adequate anti-HBs levels (≥10 mIU/mL) are not reached following the third dose, the possibility of HBsAg carriage should be investigated. Those who are HBsAg negative and do not respond should be offered further doses of vaccine. These can be given as either a fourth double dose or a further 3 doses at monthly intervals, with further testing 4 weeks later. Persistent non-responders should be informed about the need for HBIG within 72 hours of parenteral exposure to HBV.

Those at significant occupational risk who have a documented history of a primary course of hepatitis B vaccine but in whom seroconversion status is unknown, should be given a single booster dose of the vaccine and tested for anti-HBs levels 4 weeks later. If antibody level is <10 mIU/mL, give 2 further doses of hepatitis B vaccine according to the catch-up schedule, and re-test for anti-HBs levels at least 3-4 weeks after the second dose.

**(vi) Management of infants born to hepatitis B carrier mothers**
Routine antenatal screening for HBsAg is essential for correct implementation of the strategy to prevent newborn infants from becoming infected with, and therefore carriers of, HBV. Infants born to HBsAg-positive mothers should be given HBIG and a dose of thiomersal free monovalent hepatitis B vaccine on the day of birth. The dose of HBIG is 100 IU to be given by IM injection. Administration of HBIG is preferable within 12 hours of birth, as its efficacy decreases markedly if administration is delayed beyond 48 hours of birth.

The first dose of monovalent hepatitis B vaccine should be given at the same time as HBIG but in the *opposite thigh.* This regimen results in seroconversion rates of over 90% in neonates, despite concurrent administration of HBIG. If this is not possible, vaccination should not be delayed beyond 7

days of birth. Three subsequent doses of a multivalent/combination vaccine should be given at 2, 4 and either 6 or 12 months of age (depending on the vaccine used), so that the infant is given a total of 4 doses of hepatitis B-containing vaccines.

**(vii) Universal adolescent vaccination against hepatitis B**
Vaccination of all adolescents 10 to 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. Please refer to your State/Territory health department for further information.

**(viii) Other groups for whom hepatitis B vaccination is recommended**
*Note: the combined hepatitis A/hepatitis B vaccine should be considered for susceptible individuals in the groups marked with an asterisk **(*)**.*

- **Household contacts (other than sexual partners) of acute and chronic hepatitis B carriers**

There is a low, but definite, risk of transmission from a patient with acute or chronic hepatitis B. This can be reduced by not sharing household items which can penetrate skin (such as combs, nail brushes, tooth brushes and razors). Cutlery, crockery and other household items are not sources of infection.

The risk of contacts acquiring hepatitis B infection varies according to the HBeAg status of the carrier, and with cultural and socioeconomic factors. However, it should be recognised that in many situations, a number of family members will have been exposed by the time the risk is recognised. Testing before planned vaccination is recommended for such families as well as members of families who have migrated from high prevalence countries.

- **Sexual contacts**

Susceptible (anti-HBs negative) sexual partners of patients with acute hepatitis B should be offered post-exposure HBIG and hepatitis B vaccination; both should be initiated as soon as possible. Susceptible (anti-HBs negative) partners of asymptomatic carriers should also be offered vaccination.

Hepatitis B is relatively common in clients of sexual health services and vaccination should be offered to susceptible individuals at the time of first attendance.

*****Sexually active men who have sex with men should be vaccinated, unless they are already HBsAg positive or have serological evidence of past or continuing infection. The combined hepatitis A and B vaccine may be appropriate for men who have sex with men, if they are not immune to either disease, as they are at risk of both.

- **Haemodialysis patients, HIV-positive individuals and other immunosuppressed adults**

Dialysis patients, HIV-positive individuals and other immunocompromised adults should be given a larger than usual dose of hepatitis B vaccine. They should be given either (i) 1 mL of normal adult formulation in each arm on each occasion; or (ii) a single dose of dialysis formulation vaccine on each occasion, at 0, 1 and 6 months.

- ***Injecting drug users**

Injecting drug users who have not been infected with hepatitis B should be vaccinated.

- ***Recipients of certain blood products**

Screening of all blood donors for HBsAg has greatly decreased the incidence of transfusion-related hepatitis B virus infection. However, patients with clotting disorders who receive blood product concentrates may have an elevated risk of hepatitis B virus infection, and they should therefore be vaccinated.

- ***Individuals with chronic liver disease and/or hepatitis C**

Hepatitis B vaccination is recommended for those in this category who are seronegative for hepatitis B.[21]

- ***Residents and staff of facilities for persons with intellectual disabilities**

Vaccination of staff and susceptible residents is recommended in both residential and non-residential care of persons with intellectual disabilities.

- **Individuals adopting children from overseas**

These children should be tested for hepatitis B, and if they are HBsAg positive, members of the adoptive family should be vaccinated.

- ***Liver transplant recipients**

Such individuals should be vaccinated prior to transplantation if seronegative for hepatitis B, as they may be at increased risk of infection from the transplanted organ.

- ***Inmates and staff of long-term correctional facilities**

Inmates are at risk of hepatitis B because of the prevalence of homosexual intercourse, injecting drug use and amateur tattooing in some correctional facilities. Therefore they should be screened upon incarceration, and vaccinated if susceptible.

- **Health-care workers, dentists, embalmers, tatooists and body-piercers**

The risk to such workers differs considerably from setting to setting in different parts of Australia, but it is recommended that all staff directly involved in patient care, embalming or in the handling of human blood or tissue be vaccinated. Standard precautions against exposure to blood or body fluids should be used as a matter of routine.

- **Others at risk**
  - (i) Police, members of the armed forces and emergency services staff should be vaccinated if they are assigned to duties which may involve exposure.
  - (ii) Long-term travellers to regions of high endemicity, and those residing for some time in such regions who expect to have close personal contact with local residents should be vaccinated. Short-term tourists or business travellers are at very little risk of hepatitis B, provided they avoid exposure through sexual contact, injecting drug use, tattooing and body piercing.
  - (iii) Staff of child day-care centres will normally be at minimal risk of hepatitis B. If advice on risk is sought, the inquiry should be directed to the local public health authority.
  - (iv) Contact sports generally carry a very low risk of hepatitis B infection. Although the risk is very low vaccination should not be discouraged.
  - (v) As the risk in Australian schools is very low[22], vaccination of classroom contacts is seldom indicated. Nevertheless, vaccination of school children and adolescents should be encouraged.

**(ix) Post-exposure prophylaxis for hepatitis B**

Following significant exposure (percutaneous, ocular, or mucous membrane) to blood or potentially blood-contaminated secretions, the source individual should be tested for HBsAg as soon as possible.

If the person exposed has not been previously vaccinated against hepatitis B, his/her anti-HBs level should be determined immediately. If the person exposed is anti-HBs negative, and the source is either HBsAg positive, or cannot be identified and tested rapidly, administer a single dose of HBIG of 100 IU for children up to 30 kg weight (about 5 years of age) and 400 IU for all others within 72 hours. Also give hepatitis B vaccine (by IM injection into either the deltoid or anterolateral thigh) as soon as possible, but within 7 days of exposure. Two further doses of vaccine should be given, one and 6 months after the first dose.

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) following vaccination. If the response to previous vaccination is unknown, the anti-HBs level should be determined as quickly as possible. If the anti-HBs is <10 IU/mL, HBIG and vaccine should be administered as above.

In most instances, it is advisable to offer a course of hepatitis B vaccine to the non-immune health-care worker sustaining a non-hepatitis B virus needlestick injury, since the injury itself is evidence that they work in an area with a significant risk of exposure.

**Table 3.9.2: Post-exposure prophylaxis for non-immune individuals exposed to a HbsAg positive person**

| Type of exposure | Hepatitis B immunoglobulin | | Vaccine | Administration |
|---|---|---|---|---|
| ***Perinatal*** (exposure of babies during and after birth) | 100 IU by IM injection | Within 12 hours of birth, preferably immediately after birth | 0.5 mL by IM injection | Immediately after birth (preferably within 24 hours; no later than 7 days)* then repeat at 2, 4 and either 6 or 12 months. |
| ***Percutaneous*** | 400 IU by IM injection | Single dose within 72 hours | 0.5 or 1 mL by IM injection depending on age | Within 7 days*, repeat at 1and 6 months after first dose |
| ***Sexual*** | 400 IU by IM injection | Within 14 days of sexual contact | 0.5 or 1 mL by IM injection depending on age | Within 14 days*, repeat at 1 and 6 months after first dose |

*The first dose can be given at the same time as the HBIG, but should be administered at a separate site.

## Adverse events and precautions

**(i)** Adverse events after hepatitis B vaccination are transient and minor, and include soreness at the injection site (5%), fever (2 to 3%, usually low grade), nausea, dizziness, malaise, myalgia and arthralgia. Fever can be expected in 0.6 to 3.7% of neonates immunised with hepatitis B vaccine.

**(ii)** Anaphylaxis has been reported very rarely in adults. 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.[23] There have been a few reports of generalised febrile reactions attributed to yeast allergy, and exceptional instances of polyarteritis nodosa have been reported.

**(iii)** Adverse events related to components in the multivalent/combination vaccines are covered in the appropriate chapters.

**(iv) Effect of vaccination on carriers**
The vaccine produces neither therapeutic effects nor adverse events in hepatitis B virus carriers.

## Contraindications

- Anaphylactic sensitivity to yeast or to any of the vaccine components.
- Previous anaphylactic reaction to a hepatitis B vaccine.

## Use in pregnancy

Pregnancy should not be considered a contraindication to the use of hepatitis B vaccine for whom it would otherwise be indicated.

## Conflicts with product information

None.

## Hepatitis B immunoglobulin (HBIG)

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 antibody to HBsAg. As

stocks of HBIG are very limited, use should be strictly reserved for those who are at high risk, such as babies born to hepatitis B carrier mothers and health-care workers who are exposed to the blood of HBsAg-positive individuals through occupational exposure. Requests should be directed to the Director of the Australian Red Cross Blood Service in your State/Territory.

- **Hepatitis B immunoglobulin** – CSL Bioplasma (immunoglobulin prepared from human plasma containing high levels of antibody to surface antigen of the hepatitis B virus); 100 IU and 400 IU ampoules (the actual volume is stated on the label on the vial).

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# 3.10 IMMUNOGLOBULIN PREPARATIONS

## Introduction

Passive immunity can be provided by administration of human immunoglobulin.[1-3] The protection afforded is immediate, but is transient and lasts for only a few weeks, as the half-life of IgG, the major constituent, is between 3 and 4 weeks.

There are two types of immunoglobulin, normal and specific. It is important to recognise that separate immunoglobulin preparations are provided for intramuscular (IM) use and for intravenous use. These have different properties, and the preparations should *only* be given by the recommended route. Administration of IM immunoglobulin by the intravenous route will lead to severe reactions.

- **Normal human immunoglobulin (NHIG)**
  This is derived from the pooled plasma of blood donors. It contains antibody to microbial agents which are prevalent in the general population.

- **Specific immunoglobulins**
  These products are used to protect individuals against specific microbial agents such as cytomegalovirus, Australian bat lyssavirus, hepatitis B,[4] rabies and varicella-zoster viruses,[5,6] and tetanus and diphtheria toxins. Each of the specific immunoglobulins is described in more detail in this *Handbook* in the chapter or section relevant to the specific infection.

Most 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.

The first monoclonal antibody against an organism, respiratory syncytial virus (RSV),[7,8] is registered for use in Australia (see also Part 3.21, 'Respiratory syncytial virus'). Such products are not derived from blood donations.

Adverse events and storage requirements for specific immunoglobulins are similar to those for NHIG, and therefore are not listed under each specific immunoglobulin.

Donors of blood used for the production of NHIG and specific immunoglobulin products are screened and products treated to minimise the risk of the immunoglobulin preparations containing HIV, HBV, or hepatitis C virus (HCV). A pasteurisation step is usually used during manufacture. The risk of prion transmission remains theoretical.

## Potential interaction with vaccines

### Live attenuated virus vaccines

- Passively acquired antibody can interfere with the response to live attenuated virus vaccines by preventing vaccine strain viral replication after vaccine administration. Therefore, administration of live attenuated virus vaccines, such as measles and varicella-zoster vaccines, should be deferred for at least 3 months after the intramuscular administration of NHIG, and for at least 9 months after the administration of NHIG (intravenous).[9] For the same reason, immunoglobulin products should not be administered until at least 2 weeks after a vaccine has been given. However, Rh (D) immunoglobulin (anti-D) does not interfere with the antibody response to MMR vaccines and the two may be given at the same time in different sites with separate syringes or at anytime in relation to each other.

### Inactivated vaccines

- Inactivated vaccines such as tetanus, hepatitis B or rabies may be administered concurrently with passive antibody, using separate syringes and separate injection sites to induce passive/active immunity. This usually would occur when there has been actual or possible acute exposure.

## Availability of immunoglobulins

CSL Bioplasma supplies NHIG for intramuscular use. Rabies immunoglobulin can only be obtained upon application from State/Territory health authorities. RSV monoclonal antibody (Synagis; Abbott Australasia) is available commercially.

The specific immunoglobulins and the CSL Bioplasma NHIG for intravenous use, which are derived from Australian donated plasma, can only be obtained from the Australian Red Cross Blood Service with the permission of the State Director. The State Directors can be contacted by telephone (ACT 02 6206 6006; NSW 02 9229 4444; NT 08 8927 7855; QLD 07 3835 1333; SA 08 8422 1200; TAS 03 6230 6230 VIC 03 9694 0111; WA 08 9325 3333). The Australian Red Cross Blood Service supplies these products free of charge.

## Transport, storage and handling

All immunoglobulins must be protected from light and stored in a refrigerator at 2°C to 8°C. They must not be frozen.

## Normal human immunoglobulin (NHIG) – intramuscular use

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, in the United States as a 16.5% solution, and in the United Kingdom as a 10% solution.

- **Normal human immunoglobulin (NHIG)** – CSL Bioplasma – 160 mg/mL IgG fraction of pooled normal human plasma 2 mL and 5 mL vials for IM injection.

### Dosage and administration

NHIG should be given by deep IM injection using a large (19 or 20) gauge needle. The NHIG should be introduced slowly into the muscle to reduce pain. This product should 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 intravenous use (NHIG (intravenous)) has been developed for patients requiring large doses of immunoglobulin.

## Recommendations

Immunoglobulin preparations may be given to susceptible individuals 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. 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.

**(i) Prevention of hepatitis A** (see also Part 3.8, 'Hepatitis A')
NHIG contains sufficiently high levels of antibody against hepatitis A to be able to prevent or ameliorate infection in susceptible individuals.[10,11]

Hepatitis A vaccine is strongly preferred for the protection of travellers. Because NHIG is now in short supply it should only be given (at the same time as a dose of hepatitis A vaccine) to those, such as aid-workers to be deployed within 2 weeks, who will be living in quite inadequate environmental circumstances.[12,13]

NHIG is very effective in controlling the spread of a common source outbreak of hepatitis A in either a family or a closed community setting.[14]

**(ii) Prevention of hepatitis B**
See Part 3.9, 'Hepatitis B', under 'Management of infants born to hepatitis B carrier mothers' and 'Post-exposure prophylaxis for hepatitis B.'

**(iii) Prevention of measles** (see also Part 3.13, 'Measles').
NHIG contains a sufficiently high concentration of antibody against measles to be able to prevent or ameliorate infection in susceptible individuals. Passive protection against measles particularly may be required if the exposed individual has an underlying immunological disorder (AIDS, immunosuppressive therapy), or to control an outbreak of measles among non-immunised individuals, eg. in a child-care centre. The use of NHIG should be considered in HIV-positive persons exposed to a patient with measles.

**(iv) Prevention of varicella** (see also Part 3.27, 'Varicella-zoster')
Varicella should be prevented or made less severe in infants under 1 month of age, in children who are being treated with immunosuppressive therapy, and in pregnant women.[5,6] Zoster immunoglobulin (ZIG) should be given as soon as possible, and preferably within 96 hours, after the exposure. ZIG is recommended for non-immune HIV-positive persons within 10 days of exposure to clinical cases of either varicella or 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. The dose of NHIG is 0.4–1.0 mL per kg body weight.

**(v) Immune deficiency**
Patients with abnormal antibody production (primary hypogammaglobulinaemia, multiple myeloma, chronic lymphoblastic leukaemia) are usually treated with the intravenous preparation of normal human immunoglobulin (NHIG (intravenous)).[2]

However, in some cases, NHIG is given by IM injection in a dose of 0.6–0.9 mL/kg every 2 to 4 weeks. The aim of therapy is to maintain serum IgG levels above 4.0 g/L in adult patients and at or above the fifth centile for age in children. Some patients may receive the IM (160 mg/mL) preparation by SC infusion.

NB. 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.

## Adverse events and precautions

Local tenderness and muscle stiffness at the site of injection sometimes occur and may persist for several hours after injection. Systemic adverse events such as urticaria and angio-oedema may occur. Sometimes the recipient may develop erythema or low-grade fever.

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. In highly allergic individuals, repeated injections may lead to anaphylaxis.

### Contraindications

Hypersensitivity reactions occur rarely but may be more common in patients receiving repeated injections. It is recommended that NHIG should not be given to individuals with selective absolute IgA deficiency, as the small amounts of IgA in NHIG could theoretically lead to the development of anti-IgA antibodies in these individuals.

## Normal human immunoglobulin (NHIG) – intravenous use

Normal human immunoglobulin (intravenous) is usually abbreviated as NHIG (intravenous).

- **Intragam P** – CSL Bioplasma. A sterile preservative-free solution of immunoglobulin G (IgG) 60 mg/mL prepared from Australian blood donations and made available through the Australian Red Cross Blood Service. The manufacturing process includes pasteurisation. Intragam P contains only trace amounts of IgA, and the final solution contains 100 mg/mL maltose. It is supplied as 0.6 g in 10 mL, 3 g in 50 mL and 12 g in 200 mL bottles (for intravenous use).

- **Sandoglobulin** – CSL Bioplasma. A sterile lyophilised preparation for reconstitution, containing human gammaglobulin. The product is reconstituted with sodium chloride 0.9% solution to a sterile 3 or 6% solution. Available in 6g vials (for intravenous use).

### Dosage and administration

The infusion should be commenced slowly and the rate increased gradually. Patients should be closely observed for the duration of the infusion. The patient's pulse, blood pressure and respiration rate should be recorded at 15 minute intervals and the temperature every hour. All these observations should also be made and recorded prior to the commencement of the infusion.

The dose for replacement therapy in immune deficiency is 0.4–0.6 g/kg every 3 to 4 weeks. In Kawasaki disease, a single dose of 2g/kg, given over at least 6 to 8 hours is recommended, repeated once if fever fails to resolve within 48 hours. Doses should be calculated to the nearest (next highest) bottle so as not to waste any immunoglobulin. Giving slightly more than the calculated dose per kilogram will not be harmful.

### Recommendations

**(i) Antibody deficiency disorders**

NHIG (intravenous) is indicated for patients with antibody deficiency disorders requiring large doses of immunoglobulin. Therapy in these patients is usually administered at monthly intervals. NHIG (intravenous) produces higher serum concentrations of IgG after administration than the IM preparation.[2]

**(ii) Kawasaki disease**

In clinical studies, NHIG (intravenous) has been found to be effective in the acute phase of Kawasaki disease, as it reduces the risk of coronary artery involvement, and is associated with more rapid resolution of other acute phase features of the disease.[15-19]

**(iii) Other uses**

NHIG (intravenous) has been used in the management of immune thrombocytopenia,[20] Guillain-Barré syndrome,[21,22] chronic inflammatory demyelinating polyneuropathy,[22] post-transfusional purpura, in patients with bacterial infections associated with secondary immunodeficiency, and in other inflammatory and infective disorders.[3]

(Note: Some recommendations in this section are not included in the current registered indications for Intragam. Potential users of NHIG (intravenous) in these circumstances should consult with the Australian Red Cross Blood Service).

### Adverse events and precautions

Adverse events with NHIG (intravenous) consist of shivering, chest and back pains and moderate pyrexia. Severe headache, sometimes attributed to aseptic meningitis, has also been observed with NHIG (intravenous). This can be ameliorated by slowing the infusion or by mixing the 60 mg/mL preparation with 4 volumes of normal saline prior to administration. There have been isolated reports of renal dysfunction and acute renal failure following the administration of NHIG (intravenous). To date, anaphylactic shock has not been experienced with NHIG (intravenous). Subjects with absolute selective IgA deficiency have an increased risk of severe adverse events following NHIG (intravenous).

### Contraindications

Individuals who are known to have had an anaphylactic or severe systemic response to NHIG should not receive further immunoglobulin. Individuals with absolute selective IgA deficiency are recommended to not receive immune globulin preparations.

## References


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# 3.11 INFLUENZA

## Virology

The influenza viruses are orthomyxoviruses that are classified as types A, B or C based on the antigenic characteristics of their internal proteins, the nucleoprotein and matrix protein.[1] Influenza A and B are clinically important in human disease. These viruses possess 2 surface glycoprotein antigens, the haemagglutinin (H) which is involved in cell attachment during the infection process, and the neuraminidase (N) with enzymic activity which facilitates the release of newly synthesised virus from the cell. The influenza A viruses can be segregated into subtypes based on differences in these surface antigens, whereas influenza B cannot be segregated into subtypes. Antibody against the surface antigens, particularly the haemagglutinin, reduces the chance of infection or severe illness due to influenza. A new family of anti-influenza drugs that interfere with the enzymic activity of the neuraminidase reduce viral replication and can have a therapeutic benefit if administered within 48 hours of onset of symptoms.

Both influenza A and influenza B viruses undergo frequent changes in their surface antigens via two mechanisms, antigenic drift and antigenic shift. Antigenic drift results from ongoing point mutations in the surface antigens, is responsible for annual outbreaks and epidemics and is the reason that the strain composition of influenza vaccines requires annual review. Antigenic shift (which occurs occasionally and unpredictably) results from the establishment of a new subtype of influenza A in the human population and is usually associated with pandemic influenza. These new human subtypes are derived from viruses in animal or avian reservoirs and may adapt to humans by genetic reassortment with human influenza viruses. There were 3 pandemics in the twentieth Century and recently 2 avian influenza virus subtypes A(H5N1) and A(H9N2) have been transmitted from poultry to a small number

of people but have not spread from person to person. Genetic reassortment of such viruses with human influenza viruses is considered to pose a pandemic threat. Since 1977, 2 subtypes of influenza A, A(H1N1) and A(H3N2) have co-circulated in the human population together with influenza B.

## Clinical features

Influenza is transmitted from person to person via virus-containing respiratory droplets, produced during coughing or sneezing.[2] Influenza virus causes a wide spectrum of disease from asymptomatic infection to respiratory illness with systemic features, to multisystem complications and death from primary viral or secondary bacterial pneumonia. The clinical outcome is influenced by the patient's age, prior exposure to antigenically related influenza virus, the virulence of the viral strain, the presence of chronic medical conditions (eg. heart or lung disease, renal failure and diabetes), pregnancy and smoking. 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.

In adults, the onset of illness due to influenza A is usually abrupt, after an incubation period of one 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. Infections due to influenza A(H3N2) strains are normally more severe than influenza B or influenza A(H1N1) strains. Influenza B infection is usually difficult to distinguish from influenza A, although in children the disease may be less severe.

The clinical features of influenza A in infants and children are similar to those in adults. However, temperatures may be higher in children (and may include febrile convulsions) and otitis media and gastrointestinal manifestations are more prominent. Infection in neonates may be more non-specific.

Complications of influenza include acute bronchitis, croup, acute otitis media, pneumonia (both primary viral and secondary bacterial pneumonia, the latter particularly associated with staphylococcal pneumonia), cardiovascular complications including myocarditis and pericarditis, post-infectious encephalitis, Reye's syndrome and various haematological abnormalities. Primary viral pneumonia occurs rarely, but secondary bacterial pneumonia is a frequent complication in individuals 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.

## Epidemiology

In most years, minor or major epidemics of type A or type B influenza occur, usually during the winter months. During epidemics, the mortality rises, especially among the elderly and people with chronic diseases, and there is increased morbidity and hospitalisation for pneumonia and exacerbation of chronic diseases.[3] Every 10 to 30 years, new subtypes of influenza A emerge through antigenic shift, and cause pandemics in which a quarter or more of the population may be affected over a short period.

## Vaccines

- **Fluad** – Delpharm Consultants/Chiron (inactivated influenza vaccine). 0.5 mL pre-filled syringe; adjuvanted with MF59C.1. Also contains water, sodium chloride, potassium chloride, potassium phosphate monobasic, sodium phosphate dibasic, magnesium chloride hexahydrate, calcium chloride dihydrate and 0.05 mg thiomersal. May contain traces of kanamycin, neomycin, and formaldehyde.

- **Fluarix** – GlaxoSmithKline (inactivated influenza vaccine). 0.5 mL pre-filled syringe; also contains other excipients including polysorbate 80/octoxinol 9 and traces of thiomersal and formaldehyde. May contain traces of gentamicin.

- **Fluvax** – CSL Vaccines (inactivated influenza vaccine). 0.5 mL pre-filled syringe. May contain traces of neomycin, polymyxin and gentamicin.

- **Fluvirin** – Medeva/Ebos Health & Science (inactivated influenza vaccine). 0.5 mL pre-filled syringe; also contains water, sodium phosphate di-basic, potassium phosphate-monobasic and sodium choride. May contain traces of neomycin and polymyxin.

- **Influvac –** Solvay Pharmaceuticals (inactivated influenza vaccine). 0.5 mL pre-filled syringe; also contains potassium chloride, calcium chloride, magnesium chloride and thiomersal (0.01% w/v).

"***Vaxigrip Junior** – Aventis Pasteur (inactivated influenza vaccine). 0.25 mL pre-filled syringe; also contains formaldehyde and buffered saline. May also contain traces of neomycin.*"

- **Vaxigrip** – Aventis Pasteur (inactivated influenza vaccine). 0.5 mL pre-filled syringe; also contains formaldehyde and buffered saline. May also contain traces of neomycin.

*Fluvax, Fluarix and Vaxigrip each have a marking on the syringe to allow preparation of a 0.25 mL dose suitable for paediatric use.*

All the influenza vaccines currently available in Australia are either split virion or subunit vaccines prepared from purified inactivated influenza virus which has been cultivated in embryonated hens eggs. Split virion and subunit vaccines are generally considered to be equivalent with respect to safety and efficacy and both are substantially free of the systemic reactions sometimes induced by whole virus vaccines. Because the vaccine viruses are cultivated in embryonated hens eggs the vaccine may contain traces of egg-derived proteins. Manufacturing processes vary by manufacturer and different chemicals (formaldehyde or betapropiolactone) may be used to inactivate the virus. The vaccines distributed in Australia may contain thiomersal, a mercury-containing compound, as preservative and other antibacterials or antibiotics may be used in the manufacturing process. The package insert should be consulted for additional information.

Influenza vaccines normally contain 3 strains of virus, two current influenza A subtypes and influenza B, representing recently circulating viruses. The final product contains 15 µg of viral haemagglutinin, the principal surface antigen, for each virus strain. The composition of vaccines for use in Australia is determined annually by the Australian Influenza Vaccine Committee.

Other forms of influenza vaccines (such as live attentuated intranasal vaccine) are being developed, but have not yet been licensed in the USA or Australia.[4]

The 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. In healthy persons under 65 years of age, influenza vaccine is 70 to 90% effective when the antigenic match between vaccine and circulating viruses is close.[5] Among elderly persons, the vaccine is 30 to 70% effective in preventing all hospitalisation for pneumonia and influenza for those living outside nursing homes or similar chronic-care facilities. For those residing in nursing homes, influenza vaccine is most effective in preventing severe illness, secondary complications and deaths. In such a population, the vaccine can be 50 to 60% effective in preventing hospitalisation or pneumonia and 80% effective in preventing death, even though the effectiveness in preventing influenza illness may be lower.[6] 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. To provide continuing protection, annual vaccination with vaccine containing the most recent strains is necessary.

## Transport, storage and handling

Store in refrigerator at 2°C to 8°C. Do not freeze. Transport according to general guidelines (see Part 1.10, 'Transport, storage and handling of vaccines'). If vaccine has been exposed to temperatures less than 0°C, do not use. At the end of each year, vaccine should be appropriately discarded to avoid inadvertently using a product with incorrect formulation for the following year.

## Dosage and administration

Shake the pre-filled syringe vigorously before injection. Influenza vaccine is administered by either IM or SC injection in the deltoid area for adults and children, and the anterolateral aspect of the thigh for infants. The IM route causes fewer local reactions and is preferred.[7]

**Table 3.11.1: Recommended doses of influenza vaccine**

| Age | Dose | Number of doses (first immunisation) | Number of doses (subsequent years) |
|---|---|---|---|
| 6 months–2 years | 0.125 mL | 2* | 1 |
| 2–6 years | 0.25 mL | 2* | 1 |
| 6–9 years | 0.5 mL | 2* | 1 |
| >9 years | 0.5 mL | 1 | 1 |

*Two doses at least one month apart are recommended for children aged under 9 years who are receiving influenza vaccine for the first time. The same vial should not be re-used for the 2 doses.
Note:
(i) Some influenza vaccines available in Australia are packed in syringes graduated for measurement of recommended paediatric doses. Fluvax, Fluarix and Vaxigrip each have a marking on the syringe to allow preparation of a 0.25 mL dose. A tuberculin syringe can be used to measure the dose of vaccine not packed in graduated syringes. Excess vaccine is expelled from the syringe and the remaining volume injected.

(ii) All of the product information sheets have some differences from Table 3.11.1. Fluvirin does not have a dose recommendation below 4 years of age. The dosage recommendations for Fluvax start at 3 months of age. Influvac is indicated for use in adults aged 18 years and over. Fluad is registered for use in people 65 years of age and over only.

Vaccination is best undertaken in autumn, in anticipation of winter outbreaks of influenza. However, vaccination can be given as early as February. In autumn the opportunities to provide influenza vaccination to persons at increased risk should not be missed when they present for routine care.

As protection is usually achieved within 10 to 14 days, vaccination can still be offered to adults and children after influenza virus activity has been documented in a community.

Influenza vaccine can be administered concurrently with other vaccines, including pneumococcal polysaccharide vaccine and all the scheduled childhood vaccines.

## Recommendations

The administration of inactivated influenza vaccine to individuals at risk of complications of infection is the single most important measure in preventing or attenuating influenza infection and preventing mortality. After vaccination, most vaccinated adults develop antibody titres that are likely to protect them against the strains of virus represented in the vaccine. In addition, the individual is protected against many related variants. Infants, the very elderly, and patients with impaired immunity may develop lower post-vaccination antibody titres. Under these circumstances, influenza vaccine may be more effective in preventing lower respiratory tract involvement or other complications of influenza than in preventing infection.

Annual vaccination is recommended for individuals who are at increased risk of influenza-related complications (listed below), including all individuals aged 65 years and older. It is also recommended for all Aboriginal and Torres Strait Islander people aged 50 years and older, and for those aged 15–49 years with underlying medical conditions.

Influenza vaccine should be administered to any person who wishes to reduce the likelihood of becoming ill with influenza. Persons who provide essential community services should be considered for vaccination to minimise disruption of essential activities during influenza outbreaks.

Influenza vaccine can be administered to children as young as 6 months, however there is an increased risk of minor adverse events in children under 5 years of age (see below, ‘Adverse events and precautions’).

**Annual influenza vaccination is recommended for the following groups** *(levels II to III evidence)*
**(i)** All individuals aged 65 years and older.[3,8-11] Concomitant influenza and pneumococcal polysaccharide vaccines have been shown to reduce hospitalisations from pneumonia and all cause mortality by about half in adults over 65 years of age. Annual influenza vaccination, and pneumococcal polysaccharide vaccination, are recommended for Aboriginal and Torres Strait Islander people aged 50 years and older, in view of the enormously increased risk of hospitalisation and death from pneumonia (see also Part 3.18, 'Pneumococcal infections').

**(ii)** Children (≥6 months of age) and adults with chronic cardiac conditions including cyanotic congenital heart disease, coronary artery disease and congestive heart disease.[12,13] Influenza causes increased morbidity and mortality in children with congenital heart disease and adults with coronary artery disease and congestive heart disease.[12]

**(iii)** Children (≥6 months of age) and adults with chronic suppurative lung disease, including bronchiectasis, cystic fibrosis and chronic emphysema.[14] Patients with suppurative lung disease,

bronchiectasis and cystic fibrosis, are at greatly increased risk from influenza, which may cause irreversible deterioration in lung function.

**(iv)** Children (≥6 months of age) and adults with chronic illnesses requiring regular medical follow-up or hospitalisation in the preceding year, including diabetes mellitus, chronic metabolic diseases, chronic renal failure, haemoglobinopathies or immunosuppression (including immunosuppression caused by drugs).[6,15,16]

**(v)** Persons with immune deficiency, including HIV.[17,18] Patients with immune deficiency, including HIV, malignancy and chronic steroid use are at greatly increased risk from influenza, although they also have a reduced immune response to the vaccine. Whilst 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.[18] Influenza vaccine has been shown in a randomised controlled trial to reduce the incidence of influenza in HIV-infected patients.[18]

**(vi)** Residents of nursing homes and other long-term care facilities, due to high rates of transmission during outbreaks.[3,7-11,19]

**(vii)** Contacts of high risk patients. The following can transmit influenza to high-risk patients, and it has been shown that vaccinating them protects those at high-risk: health-care providers,[20] (particularly of immunocompromised patients), staff of nursing homes and long-term care facilities, household members (including children 6 months or older) of persons in high-risk groups.

**In the following situations, the benefits of influenza immunisation are likely to outweigh the risks, but there is limited evidence from clinical trials**

**(i)** Asthma. Influenza causes exacerbation of wheezing, which can be severe, although only a minority (about 10%) of episodes of virus-induced wheezing is due to influenza. There are no randomised controlled trials of influenza vaccine efficacy in asthma. The patients most likely to benefit are those with more severe asthma, such as those requiring frequent hospital visits and it is recommended that these receive influenza vaccine annually.[21-23]

**(ii)** Aspirin therapy. Children (aged 6 months to 10 years) on long-term aspirin therapy, which increases the risk of Reye's syndrome after influenza.

**(iii)** Pregnancy. The benefits of influenza immunisation in preventing influenza during the second or third trimester (1 to 2 hospitalisations prevented per 1000 women immunised) outweigh the risks of giving an inactivated vaccine in early pregnancy (no evidence of congenital malformations or other damage to the fetus). It is therefore recommended that influenza vaccine be offered in advance to women planning a pregnancy, and to pregnant women who will be in the second or third trimester during the influenza season, including those in the first trimester at the time of vaccination.[24,25]

**(iv)** Workplace. Mass vaccination of individuals in particular industries or worksites cannot usually be justified on public health grounds. However, the cost-effectiveness of influenza vaccination in industry varies from year to year, depending on the amount of circulating influenza.[6]

**(v)** Travellers. Large tourist groups, especially those including elderly persons, are at risk of influenza if travelling to areas of the world where influenza is currently circulating. Influenza vaccination, preferably using the strain prevalent in the areas in which they will be travelling, is recommended if travelling during the influenza season, especially if there are known large epidemics.[6]

**Pandemics**

At the time of a pandemic, the priority groups and the timing of vaccination may be quite different from those during inter-pandemic periods. In addition, the number of vaccine doses required to confer protection and the optimal time for vaccination may differ. The Australian Influenza Pandemic Planning Committee has developed guidelines for vaccine use and will advise health authorities regarding priority groups, dosing schedules and timing of vaccination should a pandemic occur. See http://www.health.gov.au/pubhlth/publicat/document/influenza.pdf.

## Adverse events and precautions [19,26]

- Local reactions (induration, swelling, redness and pain) are very common (>10%).

- Fever, malaise and myalgia occur commonly (1 to 10%). These adverse events may commence within a few hours of vaccination and may last for 1 to 2 days. In children under the age of 5 years these adverse events may be more pronounced. Post-vaccination symptoms may mimic influenza infection, but the current influenza vaccine does not contain live virus and cannot cause influenza.

- Immediate adverse events (such as hives, angio-oedema, or systemic 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. Persons with a history of anaphylaxis after eating eggs or a history of a severe allergic reaction following occupational exposure to egg protein should not be given influenza vaccine.

- An association was shown between influenza vaccine used in the Northern hemisphere from 1992-94 and Guillain-Barré syndrome (GBS), with 1 to 2 cases of GBS occurring per million vaccinated. There has not been an excess number of cases of GBS notified in Australia in association with influenza vaccine.

## Contraindications

- Individuals with anaphylactic hypersensitivity to eggs should *not* be given influenza vaccine. This includes persons who, soon after ingesting eggs, develop swelling of the lips or tongue, or experience acute respiratory distress or collapse.

- Individuals with anaphylactic hypersensitivity to any of the product components should not be vaccinated.

- Individuals with an acute febrile illness (fever ≥38.5°C) should not be vaccinated until their symptoms have abated. However, minor illness with or without fever should not contraindicate the use of influenza vaccine.

- Patients with a history of Guillain-Barré Syndrome (GBS) with an onset related in time to influenza vaccination may be at increased risk of again developing GBS if given influenza vaccine. The risk should be weighed against the benefits to the individual patient of influenza vaccination. Because patients with a history of GBS have an increased likelihood of again developing the syndrome, the chance of them coincidentally developing the syndrome following influenza vaccination may be higher than in individuals with no history of GBS.

## Use in pregnancy

Influenza vaccine is recommended for pregnant women who will be in the second or third trimester during the influenza season, including those in the first trimester at the time of vaccination. See above, 'Recommendations'.

## Conflicts with product information

- The product information lists allergy to chicken feathers and some food proteins as a contraindication, whereas NHMRC recommends that patients with allergies other than anaphylaxis can be vaccinated.

- The product information for Fluvirin states that the product should not be given to children aged less than 4 years. The product information for Influvac states that it is indicated only for adults aged 18 years and over. The product information for Fluad states that it is indicated for adults 65 years of age and over. Although the NHMRC recommend that children as young as 6 months can be vaccinated if they are at risk of complications of influenza, the suitability of the vaccine formulation for use in the paediatric age group should be taken into account, as should the vaccines suitability for accurate preparation of 0.125 mL and 0.25 mL doses.

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# 3.12 JAPANESE ENCEPHALITIS

## Virology

Japanese encephalitis (JE) is caused by a mosquito-borne flavivirus.

## Clinical features

The disease is typically an acute neurological syndrome characterised by headache, fever, convulsions, focal neurological signs, depressed level of consciousness and coma. 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 syndrome.[1] It is recognised, however, that most infections are asymptomatic; published estimates of the symptomatic to asymptomatic infection ratio vary from 1:25 to 1:1000.[1]

## 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, an outbreak occurring in the Torres Strait, north Australia, in 1995.[1,2]

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 man. Indeed, man is 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. In the tropical regions (most of southeast Asia, Sri Lanka, southern India) the disease is endemic, occurring throughout the year.[1]

In some countries (Japan, Taiwan, South Korea, 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] However, elsewhere in Asia there are an estimated 50 000 cases with 15 000 deaths annually.[1]

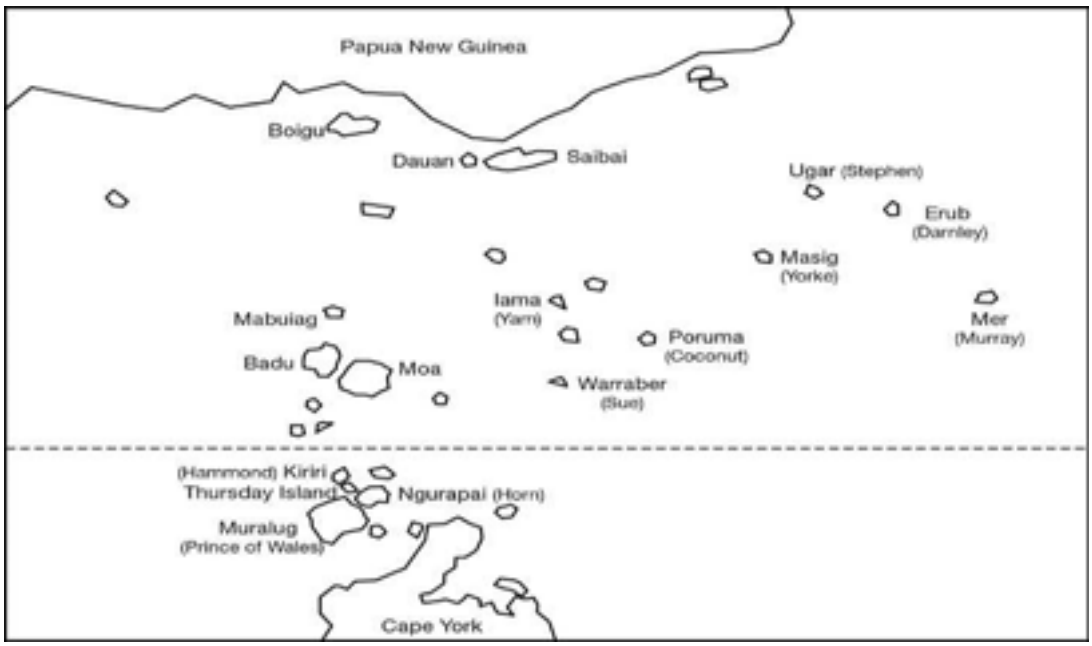
In early 1995 three cases of JE, two of them fatal, occurred on Badu Island in the Torres Strait.[2] Subsequent serological surveys showed that JE virus activity was widespread in many other remote 'outer' islands of the Torres Strait (Figure 3.12.1) at or about that time.[2] Although the 1995 outbreak was the first known incursion of JE virus into Australia, surveillance using sentinel pigs showed further incursions into the Torres Strait in the wet season of 1996 and again in 1997.

In early 1998, however, a further case of JE occurred in an unvaccinated Badu Island resident, and the first ever mainland case of JE occurred in a person working on the west coast of Cape York. [3] Furthermore, the sentinel pigs at the northern-most tip of Cape York showed, for the first time, clear evidence of JE virus activity.[3] To date there have been 5 cases of JE acquired in Australia.

Sentinel surveillance showed further incursions of JE virus into the Torres Strait in 2000 to 2003 inclusive, but not the 1999, wet seasons. Therefore, there has been serological evidence of an incursion every year from 1995 to 2003, except for 1999. The JE virus has been isolated (from pigs, mosquitoes or people) on Badu (in 1995, 1998, 2000 and 2003), on Mabuiag in 1998, at the northern-most tip of Cape York in 1998, and on Saibai in 2000.

An investigation subsequent to the 1995 outbreak of JE in the Torres Strait documented the presence of the JE virus in the Western Province of Papua New Guinea.[4] It is therefore likely that the Western Province (which is adjacent to the Torres Strait) is the source of the annual incursions of JE virus into Far North Queensland.

**Figure 3.12.1: Map of outer islands of the Torres Strait**




## Vaccine

- **JE-VAX** – Aventis Pasteur (Japanese encephalitis virus vaccine inactivated). Each reconstituted 1.0 mL dose contains formalin inactivated Japanese encephalitis virus + thiomersal 0.007%, gelatin 470 µg, formaldehyde <100 µg and mouse brain serum protein <50 ng.

The JE vaccine available in Australia is an inactivated mouse brain-derived vaccine manufactured in Japan. It is prepared by inoculating mice intracerebrally with Nakayama-NIH strain JE virus. Infected brains are harvested, homogenised then centrifuged. The supernatant is inactivated with formaldehyde and purified by ultracentrifugation; the suspension is then lyophilised. No myelin basic protein can be detected at the threshold of the assay (<2 ng/mL).

A randomised clinical trial in Thailand in the early 1980s determined that 2 doses of the inactivated mouse brain-derived vaccine, administered to children 7 days apart, had a protective efficacy of 91%.[5] However, immunogenicity studies have demonstrated that 3 doses of the vaccine are required to ensure adequate immunity in vaccinees from JE non-endemic areas.[6]

## Transport, storage and handling

The vaccine is supplied as a lyophilised powder that is reconstituted with the provided sterile water diluent. Both vaccine and diluent should be transported and stored at 2°C to 8°C. Do not freeze. Do not use the vaccine if it has been exposed to a temperature of less than 0°C. Store reconstituted vaccine at 2°C to 8°C and use within 8 hours.

## Dosage and administration

The JE vaccine is administered by the SC route. The volume injected is 0.5 mL in 1 to 3 year old children and 1.0 mL for all those, including adults, over 3 years of age. In those from non-endemic regions, including Australia, a 3-dose regimen (ie. days 0, 7 and 28) over a month is required.

## Recommendations

**(i) Travellers**

Although the risk of travellers in Asia acquiring JE is extremely low, there have been instances of even short-term travellers developing the disease. Therefore 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 outdoors 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.

Therefore JE vaccination is recommended for:

- travellers spending one month or more in rural areas of Asia, particularly if the travel is during the wet season, and/or there is considerable outdoor activity and/or the standard of accommodation is suboptimal; and

- for all other travellers spending a year or more in Asia (except for Singapore), even if much of the stay is in urban areas.

* "*travellers intending to spend a month or more in Papua New Guinea, particularly if the travel is during the wet season.*" (handbook change)

**(ii) Residents of Far North Queensland**

There have been incursions of JE virus into the outer islands of the Torres Strait (Figure 3.12.1) nearly every wet season (December–May) since first recognised in 1995. From the dates of onset of symptoms of the four JE cases in the Torres Strait, and from a review of the sentinel pig surveillance information, it is clear that the period of risk is greatest from February to March and probably negligible during the dry season (June to November inclusive).

JE vaccination is currently recommended for:

- all residents (over one year of age) of the outer islands in the Torres Strait; and
- all non-residents 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).

NB. 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 (ie. in May) have arrived 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 need the vaccine.

**(iii) Laboratory personnel**
Laboratory-acquired JE has occurred, principally in research settings where concentrated virus preparations were being handled. JE vaccination is recommended for all research laboratory personnel who potentially might be exposed to the virus.

**(iv) Booster doses**
Single booster doses are required at 3-yearly intervals.[7]

## Adverse events and precautions

Local reactions and minor systemic reactions are common following vaccination against JE.[1] About 20% experience tenderness, redness and/or swelling at the injection site, and 10% experience systemic reactions such as fever, headache, being 'off-colour', chills, dizziness, aching muscles, nausea and/or vomiting.

The vaccine's neural tissue substrate has raised concerns about the possibility of neurological adverse events following immunisation. The manufacturing process purifies the infected mouse brain suspension, so that no myelin basic protein can be detected at the detection threshold of the assay (<2 ng/mL).

Early studies in Japan, involving nearly 40 000 vaccinees, did not detect any neurological complications within a month of vaccination. However, there have been recent reports from South Korea and Japan of acute encephalomyelitis following JE vaccination. In South Korea, a booster dose of locally-produced mouse-brain derived vaccine was given every year to all children until 15 years of age, but in 1994 four cases of severe neurological illness, two of which were fatal, were reported following booster doses.[6] This led to a change in the recommended interval between booster doses from every year to every 2 years. Surveillance in Japan suggests the rate of severe neurological adverse events following JE vaccination is 1.8 cases per 1 million doses of vaccine.[6]

Hypersensitivity (allergic) reactions occur in about 0.5% (ie. 1 in 200) vaccinees. These reactions include urticaria that is often widely distributed over the body, angio-oedema of the limbs, face and throat and generalised pruritus (sometimes without a rash). In the early 1990s, apparently severe allergic reactions to the inactivated mouse brain-derived JE vaccine were reported from several industrialised countries, including Australia.[6] In a few cases, upper airway swelling with respiratory distress and hypotension occurred; some had to be hospitalised.

An important feature of the hypersensitivity reactions to JE vaccine is that they may be delayed for several days, in some cases up to 10 days, after the actual time of vaccine administration. The risk of these delayed reactions seems to be increased after the first and second doses, and they appear to be more likely to occur in those with a history of allergic reactions, especially urticaria.[6] Although the pathogenesis of the more severe hypersensitivity reactions remains uncertain, there is some evidence that gelatin, added to stabilise the vaccine, may be the provoking agent.[6] Vaccinees should remain within ready access to medical care for 10 days following vaccination.

## Contraindications

The inactivated mouse brain-derived JE vaccine is contraindicated in those less than one year of age, and those who have had a significant allergic reaction, such as generalised urticaria, to a previous dose. A past history of 'allergy' to bee-stings, medications, foods etc. must be seriously considered and may also be a contraindication to vaccination.

There are few data on the safety and efficacy of JE vaccine in immunocompromised people. A small study undertaken in Thailand has documented that HIV-infected infants respond less well to 2 doses of JE vaccine than do non-infected infants;[8] the response to further doses was not studied.

## Use in pregnancy

Although JE vaccine might pose a theoretical risk to the developing fetus, no adverse outcomes of pregnancy have ever been attributed to vaccination against JE. Because JE virus infection during the first and second trimester is also associated with miscarriage, only pregnant women at risk of acquiring JE should be offered JE vaccine.

### Conflicts with product information

The product information states that 'definitive recommendations cannot be given on the timing of booster doses at this time' and that 'a booster dose may be given after 2 years'. However, although the data are limited, they do suggest that neutralising antibody persists for at least 3 years following a 3-dose primary series.[7]

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## 3.13 MEASLES

### Virology

Measles is a paramyxovirus, genus *Morbillivirus*. It is an RNA virus with 6 structural proteins, 3 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. Measles virus has a short survival time (<2 hours) in air, and is rapidly inactivated by heat, light and acidic pH.[1]

### Clinical features

Measles is a highly infectious, acute viral illness which is spread by respiratory droplets.[1] It is infectious from the beginning of the prodromal period (3 to 5 days before the rash appears), for as many as 4 days after the appearance of the rash. The incubation period is 10 to 14 days. The prodrome, lasting 2 to 4 days, is characterised by fever, followed by cough, coryza and conjunctivitis. The rash follows, typically beginning on the face and upper neck, and then becoming generalised. Measles is often a severe disease, frequently complicated by otitis media (7%) and bronchopneumonia (6%). Acute encephalitis occurs in between 2 and 10 per 10 000 reported cases. Measles encephalitis has a mortality of 10 to 15%, and 15 to 40% of survivors of this complication have permanent brain damage. Subacute sclerosing panencephalitis (SSPE) is a late complication of measles in about 1 per 100 000 cases. SSPE causes progressive brain damage and is always fatal. Complications from measles are more common and more severe in chronically ill and very young children.[2] This is particularly true in developing countries.

### Epidemiology

In the 24 years from 1976 to 2000, measles caused 98 deaths in Australia; this number exceeded those caused by diphtheria (4), tetanus (53), pertussis (29) and poliomyelitis (4) combined.[3] Although

vaccination rates have improved, the uptake of measles vaccine in Australia has not yet reached optimal levels. In 2001, the Australian Childhood Immunisation Register recorded that 91% of children aged 2 years had been vaccinated for measles, but this is considered to be an underestimate of vaccine coverage. Following the Measles Control Campaign (which took place in 1998 and resulted in 1.7 million primary school children being vaccinated), a national serosurvey in the first quarter of 1999 showed that 89% of children aged 2 to 6 years, 94% of those aged 6 to 11 years, and 91% of those aged 12 to 18 years, were immune to measles.[4] However, persons born between 1966 and 1980 are unlikely to have received 2 doses of measles containing vaccine and may remain non-immune.[5]

The effectiveness of measles vaccine has been established in the United States.[2] In 1963, before the vaccine was registered, there were 400 000 cases reported each year. In 1994 the countries of the WHO Region of the Americas established the goal of eliminating measles in the Region by the year 2000. However, in 1997 there was a resurgence, especially in Brazil (20 000 confirmed cases). In the USA there were only 86 confirmed cases in 2000, and there is continued progress towards elimination in the Region.[6] The Eastern Mediterranean Region has established a goal for measles elimination by 2010, and the European Regional Office is also planning elimination. Measles remains a major cause of morbidity and mortality in the southeast Asian Region, where there are plans for strengthened control by the year 2003.[7]

## Vaccines

Two measles-mumps-rubella (MMR) vaccines are available in Australia. A monovalent vaccine is available for rubella, but no longer for measles or mumps. Vaccination with MMR results in sero-conversion to all 3 viruses in over 95% of recipients. Following a second dose of MMR vaccine, approximately 99% of subjects will be immune to measles.[2] Since the MMR vaccine viruses are not transmissible, there is no risk of infection from vaccinees.[2]

- **M-M-R II** – CSL Vaccines/Merck Sharp & Dohme. Live attenuated measles virus (Edmonston strain), mumps virus (Jeryl Lynn strain) and rubella virus (Wistar RA 27/3 strain). Each 0.5 mL dose contains not less than the equivalent of 1000 $TCID_{50}$ (tissue culture infectious dose 50%) of the US Reference Measles Virus; 5000 $TCID_{50}$ of the US Reference Mumps Virus; and 1000 $TCID_{50}$ of the US Reference Rubella Virus, lyophilised + 25 µg neomycin per 0.5 mL dose, a small amount of porcine gelatin as stabiliser, human albumin (0.3 mg), and fetal bovine serum (<1 part per million).

- **Priorix** – GlaxoSmithKline. Live attenuated measles virus (Schwarz strain), RIT 4385 strain of mumps virus (derived from the Jeryl Lynn strain) and the Wistar RA 27/3 rubella virus strain. Each 0.5 mL dose of the reconstituted vaccine contains not less than $10^{3.0}$ $CCID_{50}$ (cell culture infectious dose 50%) of the Schwarz measles, not less than $10^{3.7}$ $CCID_{50}$ of the RIT 4385 mumps and not less than $10^{3.0}$ $CCID_{50}$ of the Wistar RA 27/3 rubella virus strains, lyophilised + lactose, neomycin sulphate, albumin, amino acids, and sorbitol and mannitol as stabilisers.

## Transport, storage and handling

MMR vaccine is a freeze-dried preparation. Store in the dry state at 2°C to 8°C or colder and protect from light. The freeze-dried (lyophilised) form of the vaccine can be stored frozen, but the vaccine must not be frozen after it has been reconstituted with diluent (see also Part 1.10, 'Transport, storage and handling of vaccines').

Transport unconstituted vaccine (freeze-dried or lyophilised) in an insulated container with an approved time-temperature monitor. Observe national guidelines for packing vaccines in insulated containers. Maintain temperature at 2°C to 8°C. Diluent may be stored at room temperature (15°C to 30°C) but do not freeze.

The lyophilised vaccine should be reconstituted with the diluent supplied by the manufacturer and should be used within one hour of reconstitution, provided it has been kept cool and protected from sunlight. Reconstituted measles vaccine is very unstable and quickly loses potency at room temperature after reconstitution. At temperatures over 37°C it is completely inactivated after one hour. The reconstituted vaccine can be stored in the plastic syringe in a dark place between 2°C and 8°C without loss of potency and must be discarded if not used within 8 hours.

## Dosage and administration

A single dose of 0.5 mL is given by IM or SC injection.

## Recommendations

**(i)** Two doses of MMR are required, at least 4 weeks apart. MMR vaccine is recommended for all children at 12 months of age and at 4 years of age, unless there is a genuine contraindication. It is also recommended for all children who have not previously received it. A second dose of MMR vaccine is recommended for children over 4 years of age who have had only one dose of MMR vaccine. Adults born during or since 1966 should also have evidence of having received 2 doses of MMR (see also Part 1.9, 'Catch-up vaccination').

*All non-immune adults should be given MMR vaccine, provided there are no contraindications.*

MMR vaccine should be given to all susceptible persons (refer below) who are older than 12 months of age. Susceptible women should be identified during antenatal counselling and vaccinated with MMR at least 28 days before pregnancy, or immediately post-partum.

There are no ill-effects from vaccinating those with pre-existing immunity to one or more of the 3 diseases. The 2 available vaccines are interchangeable.

**(ii) Transmissibility of MMR vaccine viruses**

MMR vaccine viruses are not transmitted to contacts.[2] It is, therefore, safe to vaccinate the healthy siblings of immunocompromised children and safe for immunocompromised children to go to school with children recently vaccinated with the MMR vaccine.

**(iii) Infants and children at high risk of measles infection**

Unvaccinated children in the following groups are at particular risk from complications of measles, and should be vaccinated:

- children with chronic conditions such as cystic fibrosis, congenital heart or kidney disease, failure to thrive, Down's syndrome;
- children from the age of one year upwards in child-care centres, family day care and playgroups;
- children living in institutions;
- Aboriginal and Torres Strait Islander children;
- HIV-positive individuals, unless severely immunocompromised, may be given MMR vaccine in the absence of other contraindications[2] (see also Part 2.3, 'Groups with special vaccination requirements', page 52).

**(iv) Definition of a person who is susceptible to measles**

A susceptible person (to measles) is someone who *cannot* provide acceptable presumptive evidence of immunity to measles.

A person can be considered to have acceptable presumptive evidence of immunity to measles if they meet one of the following criteria:

- children aged 1 to 4 years who have documented evidence of having received one dose of a measles-containing vaccine; or
- persons over 4 years of age and born during or since 1966 (unless serological evidence indicates otherwise) who have documented evidence of receiving 2 doses of a measles-containing vaccine[5]; or
- persons born before 1966 (unless serological evidence indicates otherwise); or
- documented evidence of immunity; or
- documented evidence of laboratory confirmed measles.

NB: these criteria have been revised since publication of the Measles Control Guidelines.[8]

**(v) Delayed MMR vaccination**

MMR vaccine can be given to children of any age greater than 12 months, and no opportunity should be missed to ensure that this is done. Two doses are required, at least one month apart. If the primary vaccinations have not been completed at the time that MMR vaccine is due, they can be given at the same time, using separate syringes.

Adolescents and young adults who have received only one dose of the MMR vaccine require a second dose unless they have serological evidence of immunity to all 3 components. This is especially important for health and child-care workers.

**(vi) Children with a history of convulsions**
Children with a personal or close family history of convulsions should be given MMR vaccine, provided the parents understand that there may be a febrile response 5 to 12 days after vaccination.[2] Advice for reducing fever with paracetamol and other measures should be given. Doctors should seek specialist paediatric advice rather than refuse to provide MMR vaccination.

**(vii)** Children aged between 12 months and 4 years who have received one dose of MMR can be offered their second dose of MMR early (ie. at least 4 weeks after the first MMR) if they are considered at risk of coming in contact with measles.[8] This may apply during an outbreak or if a child is going to travel to a country that has a high incidence of measles. If a child receives the second dose early they are considered to have completed their MMR vaccination schedule, and therefore they do not require another dose at 4 years of age.

**(viii) Vaccination of contacts**
As vaccine-induced measles antibody develops more rapidly than that following natural infection, MMR vaccine can be used to protect susceptible contacts.[2] To be effective, the vaccine must be administered within 72 hours of exposure. If there is doubt about a person's immunity, vaccine should be given, since there are no ill effects from vaccinating individuals who are already immune. It must be noted that antibody responses to the rubella and mumps components of MMR vaccine are too slow for effective use of vaccine as prophylaxis after exposure to these infections.

Immunoglobulin is available for contacts for whom vaccine is contraindicated (see below) and for infants aged 6 to 9 months and susceptible persons who did not receive an MMR vaccination within 72 hours of contact (Table 3.13.1). Immunoglobulin needs to be given within 7 days of contact to be effective[8] (see 'Use of immunoglobulin to prevent measles' below).

**(ix) Vaccination during an outbreak**
During a confirmed measles outbreak, MMR vaccine may be given (on the direction of public health authorities) to infants aged between 9 and 12 months, and even to those aged between 6 and 9 months.[8] In these cases, another dose should be given at 12 months of age or 4 weeks after the first dose, whichever is the later. This should be followed by the standard dose of MMR at the fourth birthday.

**(x) MMR and tuberculin**
Measles virus inhibits the response to tuberculin, so tuberculin-positive individuals may become tuberculin-negative for up to a month after measles infection or MMR vaccine.[2] Mantoux testing is unreliable for at least 4 weeks after the administration of MMR. Because the measles virus may cause exacerbation of tuberculosis, patients with tuberculosis should be under treatment when vaccinated.

**(xi) Travellers**
Those born during or since 1966 should be encouraged to have MMR vaccine before embarking on international travel, if they do not have evidence of having had 2 doses of vaccine in the past. Infants travelling to endemic countries may be vaccinated between the ages of 9 and 12 months, if necessary. In these cases, another dose should be given at 12 months of age or 4 weeks after the first dose, whichever is the later. This should be followed by the standard dose of MMR at the fourth birthday.

## Adverse events and precautions

**(i)** Malaise, fever and/or a rash may occur after MMR vaccination, most commonly 7 to 10 days after vaccination and lasting about 2 to 3 days. Moderate fever (13 to 23%) and high fever >39°C (15%) are common. In a study of over 6000 children aged 1 to 2 years, the symptoms reported were similar in nature, frequency, time of onset and duration to those commonly reported after measles vaccination. In the period from 6 to 11 days after vaccination, febrile convulsions occurred in 0.1% of children, the

same rate reported in this period after measles vaccine. The rate of vaccine-induced encephalitis is about 1 in 1 million doses. Parotid swelling occurred in about 1% of children up to 4 years, usually in the third week and occasionally later.[2]

**(ii)** Reactions are much less common after the second dose of MMR than after the first dose.

**(iii)** Anaphylaxis following the administration of MMR is very rare (less than 1 in 1 million doses distributed).[2] Measles and mumps (but not rubella) vaccine viruses are grown in chick embryo tissue cultures, and although anaphylaxis following MMR was originally thought to be caused by residual egg protein, it is now recognised that the vaccine contains negligible amounts of egg protein. Therefore individuals with a serious (ie. anaphylactic) sensitivity to eggs can safely be given MMR vaccine.

It is now believed that sensitivity to other vaccine components, such as neomycin and gelatin, may be associated with anaphylaxis following the administration of MMR. Gelatin is included in M-M-R II (but not Priorix) as a stabiliser and an anaphylactic sensitivity to gelatin is a contraindication to receiving M-M-R II but not Priorix.

**(iv)** Encephalopathy occurring 6 to 15 days after measles vaccine has been reported at a rate of approximately 1 in 2 million doses. This is much less frequent than after natural measles infection.[2]

**(v)** Thrombocytopenia (usually self-limiting) is very rarely associated with the rubella or measles component of MMR.[2] Authorities differ in their opinion about whether or not the risk of MMR associated thrombocytopenia is increased in those who have previously had immune thrombocytopenia.[2,9] The most recent study found that children with immune thrombocytopenia before MMR had no vaccine-associated recurrences.[9] There are no systematic data on the outcome of a second dose of MMR in children who developed thrombocytopenia after a first dose[9] (see also Part 3.22, 'Rubella').

**(vi)** In 1998 Wakefield and colleagues from the Royal Free Hospital in the United Kingdom postulated that measles-mumps-rubella (MMR) vaccination might be causally linked with inflammatory bowel disease and autism. There has been no scientific evidence to support this claim and there is now good evidence to refute it [10] (see also Appendix 4, 'Commonly asked questions about vaccination').

**(vii)** During the Australian Measles Control Campaign in 1998, 1.7 million doses of MMR vaccine were used. There was a very low incidence of adverse events during the Campaign with only 7 reports of children with anaphylaxis/anaphylactoid reactions each of whom recovered fully following administration of adrenaline.[11]

**(viii)** Advise parents about possible symptoms, and give advice for reducing fever, including the use of paracetamol in the period 5 to 12 days after vaccination. Reassure parents that these post-vaccination syndromes are not infectious.

**(ix)** As with all suspected adverse events following vaccines, severe adverse events following MMR vaccine should be reported as set out in Part 1.6, ‘Adverse Events Following Immunisation’.

## Contraindications

MMR vaccines are contraindicated in the following:

- Persons with untreated malignant disease or altered immunity; those receiving immunosuppressive or X-ray therapy, or high-dose steroids (in children equivalent to 2 mg/kg/day prednisolone for more than a week). Note: MMR can be given to HIV positive children[2] (see Part 2.3, 'Groups with special vaccination requirements', page 52);
- Persons who have had an anaphylactic reaction following a previous dose of MMR
- Persons who have had an anaphylactic reaction to neomycin;[12]
- As gelatin is added to M-M-R II (but not Priorix), anaphylactic sensitivity to gelatin is a contraindication to M-M-R II but not Priorix;[12]
- Children who have an acute febrile illness when they present – defer MMR vaccination until after the illness has resolved;

- If MMR vaccines are given to adult women, pregnancy should be avoided for 28 days, as for rubella vaccine;[13]
- Do not give MMR vaccines within 3 months of an IM injection of normal human immunoglobulin (NHIG), within 9 months of an intravenous injection of NHIG (intravenous), or within 3 months of a whole blood transfusion because the expected immune response may be impaired;[2]
- MMR can be administered on the same day as other live virus vaccines. However, if this is not possible, MMR should be deferred for at least 4 weeks after vaccination with other live virus vaccines. The exception to this rule is OPV.

The following are *not* contraindications to MMR vaccines.

- Oral polio vaccination is not a contraindication to MMR vaccination. MMR can be given at any time before, after or with OPV.[14]
- Egg allergy, even anaphylactic egg allergy, is *not* a contraindication to vaccination with MMR.[1] At the Royal Children's Hospital, Melbourne, Aickin et al administered MMR vaccine to 400 children who had a history of egg allergy and a positive skin prick test.[15] Only 4 children had minor reactions and none had any adverse event that required treatment. Therefore children with egg allergy can be safely given MMR vaccine. However, parental concern may warrant that it be administered under close supervision. Skin testing has been shown to be of no value in the management of these cases.
- Rh (D) immunoglobulin (anti-D) does not interfere with the antibody response to MMR vaccines and the two may be given at the same time in different sites with separate syringes or at anytime in relation to each other.

## Use of immunoglobulin to prevent measles

Normal human immunoglobulin (NHIG) should be considered for contacts of patients with confirmed or suspected measles[8] (Table 3.13.1). If NHIG is administered by IM injection within 7 days of exposure, it can prevent or modify measles in non-immune persons. It should be given to:

- infants between 6 and 9 months of age if contact was within the last 7 days;
- all persons aged 9 months and over where administration of MMR vaccine would be contraindicated or where the person is assessed to be at risk;
- persons exposed to measles who are immunocompromised;
- infants under 6 months of age where the infant's mother is the person infected;
- susceptible persons who did not receive an MMR vaccination within 72 hours of contact.

If an unvaccinated child over 9 months of age has contact with measles, measles infection can be prevented by immediate vaccination (within 72 hours) with MMR vaccine.[8] This is because the incubation period of the vaccine strain (4 to 6 days) is shorter than the incubation period of wild measles virus (10 to 14 days).

Children with compromised immunity (in whom MMR vaccine is contraindicated), should be given NHIG as soon as possible (within 7 days) after exposure. Testing for measles antibody does not assist with the decision to use immunoglobulin since neither previous vaccination nor demonstrated low level serum antibody guarantees immunity to measles in immunocompromised individuals.[2,8] Testing for measles antibody may delay the appropriate use of NHIG. However, testing may be of value in making a definitive diagnosis of measles.

Infants 6 to 9 months of age who have direct contact with a person with measles are at risk of developing complications from the disease, and should be offered NHIG within 7 days of contact.[8] MMR vaccine should then be given as close as possible to 12 months of age, after an interval of at least 3 months following the administration of immunoglobulin. NHIG is not usually given to babies under 6 months old, who are protected by passive maternal antibodies (see Table 3.13.1). However, if the mother of an infant under the age of 6 months has measles, then the infant should be given immunoglobulin. The dose of NHIG is 0.2 mL/kg by IM injection for normal children and 0.5 mL/kg by IM injection for immunocompromised persons (the maximum dose is 15 mL).

Non-immune pregnant women who are exposed to measles can be given NHIG in a dose of 0.2 mL/kg.

**Table 3.13.1: Management of significant measles exposure**

| Age | Action |
|---|---|
| <6 months * | Nil |
| 6-9 months | NHIG 0.2 mL/kg IM injection |
| >9 months | MMR vaccine within 72 hours of exposure or NHIG if 3-7 days after exposure # |

* If the mother is the contact, then the infant should be given immunoglobulin.
# Immunoglobulin is not required if the person has received one or more measles containing vaccines or is assessed as being not susceptible.

## Use in pregnancy

MMR is not recommended in pregnancy[2] and pregnancy should be avoided for 28 days after vaccination (see also Part 3.22, 'Rubella').[13]

## Conflicts with product information

**(i)** The product information states that MMR should not be given to children who have received another live vaccine (including BCG and live virus vaccines) within 4 weeks, and that MMR vaccination should be deferred for at least 4 weeks after the time of the previous vaccination. However, NHMRC recommends that MMR can safely be given with, or at any time before or after, oral polio vaccines.[14]

**(ii)** The product information states that reconstituted vaccine can be used for up to 8 hours. NHMRC recommends that it be discarded after one hour, unless stored cold (2°C to 8°C) and protected from sunlight. The maximum time it can be used after opening in this circumstance is 8 hours.[16]

**(iii)** The product information also recommends that women of child-bearing age should be advised not to become pregnant for 3 months after vaccination with rubella (or MMR) whereas NHMRC recommends 28 days.[13]

**(iv)** The product information for M-M-R II does not recommend administration of MMR with DTP, but NHMRC recommends that this is safe and both are recommended at 4 years of age.[2] They can be given concomitantly at different sites.

**(v)** The product information for M-M-R II states that allergy to eggs is a contraindication to MMR, but it is established that MMR vaccine can be given safely in this situation.[2]

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# 3.14 MENINGOCOCCAL INFECTIONS

## Bacteriology

Meningococcal infections are caused by *Neisseria meningitidis* (*N. meningitidis* or meningococcus), a Gram-negative diplococcus. There are 13 known serogroups distinguished by differences in surface polysaccharides of the outer membrane capsule. Globally, serogroups A, B, C, W135 and Y most commonly cause disease. Further serotyping and serosubtyping of *N. meningitidis* is determined by differences in outer membrane proteins.[1] In Australia, serogroups B and C occur most frequently. There is no consistent relationship between serogroup or type and virulence.[2,3]

## Clinical features

*Neisseria 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 is high (about 10%) despite appropriate antibiotic therapy. 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.[2-4] Factors associated with an increased risk of carriage include smoking and living in crowded conditions.[4]

The disease is transmitted via respiratory droplets with an incubation period of between one and 10 days, but commonly 3 to 4 days.[5] The capacity of meningococcal disease to have a fulminant and rapidly fatal course in previously healthy (and usually young) individuals causes it to be greatly feared. Intensive public health follow-up is required after each single case to conduct contact tracing and to institute appropriate public health measures for contacts. As a result of all these factors, this disease causes widespread community alarm and generates significant media interest.

Persons with inherited disorders of phagocytosis associated with properdin deficiency or absence of the terminal components of complement, as well as individuals with functional or anatomical asplenia, have an increased risk of meningococcal infection.[1]

## Epidemiology

The meningococcus causes both sporadic and epidemic disease throughout the world. Serogroup A disease occurs predominantly in developing populations such as those in Africa and Asia, while serogroup B is the major cause of sporadic meningococcal disease in most developed countries. Serogroup C disease has a more cyclic pattern of occurrence, and has been increasing in incidence in the last 10 years in developed populations such as those in Australia, the United Kingdom and North America.[4] In populations with a temperate climate, disease incidence peaks in winter and spring.

In Australia, the overall notification rate of meningococcal disease to the National Notifiable Diseases Surveillance System has been increasing gradually during the past 10 years from 1.6 per 100 000 in 1991 to 3.1 per 100,000 in 2000.[4] There are considerable differences in the incidence of meningococcal disease between States, with overall annual incidences for the period 1995 to 2000 varying from 3.75 per 100 000 in Western Australia to 1.79 per 100 000 in South Australia.

Nationally, meningococcal serogroup C disease has accounted for an average of 32% of all meningococcal disease (over the period 1995 to 2001). The annual incidence rate of meningococcal serogroup C disease more than doubled during the period 1995 to 2000 from 0.56 to 1.54 cases per 100 000 population, but declined in 2001 to 1.16.[6]

There is considerable interstate variation in both the percentage of meningococcal serogroup C disease (ranging from 12% in Western Australia to 40% in Victoria), and in annual incidence (range 0.39–1.20 per 100 000). New South Wales and Victoria recorded the largest increases in incidences of meningococcal serogroup C disease up to 2000, while Victoria recorded the highest incidence each year for the years 1999 to 2001.

While meningococcal disease can affect all age groups, there is a bimodal age distribution with the highest attack rates in children under 5 years of age, and a second peak in incidence in the 15 to 24 years age group.

Overall, the incidence of meningococcal disease in Indigenous Australians is nearly 6 times that in non-Indigenous Australians. However, in Indigenous people, serogroup C causes 15% of disease, compared with about 30% in the non-Indigenous population.

## Vaccines

There are two different types of meningococcal vaccine: the tetravalent meningococcal polysaccharide vaccines (4vMenPV) and the meningococcal C conjugate vaccines (MenCCV).

**Meningococcal polysaccharide vaccines (4vMenPV)**

- Mencevax ACWY – GlaxoSmithKline (lyophilised purified capsular polysaccharides from *N. meningitidis* serogroups A, C, W135 and Y; 50 µg of each polysaccharide in 0.5 mL + phenol 0.25% as a preservative). Available as a 0.5 mL monodose vial with separate saline diluent and as 10-dose vials in packs of 50, with saline diluent for each vial.

- Menomune – Aventis Pasteur (lyophilised purified capsular polysaccharides from *N.meningitidis* serogroups A, C, W135 and Y; 50 µg of each polysaccharide in 0.5 mL). Available as a 0.5 mL monodose vial with separate saline diluent.

4vMenPVs induce antibodies in 10 to 14 days in 90% of recipients over the age of 2 years. 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 children and adults. These vaccines provide protection against serogroups A, C, W135 and Y.

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 with polysaccharide vaccine results in a reduced antibody response compared with the primary immunisation.[7] This phenomenon has been noted in both children and adults.[8-11] The demonstration of subsequent hyporesponsiveness means that vaccinating low-risk individuals may reduce the effectiveness of revaccination in a subsequent high-risk situation, although this has not been demonstrated. This hyporesponsiveness can be overcome with MenCCV although additional doses of the conjugate vaccine may be required in young children.[12,13] 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.[14,15]

**Meningococcal C conjugate vaccines (MenCCV)**

- Meningitec – Wyeth (each 0.5 mL dose contains 10µg *N. meningitidis* group C oligosaccharide conjugated to approximately 15 µg of a non-toxic *Corynebacterium diphtheriae* $CRM_{197}$ protein + aluminium phosphate adjuvant). Presented as a single dose (0.5 mL) suspension in a vial.

- Menjugate/Menjugate Syringe – CSL Vaccines/Chiron Vaccines (each 0.5 mL dose contains 10 µg *N. meningitidis* group C polysaccharide conjugated to 12.5-25 µg of a non-toxic *Corynebacterium diphtheriae* $CRM_{197}$ protein). Presented as a single dose (0.5 mL) lyophilised powder in a vial; the supplied diluent contains a suspension of aluminium hydroxide as the adjuvant. Also presented as a single dose (0.5 mL) lyophilised powder in a vial with a prefilled diluent syringe.

- NeisVac-C – Baxter Healthcare (each 0.5 mL dose contains 10 µg *N. meningitidis* group C polysaccharide conjugated to 10-20 µg of tetanus toxoid protein + aluminium hydroxide adjuvant). Presented as a single dose (0.5 mL) suspension in a pre-filled syringe.

MenCCVs confer protection against serogroup C only. In these vaccines, the oligo- or polysaccharide antigen is chemically linked (ie. 'conjugated') to a carrier protein. Conjugation changes the nature of the antibody response from a T cell-independent to a T cell-dependent response. The T cell help results in improved antibody responses especially in young children, greater functional activity, and induction of immunological memory probably resulting in long-term protection.

In studies in the United Kingdom, 98 to 100% of infants given 3 doses of MenCCV in a 2, 3, 4 month schedule developed serum bactericidal antibody (SBA) titres ≥1:8 one month after the third dose. [16,17] In children over 12 months of age, a single dose of MenCCV appears sufficient to induce protective antibody responses. In children 12 to 18 months of age receiving a single dose of MenCCV, 91 to 100% achieved SBA titres ≥1:8.[18] In older children, seroconversion rates increase with age: 96% of 3 year olds, 98% of 4 to 5 year olds and 98% of 14 to 17 year olds achieved SBA titres ≥1:8 after a single dose. Antibody concentrations decline rapidly after primary immunisation in infants and children; however, booster responses to 4vMenPV are observed, indicating that the primary series induced immunological memory.[12]

In the UK there has been a substantial reduction of 91 to 95% in cases of meningococcal serogroup C disease in the age groups targeted for immunisation with MenCCV, in a program that began in late 1999.[19] However, to date there has been no significant decrease in cases in adults ≥ 20 years of age, a group not targeted for immunisation. The number of cases of serogroup B disease has increased, but this is in keeping with the upward trend prior to the commencement of serogroup C vaccination.

## Transport, storage and handling

**Meningococcal polysaccharide vaccines (4vMenPV)**

Transport according to general guidelines (see Part 1.10, 'Transport, storage and handling of vaccines'). Unreconstituted freeze-dried 4vMenPV can be stored in either the refrigerator at 2°C to 8°C or it may be stored frozen. Diluent should not be frozen and can be stored at room temperature. Reconstituted vaccine should be stored in the refrigerator at 2° to 8°C, but must be discarded if not used within 8 hours. Protect from light. Do not freeze reconstituted vaccine. Once reconstituted, inspect for any foreign particulate matter and/or colouration prior to administration. Discard if there is discolouration or particulate matter.

**Meningococcal C conjugate vaccines (MenCCV)**

Transport according to general guidelines (see Part 1.10, 'Transport, storage and handling of vaccines'). Store MenCCV in the refrigerator at 2° to 8°C. Do not freeze. Discard if the vaccine has been frozen. During storage, a white deposit and clear supernatant may be observed in the vaccines presented as a suspension. Before use, shake well to obtain a homogeneous white suspension; discard if there is discolouration or particulate matter. Menjugate must be reconstituted with the supplied diluent.

## Dosage and administration

**Meningococcal polysaccharide vaccines**

The 4vMenPV dose is 0.5 mL regardless of age. It should be administered by SC injection. It must not be administered by either the intradermal or intravenous route. 4vMenPVs are approved for use in Australia in children over 2 years of age, adolescents and adults.

**Meningococcal C conjugate vaccines**

MenCCVs are registered for use in Australia from 6 weeks of age.

- Young infants require 3 doses of 0.5 mL at 2, 4 and 6 months of age (or with a minimum of 4 weeks between doses).
- Infants 4 to 11 months of age require 2 doses of 0.5 mL, given at least 4 weeks apart.
- Children 12 months of age, adolescents and adults require one dose of 0.5 mL only.
- All children over the age of 12 months and adolescents should have received a dose of the vaccine before the fifteenth birthday.
- In the period 2003–5, there will be a scheduled school-based catch-up immunisation program for children over 5 years of age.

MenCCV is given by IM injection. Do not mix MenCCV with other vaccines in the same syringe. Experience from the use of the conjugate Hib vaccines suggests that the different brands of the MenCCVs are interchangeable *(expert opinion).*

The NHMRC advises that MenCCVs may be administered simultaneously with other vaccines in the ASVS (see 'Conflicts with product information').

**Administration of MenCCV after administration of 4vMenPV**

On occasion both MenCCV and 4vMenPV are recommended (eg. asplenia). If MenCCV is given first, a period of ≥2 weeks should lapse before 4vMenPV is given. There are limited data available on the length of time that should lapse before administration of MenCCV after giving 4vMenPV. The NHMRC recommends a period of 6 months should lapse before the conjugate vaccine is given *(level IV evidence).*[16,20]

## Recommendations

**Meningococcal polysaccharide vaccines**

Routine vaccination with 4vMenPV is not recommended. It is recommended in the following situations *(expert opinion)*:

- persons who intend travelling to parts of the world where epidemics of group A, W135 or Y disease are frequent. A current list of those countries is available from the World Health Organization at either http://www.who.int/ith or http://www.who.int/disease-outbreak-news/;
- control of outbreaks caused by serogroup A, W135 or Y *(level II evidence for serogroup A only);*
- laboratory personnel who frequently handle *N. meningitidis*, who should also receive MenCCV;

- persons over the age of 2 years with inherited defects of properdin or complement, or functional or anatomical asplenia, who should also receive MenCCV; and
- pilgrims attending the annual Hajj (Saudi Arabian authorities require a valid certificate of vaccination as a condition to enter the country).

Revaccination is indicated for persons at high risk of infection (such as persons living in epidemic areas, and those with immunodeficiencies as defined above), particularly for children first vaccinated before 4 years of age. As antibody levels decline rapidly over 2 to 3 years, revaccination should be given 3 to 5 years later *(expert opinion).*

**Meningococcal C conjugate vaccines**
All people over the age of 6 weeks can be vaccinated with a MenCCV. The ASVS recommends that a single dose be given to children at the age of 12 months *(level III-2 evidence).* In addition, all 15 year old adolescents who have not been vaccinated previously with a conjugate vaccine should receive a single dose.

The vaccine is also recommended for *(expert opinion)*:
- control of outbreaks caused by serogroup C;
- laboratory personnel who frequently handle *N. meningitidis,* who should also receive 4vMenPV;
- persons over the age of 6 weeks with inherited defects of properdin or complement, or functional or anatomical asplenia, who should also receive 4vMenPV at ≥ 2 years of age; and
- * "*any children, adolescents or young adults who have had previous meningococcal disease (including group C disease). Previous disease is not a contraindication to receiving MenCCV because: the reported infecting serogroup may not be correct; young children may not have mounted an optimal immune response to the infection; and older persons may have an unrecognised risk factor for meningococcal disease.*"

## Adverse events following vaccination

**Meningococcal polysaccharide vaccines**
Local reactions to 4vMenPV include erythema, induration, tenderness, pain and local axillary lymphadenopathy. However, they 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.

**Meningococcal C conjugate vaccines**
Common (>10%) adverse events caused by MenCCVs are pain, redness and swelling at the site of injection, fever, irritability, anorexia and headaches. There are some age-related differences in the type of adverse event following vaccination, with systemic adverse events tending to decrease with increasing age, and local adverse events tending to increase with increasing age. Headache is more likely to be reported in the adolescent age group. Serious general adverse events are rare.[19]

**Precautions**
MenCCVs only confer protection against serogroup C *N. meningitidis*. The carrier proteins do not confer protection against either diphtheria or tetanus.

## Contraindications

**Meningococcal polysaccharide vaccines**
The only absolute contraindications to administration of a 4vMenPV are a severe hypersensitivity to any of the vaccine components, or an anaphylactic reaction following a previous dose.

**Meningococcal C conjugate vaccines**
The only absolute contraindications to administration of a MenCCV are a severe hypersensitivity to any of the vaccine components, or an anaphylactic reaction following a previous dose. Previous serogroup C disease is not a contraindication to administration of MenCCV.

As with other vaccines, administration should be postponed in subjects presenting with an acute febrile illness.

## Use in pregnancy

**Meningococcal polysaccharide vaccines**

Studies of vaccination with meningococcal and other polysaccharide vaccines during pregnancy have not documented adverse events in either pregnant women or newborns *(level III-2 evidence)*.[1]

**Meningococcal C conjugate vaccines**

Although no clinical study data are available on the use of MenCCV in pregnant women, it is unlikely that it would have any deleterious effect on the pregnancy. Routine pregnancy testing prior to vaccination is not justified.

## Conflicts with product information

**Meningococcal polysaccharide vaccines**

The NHMRC recommends revaccination with 4vMenPV within 3 to 5 years of a previous dose in the situations detailed in 'Recommendations'. The Mencevax ACWY product information states within 2 to 3 years, and the Menomune product information gives no recommended interval before revaccination.

**Meningococcal C conjugate vaccines**

The product information for all 3 conjugate vaccines state that under the age of 12 months, 3 doses of vaccine are required. The NHMRC recommends that, for infants aged between 4 to 11 months at the commencement of vaccination, 2 doses of MenCCV are sufficient *(level III-2 evidence)*.

The Meningitec product information states that the vaccine should not be administered with either the other infant vaccines in the ASVS at 2, 4 and 6 months of age, or with both IPV and varicella vaccines 'on a routine basis'. The NeisVac-C product information states that the vaccine should not be administered with IPV-containing vaccines 'on a routine basis'. However, the NHMRC states that the vaccine may be administered simultaneously with other vaccines in the ASVS *(expert opinion)*.

The product information for all 3 conjugate vaccines state that there are no data on the use of MenCCVs in lactating women, whereas the NHMRC does not consider breastfeeding in a healthy woman a reason for not immunising *(expert opinion)*.

The Meningitec product information states that an allergic reaction following a prior dose is a contraindication to further doses whereas the NHMRC states that only an anaphylactic reaction following a previous dose is a contraindication.

## Early clinical and public health management of meningococcal disease

Prompt diagnosis and emergency treatment of cases of suspected meningococcal disease are life-saving. If a diagnosis of meningococcal disease is suspected, the patient should be immediately given penicillin and transferred to hospital. The relevant Public Health Unit should be contacted as soon as possible.[4]

**Table 3.14.1: Early clinical management of suspected meningococcal disease**

| | | |
|---|---|---|
| 1. The patient should receive immediate parenteral penicillin. | Age < 1 year | 300 mg penicillin parenterally |
| | Age 1 to 9 years | 600 mg penicillin parenterally |
| | Age ≥ 10 years | 1200 mg penicillin parenterally |
| 2. The patient should be transferred to hospital urgently. | | |
| 3. The relevant Public Health Unit should be notified promptly, so that appropriate public health management can be initiated. | | |

Guidance on the early clinical and public health management of cases of invasive meningococcal disease has been developed by the Communicable Diseases Network of Australia, and is available at http://www.health.gov.au/pubhlth/cdi/pubs/pdf/mening_guide.pdf.[4]

Contrary to popular belief, a patient with meningococcal disease is not a good transmitter of the disease. It is instead the carrier passing on the bacteria to other susceptible persons that may cause further cases of meningococcal disease. Further cases may develop in household contacts in particular; the risk of secondary cases is greatest in the first 7 days, and may persist for many weeks after contact. These close contacts should receive chemoprophylaxis as advised by public health authorities; chemoprophylaxis should be given to relevant close contacts regardless of previous vaccination history. Chemoprophylaxis is not recommended for health-care workers unless they were not wearing a mask whilst engaging in either mouth-to-mouth resuscitation or intubation of a case.

Antibiotics that reduce or eliminate nasopharyngeal carriage of *N. meningitidis* include ceftriaxone, ciprofloxacin and rifampicin.

- Ceftriaxone is administered as a single IM dose of 250 mg for adults and 125 mg for children <12 years of age. Although it is considerably more expensive, ceftriaxone has a number of advantages over rifampicin: it is more likely to eradicate pharyngeal carriage, it eliminates problems with compliance and it is the preferred chemoprophylaxis for pregnant women.
- Ciprofloxacin in a single oral dose of 500 mg is effective and safe, but it should not be given to children under the age of 12 years, or to pregnant women.
- Rifampicin is given to children and adults in an oral dose of 10 mg/kg (maximum dose of 600 mg) twice daily for 2 days. The recommended dose for infants less than one month of age is 5 mg/kg twice daily for 2 days. Pharyngeal carriage will be eliminated in 75–90% of recipients unless the strain is resistant to rifampicin. The side effects of rifampicin should be explained, including orange-red discolouration of contact lenses, urine and tears, possible interference with the contraceptive pill, and interference with the metabolism of many other drugs including warfarin, phenobarbitone and phenytoin. Rifampicin is not recommended for use in pregnant women.

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*.[4] If vaccination is indicated and the organism responsible is serogroup C, MenCCV should be used in preference to 4vMenPV.

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# 3.15 MUMPS

## Virology

Mumps is a paramyxovirus with a single stranded RNA genome. It is rapidly inactivated by heat, formalin and ultraviolet light.[1]

## Clinical features

The incubation period is 12 to 25 days.[2] It is characterised by bilateral, or occasionally unilateral, parotid swelling, but some infections are asymptomatic. About 15% of reported cases occur in adolescents and adults. Benign meningeal signs appear in up to 15% of cases, but permanent sequelae are rare. Nerve deafness is one of the most serious of the rare complications (1 in 500 hospitalised cases). Orchitis (usually unilateral) has been reported in up to 20% of clinical mumps cases in post-pubertal males, but subsequent sterility is rare. Symptomatic involvement of other glands and organs has been observed less frequently (pancreatitis, oophoritis, hepatitis, myocarditis, thyroiditis).[1]

A few experimental, clinical and epidemiological studies indicate that permanent pancreatic damage may result from injury caused by direct viral invasion. However, further research is needed to

determine whether mumps infection contributes to the overall incidence of diabetes mellitus.[1] Patients may be infectious from 6 days before parotid swelling to 9 days after.[2]

## Epidemiology

Mumps is reported worldwide, and is a human disease with transmission by the airborne route or direct contact.[2] It is primarily a disease of children, with a peak incidence in the group aged 5 to 9 years.[3] Eighty percent of adults in urban areas have serological evidence of immunity. A study of mumps in Alberta, Canada, confirmed the benign outcome in most cases, but indicated the potential of mumps vaccination for reducing hospital admissions for aseptic meningitis.[4] Vaccination with the live attenuated vaccine has proved successful in the United States, with a 98% reduction in the number of reported cases between 1967 (when the vaccine was introduced) and 1985.[5,6] In Australia, there have been 10 reported deaths from mumps between 1978 and 1997.[3] In 2000, mumps was recorded as the underlying cause of death in 2 adults, both over 80 years of age.[3]

## Vaccines

Monovalent mumps vaccine is no longer available in Australia. See information on MMR vaccine in Part 3.13, 'Measles'.

## Adverse events and precautions

Aseptic meningitis has been associated with the Urabe strain of mumps vaccine but not the Jeryl Lynn strain.[6] Vaccines containing the Urabe strain are not available in Australia. The meningoencephalitis is invariably mild or asymptomatic and resolves spontaneously. When mumps virus is isolated from the cerebrospinal fluid in such cases, laboratory tests can distinguish between wild and vaccine strains. The assistance of State virology laboratories should be sought in such cases.

See also information on MMR vaccine in Part 3.13, 'Measles'.

## Contraindications

See information on MMR vaccine in Part 3.13, 'Measles'.

## Use in pregnancy

See information on MMR vaccine in Part 3.13, 'Measles'.

## Conflicts with product information

See information on MMR vaccine in Part 3.13, 'Measles'.

## Use of immunoglobulin to prevent mumps

Normal human immunoglobulin (NHIG) has not been shown to be of value in post-exposure prophylaxis for mumps.[6] Live mumps vaccine does not provide protection if given after an individual has been exposed to mumps.[6] However, if the exposure did not result in infection, the vaccine would induce protection against subsequent infection.

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# 3.16 PERTUSSIS

## 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*) which can cause a pertussis-like syndrome.[1]

## Clinical features

Pertussis is an epidemic bacterial respiratory infection. *B. pertussis* is highly infectious, spreading by respiratory droplets to 70 to 100% of susceptible household contacts and 50 to 80% of susceptible school contacts.[2] Not all school-aged children and few adults with pertussis have the characteristic paroxysmal cough with inspiratory whoop. The cough may persist for up to 3 months and is often associated with vomiting.

The overall mortality from pertussis is 0.03% but the mortality in hospitalised babies under 6 months of age is substantially higher (3.5%). Both hospitalisation and deaths are likely to be underestimated as infants,[3] particularly if preterm, may either present without characteristic symptoms or be misclassified as sudden infant death syndrome. Pertussis causes hypoxic encephalopathy, which can result in brain damage and death. The most common cause of death in pertussis infection is pertussis pneumonia, sometimes complicated by seizures and encephalopathy.[2]

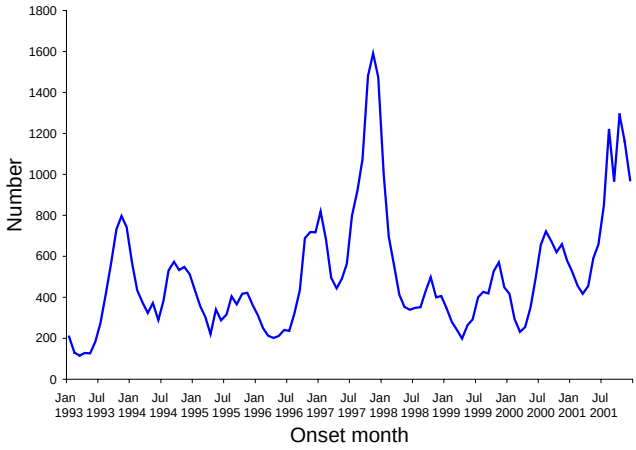
## Epidemiology

Epidemics occur every 3 to 4 years. In unvaccinated populations, these outbreaks can be very large. In vaccinated populations, smaller outbreaks with greatly reduced mortality and morbidity continue to occur every 3 to 4 years. Maternal antibody does not give adequate protection against pertussis, so babies can be infected before they are old enough to be vaccinated. In recent years among highly immunised communities, many cases of pertussis have been recognised in adults and adolescents, due to waning immunity and the increased availability of serological testing.[4,5] These individuals are a significant reservoir of infection.

Pertussis kills about 250 000 children worldwide each year. Many children are left with brain damage from pertussis infection. From 1993 to 2001, 3 epidemics of pertussis occurred in Australia. More cases were reported than for any time since the 1960s, with a total of over 34 000 cases between 1997 and 2001.[6] This increase in reporting may largely relate to increased serological diagnosis in older persons. Between 1993 and 1997 there were 9 deaths attributed to pertussis, all occurring in infants aged under 12 months.[7,8]

Introduction of a fifth dose of diphtheria, tetanus and pertussis vaccine (DTP) for 4 to 5 year old children in August 1994 has been associated with a subsequent reduction in notification rates among 5 to 9 year old children despite an overall increase in rates.[9] The pattern of decrease in notifications was consistent with a vaccine effect, occurring first among, children aged 5 and 6 years old, followed by those in the 7 to 9 year old age group.[9]

**Figure 3.16.1: Pertussis notifications by month of onset, Australia 1993–2001**




Currently in Australia, over 60% of pertussis notifications occur in persons over 10 years of age.[9] This supports the need for booster doses in individuals over the age of 10 years both to reduce morbidity in them, and to reduce transmission to those most at risk (infants <6 months of age).[10] Immunisation of adolescents, who have a high risk of pertussis infection, and adults in contact with very young infants would be expected to result in the greatest health benefits. An adult/adolescent formulation acellular pertussis-containing vaccine (dTpa) is now available for use in Australia for booster vaccination of persons aged 8 years and over (see'Recommendations' below).

## Vaccines

### (i) Acellular pertussis vaccines

Acellular pertussis-containing vaccines were funded for use in both primary and booster vaccination schedules in Australia in February 1999 and have now replaced whole-cell vaccines in the Australian Standard Vaccination Schedule. There are a number of acellular pertussis vaccines, which contain 3 or more purified components of *B. pertussis*: pertussis toxin (PT), filamentous haemagglutinin (FHA), pertactin (PRN), and fimbrial antigens or agglutinogens. Acellular pertussis vaccines with 3 or more antigens have similar efficacy to good quality whole-cell vaccines.[11]

Acellular vaccines are significantly less reactogenic than whole-cell pertussis vaccines, causing fewer local reactions and less fever and other systemic reactions. Although serious adverse events such as hypotonic-hyporesponsive episodes can still occur, they are much less common than with whole-cell vaccines.[11] Acellular vaccines are also immunogenic, safe and well tolerated in adults.[12] The adult/adolescent formulation (dTpa) contains lower concentrations of diphtheria, tetanus and pertussis antigens than infant and childhood diphtheria, tetanus and acellular pertussis (DTPa) vaccines.

As protective efficacy of both natural infection and pertussis vaccine wanes over time, booster doses are required. Recent active follow-up at 3 to 6 years of age of children who had received a primary course of 3-component DTPa at 2, 4 and 6 months without boosting have shown more than 80% protection through to 6 years of age.[13]

***Paediatric formulations***

- **Infanrix** – GlaxoSmithKline (DTPa; diphtheria-tetanus-acellular pertussis); diphtheria toxoid 30 IU, tetanus toxoid 40 IU, pertussis toxoid (PT) 25 µg, filamentous haemagglutinin (FHA) 25 µg, pertactin (PRN) 8 µg; adsorbed on to aluminium hydroxide; phenoxyethanol as preservative; 0.5 mL dose.

- **Infanrix HepB–** GlaxoSmithKline (DTPa-hepB; diphtheria-tetanus-acellular pertussis-hepatitis B); diphtheria toxoid 30 IU, tetanus toxoid 40 IU, PT 25 µg, FHA 25 µg, PRN 8 µg, recombinant hepatitis B surface antigen (HBsAg) 10 µg; adsorbed on to 0.7 mg aluminium as hydroxide and phosphate, phenoxyethanol 2.5 mg as preservative; formaldehyde <1 mg; 0.5 mL dose.

- **Infanrix Hexa** – GlaxoSmithKline (DTPa-hepB-IPV-Hib; diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliomyelitis vaccine-*Haemophilus influenzae* type b (Hib)); diphtheria toxoid 30 IU, tetanus toxoid 40 IU, PT 25 µg , FHA 25 µg, PRN 8 µg, recombinant HbsAg 10 µg, inactivated polioviruses type 1 (Mahoney) 40 D-antigen units, type 2 (MEF-1) 8 D-antigen units and type 3 (Saukett) 32 D-antigen units, purified Hib capsular polysaccharide (PRP) 10 µg

conjugated to 20–40 µg tetanus toxoid; phenoxyethanol as preservative; traces of neomycin and polymyxin; 0.5 mL dose.

- **Infanrix-IPV** – GlaxoSmithKline (DTPa-IPV; diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis vaccine); diphtheria toxoid 30 IU, tetanus toxoid 40 IU, PT 25 µg, FHA 25 µg, PRN 8 µg, inactivated polioviruses type 1 (Mahoney) 40 D-antigen units, type 2 (MEF-1) 8 D-antigen units and type 3 (Saukett) 32 D-antigen units; phenoxyethanol as preservative; traces of neomycin and polymyxin; 0.5 mL dose.

- **Infanrix Penta** – GlaxoSmithKline (DTPa-hepB-IPV; diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliomyelitis vaccine); diphtheria toxoid 30 IU, tetanus toxoid 40 IU, PT 25 µg, FHA 25 µg, PRN 8 µg, recombinant HbsAg 10 µg, inactivated polioviruses type 1 (Mahoney) 40 D-antigen units, type 2 (MEF-1) 8 D-antigen units and type 3 (Saukett) 32 D-antigen units; phenoxyethanol as preservative; traces of neomycin and polymyxin; 0.5 mL dose.

- **Pediacel** – Aventis Pasteur (DTPa-IPV-Hib (PRP-T); diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis vaccine-Hib); diphtheria toxoid >30 IU, tetanus toxoid >40 IU, PT 20 µg, FHA 20 µg, PRN 3 µg, fimbrial agglutinogens (FIM) 2+3 5 µg, inactivated poliovirused (Vero cell origin) type 1 (Mahoney) 40 D-antigen units, type 2 (MEF-I) 8 D-antigen units and type 3 (Saukett) 32 D-antigen units, PRP 10 µg conjugated to tetanus toxoid 20 µg, aluminium phosphate 1.5 mg, bovine serum albumin <50 ng; phenoxyethanol as preservative; traces of polymyxin, neomycin and streptomycin; 0.5 mL dose.

- **Poliacel –** Aventis Pasteur (DTPa-IPV/Hib (PRP-T); diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis vaccine combined with Hib); combination vaccine pack containing ActHib (PRP conjugated to tetanus protein (see Part 3.7, '*Haemophilus influenzae* type b') reconstituted with Quadracel (see below)).

- **Quadracel** – Aventis Pasteur – (DTPa-IPV; diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis vaccine); diphtheria toxoid >30 IU, tetanus toxoid >40 IU, PT 20 µg, FHA 20 µg, PRN 3 µg, FIM 2+3 5 µg, inactivated polioviruses (MRC-5 cell origin) type 1 (Mahoney) 40 D-antigen units, type 2 (MEF-I) 8 D-antigen units and type 3 (Saukett) 32 D-antigen units, aluminium phosphate 1.5 mg, bovine serum albumin <50 ng; phenoxyethanol as preservative; traces of polymyxin and neomycin; 0.5 mL dose.

- **Tripacel** – Aventis Pasteur (DTPa; diphtheria-tetanus-acellular pertussis); diphtheria toxoid >30 IU, tetanus toxoid >40 IU, PT 10 µg, FHA 5 µg, PRN 3 µg, FIM 2+3 5 µg, aluminium phosphate 1.5 mg; phenoxyethanol as preservative; 0.5 mL dose.

***Adult/adolescent formulation***

- **Boostrix** – GlaxoSmithKline (dTpa; diphtheria-tetanus-acellular pertussis); diphtheria toxoid >2 IU, tetanus toxoid >20 IU, PT 8 µg, FHA 8 µg, PRN 2.5 µg, absorbed on to 0.7 mg aluminium as hydroxide and phosphate; phenoxyethanol 2.5 mg as preservative; 0.5 mL dose.

## Transport, storage and handling

Transport according to general guidelines (see Part 1.10, 'Transport, storage and handling of vaccines'). Store in a refrigerator at 2°C to 8°C. Do not freeze. If vaccine has been exposed to temperatures less than 0°C, do not use (vaccine which has been frozen may contain a flocculant precipitate which does not resuspend).

## Dosage and administration

The dose of both DTPa and DTPa-combinations is 0.5 mL by IM injection.

## Recommendations

**(i) Primary course**

Acellular pertussis vaccine, as a component of the primary course of vaccination against diphtheria, tetanus and pertussis, is recommended for all infants from 2 months of age, unless there is an absolute contraindication. The same brand of vaccine should be used for each of the 3 doses at 2, 4 and 6

months. If it is not known which brand was used, vaccination should still be provided with an available brand.

The primary course consists of 3 doses with an interval of 2 months between each dose. In view of the high morbidity and mortality associated with pertussis under the age of 6 months, receipt of the first dose of vaccine as soon as possible after 2 months of age should be strongly emphasised. If the primary course is interrupted, it should be resumed but not repeated; doses may be given as little as 28 days apart.

**(ii) Booster doses**
**Children**
Available brands of DTPa are considered interchangeable for the booster dose. Booster doses with DTPa were previously recommended at 18 months and 4 years of age. In view of the prolonged immunity now known to result from a primary course of DTPa,[13] the 18 month dose is no longer recommended, with the fourth dose now due at 4 years of age *(level IV evidence)*. In addition, it is likely that postponing receipt of a fourth dose of DTPa until 4 years of age will reduce the proportion of children experiencing extensive local reactions, which have been well documented at 18 months of age.[14] Paediatric formulation DTPa vaccines have an upper age limit of the eighth birthday, because DTPa contains a higher dose of diphtheria toxoid than either dT or adult/adolescent formulation dTpa, which are preferred after the eighth birthday. For details on the management of children who have missed doses in the standard childhood vaccination schedule, see Part 1.9, 'Catch-up vaccination'.

**Adults and older children**
An acellular pertussis vaccine (combined with tetanus and diphtheria antigens) is registered in Australia for booster vaccination of individuals aged 10 years and older who have previously had a primary course of diphtheria-tetanus vaccine. However, the NHMRC recommends that it may be used in children aged 8 years and older (see 'Conflicts with product information').

The vaccine (Boostrix) has lower antigen content, particularly the diphtheria and pertussis antigens, than DTPa formulations for children, and is therefore referred to as dTpa. Because there are no data on the safety, immunogenicity or efficacy of dTpa when given as a primary vaccination series, dTpa should not be used where primary immunisation of an adolescent or adult for diphtheria and tetanus is incomplete. However, in adolescents and adults who received one or more doses of child-formulated diphtheria-tetanus (CDT) vaccine rather than DTP vaccine for primary immunisation, a single dose of dTpa is appropriate for protection against pertussis. Further, because data on the duration of immunity to pertussis following a single booster dose of dTpa are limited[15], no recommendation about further booster doses of dTpa can be made at this time.

A booster dose of dTpa on a single occasion is recommended for the following groups. Once a single booster dose of dTpa has been given, subsequent booster doses to the same individual should not be administered even if he/she qualifies for another of these groups:

- Adolescents at 15 to 17 years, replacing the dose of ADT (dT) that was recommended at 15 to 19 years *(level II evidence)*. This recommendation is based on the expectation, from extrapolation of data on duration of protection following a primary series, of up to 10 years immunity to pertussis following a booster dose of DTP given at 4 to 5 years of age.[13] (Most adolescents would have either had at least 3 prior doses of a pertussis-containing vaccine or been exposed to the pertussis bacterium. Therefore if documentation of previous vaccinations is not readily available, it can be safely assumed that a dose of dTpa at 15 to 17 years is indeed a booster dose.)
- Before planning pregnancy, or for both parents as soon as possible after delivery of an infant, (preferably prior to hospital discharge), unless contraindicated *(expert opinion)*.[10] This recommendation is based on evidence from a study of infants hospitalised with pertussis around Australia in 2001, which indicated that parents were the presumptive source of infection in over 50% of cases.[16]
- For adults working with young children *(expert opinion)*. Immunisation is especially recommended for health-care workers and child-care workers in contact with the youngest infants, such as maternity and nursery staff (unless contraindicated).

* "***Minimum interval between dTpa and other tetanus-containing vaccines***
*dTpa can be administered at any time following a previously administered dose of tetanus toxoid containing vaccine (expert opinion)*."

- Any adult expressing an interest in receiving a booster dose of dTpa should be encouraged to do so provided that primary course of DTP vaccine has been given in the past. With this same provision, dTpa may be used instead of ADT vaccine at 50 years of age. As mentioned above, subsequent boosters cannot be recommended at this time.

**(iii) The public health management of pertussis**

**Management of cases**

The clinical case definition of pertussis is either (i) an acute cough lasting ≥14 days with at least one of post-tussive vomiting, apnoea or whoop, or (ii) a cough of any duration in someone epidemiologically linked to a confirmed case. A detailed history is required when a case of pertussis is suspected, including date of onset, vaccination status and details of household contacts. The diagnosis can be confirmed by either culture or PCR of a per-nasal swab or nasopharyngeal aspirate, or by serological tests. A recent study has documented that assays for pertussis IgA have low sensitivity (24-64%), indicating that these tests may return false negative results,[17] however a positive test is highly reliable in the presence of appropriate symptoms.

To reduce the risk of transmission, cases should be commenced on erythromycin on clinical suspicion, but only if it is commenced within 21 days of the onset of symptoms. There is no evidence of any benefit of erythromycin if the cases have had symptoms for more than 21 days. "*The dose for babies 0 to 7 days old (regardless of duration of gestation) is 10 mg/kg/dose orally 12-hourly for 7 days; the dose for babies 8 to 28 days old is 10 mg/kg/dose orally 8-hourly for 7 days; the dose for babies and children older than 28 days is 10 mg/kg/dose orally 6-hourly for 7 days; the dose for adults is 250 mg orally 6-hourly for 7 days.*" Note that erythromycin may have no effect at all on symptoms but was found in a randomised, controlled trial to reduce infectivity of cases and contacts.18

Cases should be excluded from, for example, child-care facilities and school, until they have taken 5 days erythromycin. All cases, both suspect and confirmed, should be notified to the State/Territory public health authorities.

**Management of contacts of cases**

**(a) Vaccination**

Since a primary course of 3 or more injections is required to protect against pertussis, infant vaccination cannot be effectively used to control an outbreak. However, unvaccinated or partially vaccinated contacts up to their eighth birthday should be offered DTPa-containing vaccines (see Part 1.9, 'Catch-up vaccination').

Passive immunisation with normal human immunoglobulin has not been shown to be effective in the prevention of pertussis.

**(b) Chemoprophylaxis**

Although erythromycin reduces infectivity when used promptly in optimal circumstances,[18] in the usual clinical setting of delayed presentation and imperfect compliance, it probably has little effect in preventing the secondary transmission of pertussis.[19] In view of this and the well-established (mainly gastrointestinal) side effects of erythromycin, its use for prevention of secondary cases should be reserved for those settings where the benefit is greatest. These settings are best defined by the chance of transmission and the risk of severe complications should transmission occur. Close contacts can be defined as those who either live in the same household (but not occasional 'sleepover' contacts unless they too are at increased risk of severe disease), or stay in the same institutional setting (eg. hospital ward) as a case.

Based on these principles, erythromycin prophylaxis is recommended only for the following household or institutional contacts of pertussis cases:

- any infants <12 months of age regardless of vaccination status;
- any child aged between 12 and 24 months who has received less than 3 doses of pertussis vaccine;
- any women in the last month of pregnancy (see below);
- any child or adult who attends or works at a child-care facility.

The erythromycin doses and duration are the same as for cases (above). Erythromycin should only be given if commenced either within 21 days of the onset of any symptoms, or within 14 days of the onset

of the paroxysmal cough in the case. Unvaccinated or partially vaccinated contacts should be excluded from child-care either until they have taken 5 days of erythromycin, or for 14 days after the case is no longer considered infectious.

The newer macrolides (eg. clarithromycin) may have fewer adverse effects and may be as effective as erythromycin for chemoprophylaxis.[20]As the evidence is still very limited, their use should be limited to persons who develop or who have a past history of gastrointestinal intolerance to erythromycin. The dose of clarithromycin used in a clinical trial was 7.5 mg/kg/dose twice daily (up to a maximum dose of 500 mg twice daily) for 7 days[20] (see also 'Conflicts with product information').

Chemoprophylaxis is not recommended routinely for health-care staff caring for infected children.

**(c) Pertussis in pregnancy**
Maternal antibodies do not protect newborn babies against pertussis. For this reason, pregnant women with pertussis onset within a month of delivery should be given oral erythromycin (250 mg 4 times daily for 7 days). If the onset is within 3 weeks of delivery, their newborn babies should also be given erythromycin syrup (10 mg/kg/dose 3 times daily for 7 days).

NB. Several studies have shown a higher than expected rate of infantile hypertrophic pyloric stenosis (IHPS) in neonates given erythromycin for prophylaxis following exposure to pertussis, especially if given in the first 2 weeks of life. No safe and effective alternative to erythromycin for prophylaxis in neonates exists; however, these findings suggest caution in defining risk groups to minimise unnecessary prophylaxis. Parents of newborns prescribed erythromycin should be informed about the possible risks for IHPS and counselled about signs of developing IHPS.[21,22]

## Adverse events

**(i)** Acellular pertussis vaccines are associated with a much lower incidence of fever and local reactions than are the now obsolete whole-cell pertussis vaccines.[11] Some studies have shown an increase in the incidence of local reactions in children boosted at 18 months with the acellular vaccine that they received for their primary series. The reactogenicity associated with the fifth dose is yet to be assessed in Australia, as children who received a full primary course of acellular vaccine have not yet received their booster at 4 years of age. Current recommendations are to use the same acellular vaccine as was used in the primary course until further information is available.[23]

**(ii)** Paracetamol is not routinely recommended for children receiving acellular pertussis vaccine.

**(iii)** If a febrile convulsion occurs after a dose of DTPa, such children are at increased risk (albeit low) of further febrile convulsions following further DTPa. However, these risks can be minimised by appropriate measures to prevent fever, so vaccination is still recommended. As with all suspected adverse events to vaccines, severe adverse events following pertussis vaccination should be reported as set out in Part 1.6, 'Adverse events following immunisation'.

**(iv)** Pertussis vaccine does not cause infantile spasms or epilepsy. Vaccine-induced fever may uncommonly lead to a febrile convulsion, though much less commonly with DTPa than occurred with DTPw. The risk is even lower in infants who complete their primary course by 6 months of age.

**(v)** Sudden infant death syndrome (SIDS) is not associated with either DTPa or any pertussis-containing vaccine. Some studies suggest a decreased risk of SIDS in children who have been vaccinated (see also Appendix 4, ‘Commonly asked questions about vaccination’).

**(vi)** It is important to note that the incidence of acute neurological complications after pertussis disease in unvaccinated individuals (more than 1% of cases) is considerably higher than after vaccination (estimates range from 0 to 10 per million vaccinations).

## Contraindications and precautions

Before administration of each dose of DTPa, the child’s parent or guardian should be questioned about possible adverse events following previous dose(s). Severe adverse events that contraindicate further doses of either DTPa or other pertussis-containing vaccines are outlined below.

**Contraindications**

**(i)** Encephalopathy without another evident cause within 7 days of vaccination: defined as severe acute neurological illness + prolonged seizures ± unconsciousness ± focal signs. This does not include febrile convulsions. Such illnesses would be anticipated to require hospitalisation and to receive specialist care. Referral to specialist clinics dealing with suspected adverse events following immunisation should be considered.

*Action:* DT should be used for subsequent vaccinations instead of DTPa. If encephalopathy is vaccine-related, the pertussis component is the most likely cause. Further vaccination with diphtheria and tetanus vaccines can be undertaken but should occur under careful observation.

**(ii)** Immediate severe allergic reaction: defined as generalised urticaria, bronchospasm, hypotension, collapse or anaphylactic reaction occurring after either DTPa or other pertussis-containing vaccines.

*Action:* Do not vaccinate with same vaccine again. Use DT instead. Although the pertussis component is the most likely cause of adverse events, further vaccination with diphtheria and tetanus vaccines can be undertaken under careful observation.

**Precautions**

**(i)** Convulsion, with or without fever, or a temperature of 40.5°C or more.

*Action:* Safe to complete the course with DTPa-containing vaccine.

**(ii)** Persistent inconsolable screaming for 3 or more hours, or unusual high-pitched cry.

*Action:* Safe to complete the course with DTPa-containing vaccine.

**(iii)** Hypotonic-hyporesponsive episode (HHE): defined as an episode of pallor, limpness and unresponsiveness 1 to 48 hours after vaccination, often preceded by irritability and fever. Shallow respiration and cyanosis may also occur. The whole episode lasts from a few minutes to 36 hours. Although now very rare following DTPa, they are usually much less severe and shorter than those that occurred after DTPw. Follow-up of children with HHE shows no long-term neurological or other sequelae.[24]

*Action:* Safe to complete the course with DTPa-containing vaccine.

**(iv)** Extensive circumferential limb swelling and redness: defined as swelling and redness commencing within 48 hours of vaccination and resolving completely without sequelae.[25] The duration of swelling is one to 7 days. The pathogenesis of extensive limb swelling is unknown and has been documented for multiple products from different manufacturers.[25] In an analysis of fourth and fifth 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.[25] In this series the fourth dose was administered to toddlers in the thigh and the fifth dose to preschoolers in the deltoid region. Note: The previous recommendation was to administer booster doses of DTPa at 18 months and 4 years of age in the deltoid region, but the first (18 month) booster is no longer considered necessary (see 'Recommendations, Booster doses' above).

*Action:* A history of extensive limb swelling after a booster (as was previously recommended) at 18 months of age is not a contraindication for a fifth dose of DTPa at 4 years[14], which should still be given in this situation. Ensure the vaccine is given by IM injection. Parents of children about to receive the booster dose of DTPa (at 4 years of age) should be informed of the possible increased risk of an extensive local reaction.

**Previous pertussis infection**

Vaccination with pertussis vaccine in children who have been infected with pertussis previously is safe, and therefore previous infection is not a contraindication.

**Pre-existing neurological disease and pertussis vaccination**

Infants and children known to have active or progressive neurological disease can be safely vaccinated with acellular pertussis-containing vaccines. Pertussis vaccination may be deferred in children who have had a convulsion in the previous 3 weeks. For infants with stable neurological disease (including controlled epilepsy), or a family history of idiopathic epilepsy or other familial neurological disorder, the risks from pertussis vaccination are essentially the same as for other infants of the same age.

## Use in pregnancy

Adequate human data on use of adult/adolescent formulation dTpa during pregnancy are not available, so it should only be given in pregnancy when the possible advantages outweigh the possible risks for the fetus.

## Conflicts with product information

The product information states that the fourth dose of DTPa be given at 18 months of age, with a fifth at 4 to 5 years of age. However, the NHMRC now recommends that the fourth dose be given at 4 years of age.

The product information for Boostrix (adult/adolescent formulation dTpa) states that it is recommended for use in those aged 10 years and older. NHMRC recommends that it may be used in children aged 8 years and older.

Treatment or prophylaxis of pertussis is not an approved indication for clarithromycin, however NHMRC deems that its use for this purpose is justified if erythromycin cannot be tolerated.

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# 3.17 PLAGUE

## Bacteriology

Plague is a zoonotic infection caused by the Gram-negative bacillus, *Yersinia pestis*, which is transmitted from an animal reservoir by fleas to humans.

## Clinical features

Naturally occurring plague in humans is characterised by the abrupt onset of high fever, painful local lymphadenopathy draining from the exposure or flea-bite site and bacteraemia. Septicaemia can sometimes follow. Patients with the bubonic form of plague may develop secondary pneumonic plague, which in turn can cause primary pneumonic plague following human to human spread via the respiratory route.

## Epidemiology

Small foci of carriage of *Y. pestis* occur in black rats, small rodents and carnivores in many parts of the world, including Asia, Africa, South America and the southwestern United States. At least 2000 cases are reported annually. Plague exists in one of 2 states in nature, enzootic and epizootic. In the enzootic state, fleas have no need to seek less desirable hosts to feed upon. However, during an epizootic situation, plague bacilli are introduced into other susceptible animals, including domestic rat populations, and high mortality in these animals is often apparent. Under such circumstance man is an accidental host, usually being infected when living under unsanitary conditions close to large wild rodent populations. *Y. pestis* is a significant threat during periods of war or deprivation and has the potential for use as a biological weapon.[1]

## Vaccine

- **Plague Vaccine** – CSL Vaccines (heat killed agar-grown suspension of *Y. pestis* 3000 million per mL + phenol 0.5% as preservative).

While plague vaccines have been used since the late nineteenth century, their efficacy has not been demonstrated in controlled trials. However, field experience indicates that vaccination with plague vaccine reduces the incidence and severity of disease.[2-5] Subunit and live attenuated vaccines are in development.

## Transport, storage and handling

Transport according to general recommendations (see Part 1.10, 'Transport, storage and handling of vaccines'). Do not freeze. Store in a refrigerator at 2°C to 8°C. Protect from light.

## Dosage and administration

The vaccine is given by SC injection. The initial course consists of 2 doses for adults and adolescents, and 3 doses for children under 12 years of age, at intervals of 1 to 4 weeks. Booster doses should be given every 6 months to persons living in areas where plague is prevalent. If booster doses are required in people who have previously had adverse events following this vaccine, 0.1 mL may be given intradermally, and precautions taken to manage anaphylactic reaction.

**Table 3.17.1: Recommended dosage schedule for plague vaccine**

| Age | 1st dose | 2nd dose | 3rd dose | Booster |
|---|---|---|---|---|
| 6 months – 2 years | 0.1 mL | 0.1 mL | 0.1 mL | 0.1 mL |
| 3 – 6 years | 0.2 mL | 0.2 mL | 0.2 mL | 0.2 mL |
| 7 – 11 years | 0.3 mL | 0.3 mL | 0.3 mL | 0.3 mL |
| Over 12 years | 0.5 mL | 0.5 mL | - | 0.5 mL |

## Recommendations

Routine vaccination against human plague is not necessary, except in those at particularly high risk of infection (see below), because the disease is rare in most parts of the world. Vaccination is not generally indicated for travellers to countries reporting cases, particularly if their travel is limited to urban areas with modern hotel accommodation. However, following natural disasters, and at times when regular sanitary practices are interrupted in countries of South America, Asia, and Africa

(including South Africa), plague can extend from its usually endemic areas into urban centres. In such circumstances tourist travel to those specific locations should be avoided.

**Vaccination is recommended for:**

- all laboratory and field personnel who are working with *Y. pestis* organisms.[6] NB: Routine bacteriological precautions are sufficient to prevent accidental infection with plague in those laboratories that may, on rare occasion, handle the organism.
- persons who are either engaged in field operations or resident in plague enzootic areas where preventing exposure cannot be assured (eg. veterinarians in rural areas, medical and other aid workers in some disaster areas).

### Adverse events and precautions

Local and general adverse events following plague vaccination are usually mild and uncommon. They are more common after booster injections.

### Contraindications

The only contraindications to plague vaccine are an anaphylactic sensitivity to a component of the vaccine and anaphylaxis following a prior dose.

### Use in pregnancy

There is no evidence that plague vaccine causes fetal damage.

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## 3.18 PNEUMOCOCCAL INFECTIONS

### Bacteriology

*Streptococcus pneumoniae* are lancet shaped Gram-positive cocci. To date 90 capsular antigenic types have been recognised, each eliciting type-specific immunity. Some of these types are commonly carried in the upper respiratory tract, and some are more frequently associated with invasive disease. The emergence of antibiotic-resistant strains of this organism has become an increasing challenge for the management of invasive pneumococcal disease. Recent reports in Australia indicate that up to 21% of strains are resistant to 2 or more classes of antibiotics.[1]

### Clinical features

Invasive pneumococcal disease (IPD) is defined as isolation of *S. pneumoniae* from a normally sterile site, most commonly blood. The major clinical syndromes of IPD include pneumonia, meningitis and bacteraemia without focus. In adults, pneumococcal pneumonia is the most common clinical presentation of invasive pneumococcal disease, while in children bacteraemia accounts for more than two-thirds of cases.[2-4]

Non-invasive pneumococcal disease includes otitis media and (non-bacteraemic) pneumonia. In contrast to IPD, determination of pneumococcal aetiology for these conditions is problematic, because other organisms can cause an identical clinical picture and diagnostic specimens are often difficult to obtain.

The risk of IPD is highest in patients who cannot mount an adequate immune response to pneumococcal capsular antigens, including those with anatomical or functional asplenia, immunoglobulin deficiency, acute nephrotic syndrome, multiple myeloma, AIDS, chronic renal failure, organ transplantation and lymphoid malignancies.[3,4] Another group of patients, although generally immunocompetent, are also at increased risk of IPD; these include patients with chronic cardiovascular or pulmonary disease, diabetes mellitus, alcohol-related problems, cirrhosis, CSF leak after cranial trauma or surgery, and those who smoke.[3,5] In those without predisposing medical conditions, frequent otitis media and commencing child-care are associated with increased risk of IPD in children,[6]and tobacco smoking with increased risk in adults.[5]

## Epidemiology

The overall annual incidence of IPD in Sydney during 1997 to 1999 was estimated to be 14 per 100 000, reaching almost 100 per 100 000 at the extremes of the age range (children aged under 2 years and adults aged over 85 years).[4]

About 200 cases of pneumococcal meningitis occur each year in Australia, making *S. pneumoniae* the leading cause of meningitis in children under 5 years of age.[7] Children under one year of age have the highest risk of pneumococcal meningitis (approx 10 cases per 100 000 population).[4,7] The case-fatality rate for pneumococcal meningitis ranges from 10 to 30%, but may be as high as 80% in the very elderly.[3,4]

In the less developed world and in some groups of Indigenous Australians, the incidence of IPD is as high as 200 per 100 000 per year. However, mortality rates among Indigenous Australian people are comparable to those in non-Indigenous people, even in remote areas.[8] In Western Australia, the Northern Territory and north Queensland, the age-standardised incidence of IPD is many times higher in Indigenous people.[9-11] Most adult non-Indigenous cases have at least one risk factor for IPD, while most cases occurring in Indigenous adults have multiple risk factors. In adults, most disease-causing isolates seen in all ethnic backgrounds belong to serotypes contained in the 23-valent vaccine.[9,10,12] Aboriginal and Torres Strait Islander children under 2 years of age living in areas of high IPD incidence, such as the Northern Territory and north Queensland, have been shown to have IPD due to a diverse range of serotypes. [9-11] Only about two-thirds of isolates in these children are included among serotypes in the 7-valent pneumococcal conjugate vaccine (this compares with 85% or more among non-Indigenous children).

## Vaccines

There are currently 2 different types of pneumococcal vaccine available in Australia. The 23-valent pneumococcal polysaccharide vaccine (23vPPV) is approved for use in older children and adults who are at risk of IPD. A pneumococcal vaccine with 7 capsular polysaccharides conjugated to a mutant non-toxic diphtheria toxin ($CRM_{197}$) (7vPCV) became available in 2001 for immunisation of infants and children aged from 6 weeks to 9 years.

**Pneumococcal polysaccharide vaccine, 23-valent (23vPPV)**

- **Pneumovax 23** – CSL Vaccines/Merck Sharpe & Dohme (23-valent pneumococcal polysaccharide vaccine; 23vPPV). Single dose vials containing 25 µg of each of 23 pneumococcal polysaccharides in 0.5 mL of normal saline plus 0.25% phenol.

23vPPV contains polysaccharides derived from the 23 most frequent or most virulent capsular types of *S. pneumoniae* in the USA. These same serotypes are responsible for most IPD cases in adults in Australia. At least 90% of healthy adults respond to the vaccine with a 4-fold rise in type-specific antibody within 2 to 3 weeks. Response to vaccine is diminished in immunocompromised patients and is limited to a small number of serotypes in children less than 2 years of age.[13]

In developing countries with high attack rates, controlled trials have demonstrated that pneumococcal polysaccharide vaccine reduces mortality from pneumonia in younger adults. Although controlled

trials are not yet available for at-risk individuals with much lower attack rates in developed countries, (eg. the elderly and those with chronic diseases), observational studies have consistently shown protection (with the exception of immunocompromised persons) against IPD.[13] Protection against non-bacteraemic pneumonia is overall less clear than protection against bacteraemic infection, with conflicting results in several recent meta-analyses.[14] Nevertheless, there is evidence for benefit from pneumococcal polysaccharide vaccine when used at the population level in both the elderly in Sweden[15] and in Aboriginal and Torres Strait Islander people in north Queensland.[16]

**Pneumococcal conjugate vaccine, 7-valent (7vPCV)**

- **Prevenar** – Wyeth (7-valent pneumococcal conjugate vaccine; 7vPCV). Single-dose vials containing 2 µg of saccharides of serotypes 4, 9V, 14, 18C, 19F, 23F and 4µg of serotype 6B, conjugated to $CRM_{197}$ carrier protein and adsorbed on aluminium phosphate (0.5mg).

7vPCV is licensed in Australia for the active immunisation of infants and children aged 6 weeks to 9 years. Efficacy data from a pivotal trial found greater than 95% protective efficacy against IPD due to the serotypes contained in the vaccine.[17] Other types of pneumococcal infection (pneumonia and otitis media) not associated with a positive sterile site culture, are also reduced by 7vPCV, but the evidence is either for lower efficacy (otitis media)[18] or less well established (pneumonia).[19]

## Transport, storage and handling

**23-valent pneumococcal polysaccharide vaccine (23vPPV)**

Transport 23vPPV according to general guidelines (see Part 1.10, 'Transport, storage and handling of vaccines'). Store in a refrigerator at 2°C to 8°C. Do not freeze. 23vPPV is a clear, colourless solution. Inspect visually for particulate matter and discoloration prior to administration. Shake the vial vigorously before withdrawing dose and inject vaccine as soon as possible. No dilution or reconstitution is necessary.

**7-valent pneumococcal conjugate vaccine (7vPCV)**

Transport 7vPCV according to general guidelines (see Part 1.10, 'Transport, storage and handling of vaccines'). Store in a refrigerator at 2°C to 8°C. Do not freeze. Do not mix with any other vaccines or products in the same syringe. Administer as a separate injection. Shake vial well before use to obtain a homogeneous white suspension and use immediately after being drawn up into the syringe. Do not use if it cannot be uniformly suspended or is discoloured.

## Dosage and administration

**23-valent pneumococcal polysaccharide vaccine (23vPPV)**

The dose is 0.5 mL as a single dose, by either SC or IM injection.

**7-valent pneumococcal conjugate vaccine (7vPCV)**

The dose is 0.5 mL by IM injection. As local reactions at the injection site are more common after 7vPCV compared with vaccines containing acellular pertussis or Hib, 7vPCV should be given alone in the opposite limb to other injectable vaccines.

## Recommendations

### 23-valent pneumococcal polysaccharide vaccine

**(i) 23vPPV is recommended for:**

- all individuals aged 65 years and over;
- Aboriginal and Torres Strait Islander people aged 50 years and over;
- children aged over 5 years who have underlying chronic illnesses predisposing to IPD (including asplenia and immunocompromise). In the future, these children will be expected to have had a primary course of 7vPCV before the age of 5 years;
- individuals aged over 5 years with asplenia, either functional (including sickle-cell disease) or anatomical. Where possible, the vaccine should be given at least 14 days before splenectomy;
- immunocompromised persons aged over 5 years at increased risk of IPD (eg. patients with HIV infection before the development of AIDS, acute nephrotic syndrome, multiple myeloma, lymphoma, Hodgkin's disease and organ transplantation);

- immunocompetent persons aged over 5 years at increased risk of complications from IPD because of chronic illness (eg. chronic cardiac, renal or pulmonary disease, diabetes, alcohol-related problems);
- persons with CSF leaks (aged over 5 years);
- tobacco smokers *(level III-2 evidence);*[5]
- as a booster dose, at 18 to 24 months of age, following a primary course of 7vPCV, in Aboriginal and Torres Strait Islander children in geographic regions of high incidence (Table 3.18.4);
- as a booster dose, at 4 to 5 years of age, following a primary course of 7vPCV, in children at risk of either high incidence or severity of IPD because of predisposing medical conditions (Tables 3.18.1 and 3.18.3).

**(ii)** 23vPPV is now included in the ASVS for all Aboriginal and Torres Strait Islander adults aged 50 years and over, for those aged 15 to 49 years who have any of the high-risk underlying conditions and for non-Indigenous adults 65 years of age and over.

**(iii) Booster doses**
There are limited data on the value of revaccination with 23vPPV. Among adults 50 to 75 years, re-vaccination was associated with higher rates of local but not systemic adverse reactions and lower, though still significant, antibody rises compared with the first dose.[20] Nevertheless, there appear to be grounds for revaccination of adults at continued high risk for IPD (see below). Revaccination should not be given within 3 years of the previous dose, because of increased risk of local reactions.

**Revaccination with 23vPPV is recommended as follows:**
- non-Indigenous adults less than 65 years of age with risk factors: a single revaccination at 65 years of age or 10 years after the first dose, whichever is later;
- non-Indigenous adults 65 years and older: a single revaccination 5 years later;
- Aboriginal and Torres Strait Islander adults 15 to 49 years with risk factors: revaccination 5 years after the first dose, then again at 50 years or 10 years after the first revaccination, whichever comes later;
- Aboriginal and Torres Strait Islander adults 50 years and older: a single revaccination 5 years later.

**(iv) Penicillin prophylaxis**
In groups with the highest risk of severe IPD (those with acute nephrosis and children under the age of 5 years with congenital or acquired asplenia, or haemoglobinopathies), some authorities recommend continuous penicillin prophylaxis in addition to pneumococcal vaccine. This is likely to prove less necessary if a primary course of conjugate vaccine has been given with a 23vPPV booster at 4 to 5 years.

### 7-valent pneumococcal conjugate vaccine
**(i)** Based on the benefits from 7vPCV in relation to its price, it previously fulfilled cost-effectiveness criteria for inclusion in the immunisation schedule only for children at high risk of IPD. These high-risk children are Aboriginal and Torres Strait Islander children,[8,10,11] non-Indigenous children who reside in the central Australian region[10] and children who have certain predisposing underlying medical conditions.[3,4,13] However, 7vPCV is now recommended in the ASVS for all infants from 2 months of age, and is the preferred pneumococcal vaccine for children aged under 5 years.

**(ii)** The recommended schedule of administration of 7vPCV is as follows:
- 7vPCV should be administered to all children in a primary series of 3 doses (at 2, 4 and 6 months). Unless there is an increased risk of IPD (see below), a fourth booster dose is considered unnecessary. This recommendation, of no booster dose, is based on equivalent efficacy estimates from the pivotal randomised control trial for 3 doses and 4 doses (*level II evidence*).[17]
- The primary series of 7vPCV (at 2, 4 and 6 months) should be followed at 18 to 24 months of age by a dose of 23vPPV for all Aboriginal and Torres Strait Islander children living in areas where there is a high incidence of IPD. This recommendation is based on: (i) lower serotype coverage from the 7vPCV in those populations *(level IV evidence)*, [9-11] (ii) adequate boosting responses to serotypes contained in the 7vPCV following 23vPPV *(level IV evidence)*, [21,22] and (iii) adequate

primary responses to some serotypes in the 23vPPV from 18 to 24 months of age *(level IV evidence).*[23,24]

- Some other groups of children have recently been shown to have a significantly increased incidence of IPD and so qualify for inclusion under medical predisposing factors. These include all children with chronic lung disease following complications of prematurity, all children born at less than 28 weeks gestation, and children with Down's syndrome, insulin-dependent diabetes or cystic fibrosis (see Table 3.18.1).
- Children with underlying medical conditions predisposing them to IPD should receive an additional (fourth) dose of 7vPCV at 12 months and a booster dose of 23vPPV at 4 to 5 years of age (Table 3.18.2). This is based on lower immune responses to certain serotypes in the 7vPCV among such children, which can be enhanced by an additional dose *(level IV evidence),*[25] and their continuing susceptibility to IPD with a higher prevalence of serotypes not contained in the 7vPCV seen with increasing age.
- Catch-up immunisation for low-risk children aged 3 to 23 months can be considered and is likely to be especially beneficial for those commencing child-care.
- The recommended vaccination schedules (including catch-up vaccination for children with and without a previous history of pneumococcal vaccination) are summarised in Tables 3.18.3 to 3.18.5.

**Table 3.18.1: Children under the age of 5 years with underlying medical conditions predisposing them to IPD**

**Diseases compromising immune response to pneumococcal infection**

- congenital immune deficiency including symptomatic IgG subclass or isolated IgA deficiency, but excluding children where monthly immunoglobulin infusion is required
- immunosuppressive therapy (including corticosteroid therapy equivalent to greater than 2mg/kg per day of prednisone for more than 2 weeks) or radiation therapy, where there is sufficient immune reconstitution for vaccine response to be expected
- compromised splenic function due to sickle haemoglobinopathies, or congenital or acquired asplenia
- HIV infection, before and after development of AIDS
- renal failure, or relapsing or persistent nephrotic syndrome
- Down's syndrome.

**Anatomical or metabolic abnormalities associated with higher rates or severity of IPD:**

- cardiac disease associated with cyanosis or cardiac failure
- all premature infants with chronic lung disease
- all infants born at less than 28 weeks gestation
- cystic fibrosis
- insulin-dependent diabetes mellitus
- proven or presumptive cerebrospinal fluid leak
- intracranial shunts and cochlear implants.

**Table 3.18.2: Categories of IPD in children under the age of 5 years, according to disease incidence**

- Highest incidence and serotype diversity (Tables 3.18.3 and 3.18.4): Children with underlying medical conditions (Table 3.18.1), and Aboriginal children aged under 5 years residing in Central Australia[#].
- High incidence and serotype diversity (Table 3.18.4): Aboriginal and Torres Strait Islander children under the age of 2 years residing elsewhere in the Northern Territory (ie. other than in Central Australia), Western Australia, South Australia and Queensland.

- Low to moderate incidence and serotype diversity (Table 3.18.5): Aboriginal and Torres Strait Islander children under the age of 2 years residing in New South Wales, Australian Capital Territory, Victoria and Tasmania, and all non-Indigenous children without underlying medical conditions.

[#] Central Australia includes the southern part of the Northern Territory, and eastern areas of Western Australia and northern parts of South Australia adjacent to this. Consult authorities in the relevant State or Territory for more detailed advice.

**How to use the pneumococcal vaccine tables**

1. Children with any of the underlying medical conditions listed in Table 3.18.1: go to Table 3.18.3.

2. Children who do not have any of the underlying medical conditions listed in Table 3.18.1 and are:

(i) Aboriginal children under the age of 5 years residing in Central Australia and Aboriginal and Torres Strait Islander children under the age of 2 years residing in the remainder of the Northern Territory, South Australia, Western Australia and Queensland: go to Table 3.18.4.

(ii) Aboriginal and Torres Strait Islander children under the age of 2 years residing in New South Wales, Australian Capital Territory, Victoria and Tasmania, and all other non-Indigenous children under the age of 2 years: go to Table 3.18.5.

< Click to see updated table p 10

**Table 3.18.3: Primary and catch-up pneumococcal vaccination schedule for children under the age of 5 years with predisposing medical conditions**

| No previous pneumococcal vaccination history | Age at first dose (months) | Primary 7vPCV schedule | Additional pneumococcal vaccine doses |
|---|---|---|---|
| | 2–6 | 3 doses, 2 months apart | 7vPCV at 12 months of age<br>Give 23vPPV at 4–5 years of age |
| | 7–11 | 2 doses, 2 months apart | 7vPCV at 12 months of age or at least 2 months after the last dose (whichever is the later)<br>Give 23vPPV at 4–5 years of age |
| | 12–59 | 2 doses, 2 months apart | No further 7vPCV doses<br>Give 23vPPV at 4–5 years of age |
| **Previous pneumococcal vaccination history** | **Age at first presentation (months)** | **Previous pneumococcal vaccine history** | **Additional doses** |
| Previous 7vPCV, no previous 23vPPV | 7–11 | 1 or 2 doses | 1 dose of 7vPCV now and another at 12 months or at least 2 months after the last dose (whichever is later). Give 23vPPV at 4–5 years of age |
| | 12–59 | Any incomplete schedule | 1 dose of 7vPCV now. Give 23vPPV at 4–5 years of age at least 2 months after last dose |
| Previous 23vPPv, no previous 7vPCV | 25–59 | Any doses of 23vPPV | 1 dose 7vPCV at least 2 months after 23vPPV |

**Table 3.18.4: Primary and catch-up pneumococcal vaccination schedule for Aboriginal and Torres Strait Islander children, under the age of 5 years living in Central Australia and under the age of 2 years residing in Northern Territory (outside Central Australia), South Australia, Western Australia and Queensland, who do not have a predisposing medical condition**

| No previous pneumococcal vaccine | Age at first dose (months) | Primary 7vPCV schedule | Additional pneumococcal vaccine doses |
|---|---|---|---|
| | 2–6 | 3 doses, 2 months apart | 23vPPV at 18–24 months* of age |
| | 7–17 | 2 doses, 2 months apart | 23vPPV at 18–24 months* of age and at least 2 months after last dose of 7vPCV (whichever is later) |
| | 18–23 | 1 dose | 23vPPV ≥2 months later |
| | 24–59 ** | 1 dose | 23vPPV ≥2 months later |
| **Previous pneumococcal vaccination** | **Age at first dose (months)** | **Previous 7vPCV history** | **Additional pneumococcal vaccine doses** |
| Previous 7vPCV | <7 | 1 dose | 1 dose of 7vPCV now and a third dose >2 months later. Give 23vPPV at 18–24 months* of age or at least 2 months after the last dose of 7vPCV, whichever is later |
| | <7 | 2 doses | Third dose of 7vPCV > 2 months after last dose. Give 23vPPV at 18–24 months* of age or at least 2 months after the last dose of 7vPCV, whichever is later |
| | 7–23 | 1 dose | Second dose of 7vPCV >2 months after last dose. Give 23vPPV at 18–24 months* of age or at least 2 months after the last dose of 7vPCV, whichever is the later |
| | 24–59 | 1 or more doses of 7vPCV | Give 23vPPV at 18–24 months* of age or at least 2 months after the last dose of 7vPCV, whichever is later |

*The age of 23vPPV varies between jurisdictions. Consult your State or Territory authority regarding the scheduled age.

**This age group is applicable only in the Central Australian region, which includes parts of Northern Territory, South Australia and Western Australia.

**Table 3.18.5: Primary and catch-up pneumococcal vaccination schedule for Aboriginal and Torres Strait Islander children living in New South Wales, Australian Capital Territory, Victoria and Tasmania, and non-indigenous children under the age of 2 years who do not have underlying medical conditions**

| No previous pneumococcal vaccine | Age at first dose (months) | Primary 7vPCV schedule | Additional pneumococcal vaccine doses |
|---|---|---|---|
| | 2–6 | 3 doses, 2 months apart | None |
| | 7–17 | 2 doses, 2 months apart | None |
| | 18–23 | 1 dose | None |

| Previous 7vPCV | Age at presentation (months) | Previous 7vPCV history | Additional 7v PCV doses |
|---|---|---|---|
| | 7–11 | 1 previous dose at < 7 months | 1 dose of 7vPCV now and a third dose ≥2 months later |
| | 7–11 | 2 previous doses at < 7 months | Third dose of 7vPCV ≥2 months after the last dose |
| | 12–23 | Any incomplete schedule | 1 dose of 7vPCV ≥2 months after the last dose |

## Adverse events and precautions

**23-valent pneumococcal polysaccharide vaccine**

About half the recipients of 23vPPV will experience some soreness after the first dose, but pain or swelling severe enough to limit arm movement occurs in less than 5% of recipients.[20] Low grade fever occurs occasionally, but fever above 39°C occurs in less than 0.5% of recipients.[20] A first revaccination is associated with an increase in local adverse events, with about three-quarters experiencing soreness at the injection site, and ≥10% of recipients experiencing a moderate or greater limitation, albeit temporary, of arm movement.[20] However, revaccination is not associated with an increase in systemic adverse events such as fever or headache.

**7-valent pneumococcal conjugate vaccine**

Among the most commonly reported adverse events are injection site reactions and fever. 7vPCV is associated with more local reactions than DTPa, with rates of erythema ranging from 10.0 to 11.6% for 7vPCV compared with 6.7 to 11.4% for DTPa. Except for erythema (10.0, 11.3, 13.8, 10.9% after each dose respectively) there is no pattern of increasing local reactogenicity with subsequent doses.[17] A higher rate of local reactions has been observed in older children after a single dose. Prophylactic antipyretic medication is recommended in children who have seizure disorders or a prior history of febrile seizures.

## Contraindications

**23-valent pneumococcal polysaccharide vaccine**

The only absolute contraindications to 23vPPV are anaphylaxis after a previous dose of the vaccine or anaphylactic sensitivity to any vaccine components.

Relative contraindications include the following:

- age less than 2 years – the immune response in infants and very young children is restricted to a few serotypes, so benefits of immunisation are limited, unless previously given one or more doses of 7vPCV.
- recent use of immunosuppressants or radiation of lymph nodes. However, once it is considered that these patients are immunologically 'stabilised' they should promptly be vaccinated.

**7-valent pneumococcal conjugate vaccine**

The only absolute contraindications to vaccination with 7vPCV are an anaphylactic sensitivity to either a previous dose or to any components of the vaccine.

## Use in pregnancy

**23-valent pneumococcal polysaccharide vaccine**

Although 23vPPV has been administered in pregnancy in the context of clinical trials with no evidence of adverse effects, data are limited and deferral of vaccination is recommended unless the risk of IPD is very high.[26] Women who are candidates for pneumococcal vaccine ideally should be vaccinated before pregnancy.

**7-valent pneumococcal conjugate vaccine**
Vaccination during pregnancy is neither indicated nor recommended. It has not been evaluated for potential harmful effects in animals or humans.

## Conflicts with product information

**23-valent pneumococcal polysaccharide vaccine**
23vPPV is licensed for use only in children over 24 months of age, but NHMRC considers that it can be used from 18 months of age in children who have previously received 7vPCV.

**7-valent pneumococcal conjugate vaccine**
The product information recommends a 4-dose 7vPCV schedule for immunisation commencing at 2 months of age with doses at 2, 4, 6 and 12 months, 3 doses for immunisation commencing between 7 and 12 months of age and 2 doses for immunisation commencing between 13 and 23 months of age. NHMRC considers that one dose less than that stated in the product information is adequate for children either under 12 months or over 18 months of age who are not at high risk of IPD (Table 3.18.5).

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# 3.19 POLIOMYELITIS

## Virology

Poliovirus is an enterovirus in the family Picornaviridae.[1] It has an RNA genome, and is a transient inhabitant of the gastrointestinal tract (GIT). There are 3 poliovirus serotypes, P1, P2 and P3. The virus enters through the mouth, multiplies in the pharynx and GIT and continues to be excreted in the stools for several weeks. The virus invades local lymphoid tissue, enters the blood stream and may then infect and replicate in cells of the central nervous system.[2]

## Clinical features

Poliomyelitis is an acute illness following gastrointestinal infection by one of the 3 types of poliovirus. Transmission is through faecal-oral spread. 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. Aseptic meningitis may also occur. Paralytic polio may be spinal (79%), bulbar (2%) or bulbospinal (19%). The case-fatality rate in paralytic polio is 2 to 5% in children, 15 to 30% in adults and up to 75% in bulbar polio. The infection rate in households with susceptible young children can reach 100%. The proportion 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. Cases are most infectious from 7 to 10 days before to 7 to 10 days after the onset of symptoms. The vaccine virus may be shed in the faeces for 6 weeks or more,[2] and for up to several years in immunodeficient subjects.

## Epidemiology

The incidence of poliomyelitis has been dramatically reduced worldwide,[3] but cases still occur in developing countries, particularly in the Indian subcontinent, the Eastern Mediterranean and Africa. The World Health Organization aims to eradicate poliomyelitis by the year 2005 or soon after. In 1994, the continents of North and South America were certified to be free of polio,[4]and the Western Pacific region (including Australia) in 2000. In countries where the disease incidence is low but transmission is still occurring, poliomyelitis cases are seen sporadically or as outbreaks amongst non-vaccinated individuals. 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 last notified case of wild poliomyelitis in Australia occurred in 1978, but there have been 2 vaccine-associated cases, notified in 1986 and 1995.[5]

## Vaccines

***Inactivated poliovirus vaccines***

- **IPOL –** Aventis Pasteur (IPV; inactivated poliomyelitis vaccine); poliovirus types 1, 2 and 3 grown on monkey kidney VERO cells, inactivated with formaldehyde. Traces of formaldehyde are present in the vaccine and traces of neomycin, streptomycin and polymyxin B may also be present.

- **Combination vaccines that include both DTPa and IPV (Infanrix Hexa, Infanrix-IPV, Infanrix Penta, Pediacel, Poliacel, Quadracel)** – see Part 3.16, 'Pertussis'.

Inactivated poliomyelitis vaccine (IPV) and IPV-containing combination vaccines contain polioviruses of types 1, 2 and 3 inactivated by formaldehyde. A course of 3 injections with an interval of 2 months between each dose produces long-lasting immunity (both mucosal and humoral) to all 3 poliovirus types. IPV produces considerably lower levels of intestinal immunity than OPV.

***Live oral poliomyelitis vaccine***

- **Polio Sabin –** GlaxoSmithKline (OPV; oral poliomyelitis vaccine); live attenuated poliovirus (types 1, 2, and 3) + neomycin B sulphate 5 µg per dose.

Live oral poliomyelitis vaccine (OPV) has been routinely used for vaccination in Australia since 1960, and is always given as 2 drops by mouth. It contains live attenuated strains of poliovirus types 1, 2 and 3, grown in cultures of monkey kidney cells or on human diploid cells. The attenuated viruses become established in the intestine and promote antibody formation in both the blood and the gut epithelium, providing local resistance to subsequent challenge with wild polioviruses. This reduces the frequency of symptomless excretion of wild poliovirus in the community.

OPV inhibits simultaneous infection by wild polioviruses and is thus of value in the control of epidemics. Vaccine strain poliovirus may persist in the faeces for up to 6 weeks after administration of OPV. Whilst many recipients are protected after a single dose, a course of 3 doses should produce long-lasting immunity to all 3 poliovirus types.

## Transport, storage and handling

**Inactivated poliomyelitis vaccine**
Transport according to general guidelines (see Part 1.10, 'Transport, storage and handling of vaccines'). Store IPV in a refrigerator at 2°C to 8°C. Do not freeze. IPV should be perfectly clear and pink or red in colour. Any vaccine showing particulate matter, turbidity or change of colour should be discarded.

**Oral poliomyelitis vaccine**
**(i)** Transport in insulated containers. Maintain temperature at 2 °C to 8°C or can be transported with ice. OPV should be transported with an approved time-temperature monitor which is capable of indicating exposures to temperatures greater than 10°C over a 2-week period. Observe national guidelines for packing vaccines in insulated containers.

**(ii)** If time-temperature monitor indicates that OPV has been exposed to temperatures above 8°C or more, do not use. Store OPV vaccine in freezer or store (unopened) in refrigerator at 2°C to 8°C. Keep lid on OPV container. Once OPV container is opened, OPV may lose potency due to exposure to air. Protect from light.

**(iii)** OPV contains phenol red as a pH indicator. The usual colour is pink. Opened multi-dose vials of OPV can be used in subsequent sessions if the following conditions are met:
- the expiry date has not passed
- it has been stored under appropriate cold-chain conditions (at 2°C to 8°C)
- opened vials of OPV which have been taken out of the health-care centre for outreach vaccination activities are discarded at the end of the day.

**(iv)** OPV may also be stored at –20°C. Frozen OPV should be rapidly thawed and mixed by rolling the vial between the fingers, with the colour remaining pink/orange/yellow. If this procedure is followed, a maximum of 10 freeze-thaw cycles are permissible provided that the cumulative duration of the thaw does not exceed 24 hours and provided the temperature does not exceed 8°C during the period of thawing.

**(v)** OPV is only for oral use; it must never be given by injection. Plastic spoons used for OPV must be disposed of immediately following administration of vaccine and at its point of use.

## Dosage and adminstration
The dose of IPV (IPOL) and of the IPV-containing combination vaccines is 0.5 mL. IPV is given by SC injection, whereas the IPV-containing vaccines are administered by IM injection.

The dose of OPV is 2 drops given by the oral route. This should be repeated if the baby vomits within 10 minutes of administration.

**Interchangeability of OPV and IPV**
IPV and OPV may be used interchangeably in the schedule, except where contraindications exist to OPV. 6 "*Children commenced on OPV may complete their polio immunisation schedule using IPV or IPV-containing vaccines.*"

**Preterm infants**

"*Extra doses of IPV or IPV-containing vaccines are not needed for babies born prematurely.*"

## Global eradication of polio
Because of the rapid progress in global polio eradication and diminished risk of wild virus associated disease, IPV is now preferred in the USA for all 4 doses of polio vaccine. This change came about because of concern about the 8 to 10 cases of vaccine-associated paralytic poliomyelitis (VAPP) out of a birth cohort of 2 million per year, or 4 to 5 cases per million children, reported each year in the USA.[2] The advantage of using IPV is that it cannot cause VAPP. The disadvantages of IPV are the complexity of the schedule, the increased number of injections required at each vaccination visit for young infants, unless IPV-containing combination vaccines are used, and the very much greater cost of IPV than OPV in countries such as Australia, compared with the USA. The WHO strongly supports the use of OPV to achieve global eradication of poliomyelitis, especially in countries with continued or recent

circulation of wild type poliovirus.[7] This recommendation is endorsed by the US and European authorities including those who routinely use IPV. Within a few years of eradication (possibly as early as 2007), polio vaccination may no longer be necessary. [7]

There have been only 2 cases of VAPP in Australia in the past 13 years, from birth cohorts of about 260 000 children per year (0.5 cases per million children), which is 10 times lower than the US rate.[5] Because affordable combination vaccines containing IPV are now available in Australia, it is recommended to use these to abolish any risk of VAPP.

## Recommendations

**Primary vaccination of infants and children**

**(i)** IPV, IPV-containing vaccines or oral poliomyelitis vaccine (OPV) are recommended for infants from 2 months of age *(level III-3 evidence).* Although both OPV and IPV are appropriate alternatives, providers should inform parents/caregivers that IPV-combination vaccines are preferred because of the proven but extremely rare risk of VAPP following OPV (see 'Adverse events and precautions' below).

**(ii)** The primary course consists of 3 separate doses of vaccine. An interval of 2 months between each dose is recommended so that the vaccine can be given at the same time as DTPa and Hib vaccines.

**(iii)** Immunosuppressed individuals and their close contacts *must* be vaccinated with IPV or IPV-containing combination vaccines because of the small risk of VAPP caused by live poliovirus in OPV in these individuals *(level III evidence).*

**(iv)** If OPV is used, the following recommendations apply:

- Breastfeeding does not interfere with the antibody response to OPV and vaccination should not be delayed on this account *(level IV evidence).* For preterm or hospitalised babies, OPV, which might spread the live vaccine virus to other babies in the hospital, should not be given until the time of discharge. Alternatively, IPV can be used.
- Faecal excretion of vaccine virus from OPV can last for 6 weeks and may lead to infection of unvaccinated contacts *(level IV evidence).* There is a slightly increased risk of VAPP in non-immune adults (those with no history of previous poliomyelitis vaccination). The contacts of a recently vaccinated baby should be advised of the need for strict personal hygiene, particularly for washing their hands after changing the baby's nappies, and about safe disposal of nappies.

**(v) Booster doses**

**Children**

A booster dose of poliomyelitis vaccine should be given at 4 years of age, at the same time as the booster dose of DTPa. A fifth dose of polio vaccine is no longer considered necessary, because other countries which do not use a fifth dose, such as the USA and UK, have eradicated poliomyelitis *(level III-3 evidence).*

**Adults**

Booster doses for adults are not necessary unless they are at special risk, such as:

- travellers to areas or countries where poliomyelitis is epidemic or endemic;
- health-care workers in possible contact with poliomyelitis cases.

For those exposed to a continuing risk of infection, a single booster dose is desirable every 10 years.

**(vi) Vaccination of parents whose children are being vaccinated**

Unvaccinated or incompletely vaccinated household contacts of children who are to be given OPV should be offered a basic course of OPV at the same time as the children. If the contacts prefer to be given IPV then the child's OPV should be deferred until after their parent's second dose of IPV, because the risk of infection from the child occurs before immunity develops in response to IPV in the contact.

**(vii) Primary vaccination of adults**

A course of 3 doses of OPV or IPV at intervals of 1 to 2 months is recommended for the primary vaccination of adults. No adult should remain unvaccinated against poliomyelitis.

**(viii) Vaccination of immunocompromised individuals and their household contacts**
In individuals for whom a live vaccine is contraindicated (such as individuals with immunosuppression from disease or chemotherapy), IPV or an IPV-containing vaccine must be used for poliomyelitis vaccination. They should also be used for siblings and other household contacts of immunosuppressed individuals. A primary course of 3 doses of IPV or IPV-containing vaccine at intervals of 1 to 2 months should be given. Individuals who are immunocompromised should receive a fourth dose 12 months after the third. Booster doses should also be given at the normal age. HIV-positive individuals and their household contacts must receive IPV.

## Adverse events and precautions

Cases of vaccine-associated paralytic poliomyelitis (VAPP) have been reported in recipients of OPV and their contacts. It has been estimated that one case of VAPP occurs for every 2.4 million doses of OPV distributed.[6] The risk is greater for the first dose than for subsequent doses and is slightly greater for adults than children.

IPV-containing vaccines commonly cause erythema (33%), pain (13%), and induration (1%). Other symptoms reported in 5 to 10% of young recipients are fever, crying and decreased appetite.

Although an Institute of Medicine Committee noted an increased risk of Guillain-Barré syndrome following OPV administration in 2 studies in Finland,[8,9] reanalysis of these data and subsequent study in the United States indicate that the risk is probably not increased.[10]

## Contraindications

IPV or IPV-containing vaccines are contraindicated in the following circumstances:

- acute or febrile illness (temperature ≥38.5°C) – vaccination should be postponed;
- history of anaphylactic reaction to previous dose of the vaccine or to any of the vaccine components.

IPV may be given at the same time as inactivated vaccines and with other live virus vaccines. It may also be given shortly before, after, or with MMR vaccine. When BCG is given to infants, there is no need to delay vaccination with IPV.

Both OPV and IPV contain trace amounts of antibiotics (both contain neomycin; IPV also contains trace amounts of polymyxin and streptomycin) but these do not contraindicate their use except in cases of documented anaphylaxis.

Recent administration of immunoglobulin or blood transfusion is not a contraindication to poliomyelitis vaccine administration, although vaccine efficacy may be diminished. OPV or IPV may be given either before or after immunoglobulin.

OPV is contraindicated in the following circumstances:

- acute or febrile illness (temperature ≥38.5°C) – vaccination should be postponed
- vomiting or diarrhoea – vaccination should be postponed
- individuals or household contacts receiving high-dose oral or injectable corticosteroids or immunosuppressive therapy, including whole-body irradiation – IPV should be used instead
- malignant conditions (in the individual or household contacts) that involve the reticulo-endothelial system (such as lymphoma, leukaemia, and Hodgkin's disease) and where the normal immunological mechanism may be impaired as, for example, in hypogammaglobulinaemia
- HIV infection in the individual or in their household contacts.

## Use in pregnancy

Although there is no evidence that attenuated polioviruses have an adverse effect on the fetus, in accordance with general principles, OPV should not be given to pregnant women unless they are at definite risk from poliomyelitis. IPV-containing vaccines are safe in pregnancy.

## Conflicts with product information

The product information for IPV suggests that the fourth dose be given 12 months after the third dose for both adults and children, followed by a fifth dose for children at age 4 years. NHMRC recommends the fourth dose for children at age 4 years and no fourth dose for adults unless they are at special risk.

The product information suggests that any sensitivity to vaccine components is a contraindication, whereas NHMRC recommends that the only contraindication is an anaphylactic reaction to a previous dose or to any of the vaccine components.

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# 3.20 Q FEVER

## Bacteriology

Q fever is caused by *Coxiella burnetii*, an obligate intracellular bacterium. In vivo it multiplies in the macrophage phagolysosome. A complex multiplication cycle is postulated with an intracellular replicative form (large cell variant: LCV~1.0 µm) and a small dense resistant form (small cell variant: SCV) which serves to transmit infection between cells or hosts.[1] The SCV (0.2–0.5 µm) appears in smears from infected tissues or cells as a small, Gram-variable, weakly acid-fast coccobacillus.

*C. burnetii* is phylogenetically distant from other human bacterial pathogens but sometimes shows serological cross-reactivity with *Legionella* and *Bartonella* species. It is slightly more resistant to heat than other vegetative bacteria but nevertheless is inactivated at pasteurisation temperatures. The

organism survives well in soil, water and dust and thus may be disseminated on fomites such as wool, hides, clothing, straw and packing materials.[2,3]

## Clinical features

Acute primary Q fever has an incubation period of 2 to 3½ weeks, depending on the inoculum size. It commonly presents with rapid onset of high fever, rigors, profuse sweats, extreme fatigue, muscle and joint pain, severe headache and photophobia.[4] As the attack progresses there is usually evidence of hepatitis, sometimes with frank jaundice; a proportion of patients may have pneumonia. The acute illness lasts 1 to 3 weeks or so and may be accompanied by substantial weight loss in the more severe cases.

*C. burnetii* may persist after the primary infection to cause subacute endocarditis and granulomatous lesions in bone, joints, liver, lung, testis and soft tissues. It may recrudesce in late pregnancy sometimes with fetal damage.[5,6] Recent studies have also identified a prolonged post Q fever fatigue syndrome.[7-9]

## Epidemiology

Between 400 to 600 human Q fever infections are notified in Australia each year and many more go unrecognised. Q fever is primarily an occupational disease of workers from the meat and livestock industries, 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 or processing plants.

The infection may be transmitted to humans during contact with infected animals (eg. transporting and slaughtering), or with infected uterine or placental tissue. A variety of animals, both domestic and wild, may be infected, but remain well. These include kangaroos, dogs, cats, cattle, sheep, wallabies and goats. Of these animals, parturient cattle, sheep and goats are often the most significant source for human infection. The organism is mainly transmitted by the respiratory route by droplet infection through aerosols, or inhalation of 'dry' organisms in infected dust. *C. burnetii* can be found in milk, excreta and the placentas of infected farm animals; companion animals such as cats and dogs may also be an occasional source of infection.

## Vaccine[10,11]

- **Q-Vax** – CSL Vaccines (purified killed suspension of *Coxiella burnetii* 25 µg per 0.5 mL; thiomersal 0.01% w/v).

Q fever vaccine consists of a purified killed suspension of *C. burnetii.* It is prepared from 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. 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.[11] Although the seroconversion rate may be low (50 to 80%), long-term cell-mediated immunity develops[12] and the vaccine has been shown to be protective in open and placebo-controlled trials, and in 2 post-licensing trials to have a vaccine efficacy of 100%.[13-16]

During recent years, with much larger numbers vaccinated, a few instances (12 by beginning 2002) of laboratory proven Q fever have been observed in vaccinated subjects.[17] It is important that these apparent vaccine failures are fully investigated and they should be reported to the manufacturer.

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.[10]

## Transport, storage and handling

Transport according to general guidelines. Do not freeze or store vaccine in direct contact with ice packs. If vaccine has been exposed to temperature less than 0°C, do not use. Store in a refrigerator at 2°C to 8°C. Protect from light.

## Dosage and administration

A single dose of 0.5 mL of Q-Vax is given by SC injection after ascertaining that serological and skin testing have been performed and that both the tests are negative (see below 'Prevaccination testing').

## Recommendations

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, sheep, goats and kangaroos or their products. It also includes veterinarians and laboratory personnel handling veterinary specimens (see also Part 2.3 'Groups with special vaccination requirements' and Table 2.3.2).

**Prevaccination testing**

**(i)** Before vaccination, persons with a negative history of previous 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.

**(ii)** If the person has a positive history of previous infection with Q fever, or has already been vaccinated for Q fever, skin testing and serology are *not* required and vaccination is *contraindicated.*

**(iii)** Note that a few subjects who have had verified Q fever in the past show no response to serological or skin testing. However, such subjects may experience serious reactions to administration of Q fever vaccine. Thus, it is vital 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; those who have worked for more than 10 years in the livestock or meat industries should be questioned particularly carefully. If there is any doubt about results of skin or blood testing, these tests should be repeated in 10 days.

**(iv)** 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 utilise enzyme immunoassay (EIA) or immunofluorescent antibody (IFA) to detect IgG antibody to *C. burnetii* as an indicator of past exposure. Subjects CF antibody positive at 1 in 2.5, IFA positive at 10 or more, or with a definite positive absorbence value in the EIA should *not* be vaccinated (see Table 3.20.1).

**(v)** Skin testing and interpretation should only be carried out by experienced personnel. For further information on training contact either CSL Vaccines or the local public health unit. Skin testing is performed by diluting 0.1 mL of vaccine in 30 mL of sodium chloride (injection grade). Diluted vaccine for skin testing should be freshly prepared, stored at 2°C to 8°C and used within 6 hours. 0.1 mL of the diluted vaccine is injected intradermally into the volar surface of the forearm using methylated spirits as a skin cleansing agent (commercial isopropyl alcohol skin wipes are not satisfactory for this purpose). 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.

**Table 3.20.1: Interpretation of skin and antibody test results.**[17]

| Serology | Skin test | Interpretation |
|---|---|---|
| *Positive antibody test | Positive, induration present | Sensitised; do not vaccinate |
| †Negative antibody test | Positive, induration present | Sensitised; do not vaccinate |
| ‡Borderline antibody test | No induration | Indeterminate (see (vi) below) |
| †Negative antibody test | Induration just palpable | Indeterminate (see (vi) below) |
| †Negative antibody test | Negative, no induration | Non-immune, vaccinate |

*Positive antibody test: CF antibody positive at 1 in 2.5 dilution or greater; or IFA positive at 1 in 10 dilution or greater.

†Negative antibody test: CF antibody negative at 1 in 2.5 dilution; or IFA negative at 1 in 10 dilution.

‡Borderline antibody test: CF antibody positive at 1 in 2.5 dilution but not higher; or IFA positive at 1 in 10-20 dilution but not higher.

**(vi)** Test results are indeterminate when skin test induration is just palpable but antibodies are not detected *or* when the skin test is negative but there is a borderline level of antibodies in one or other of the serological tests. An indeterminate result, which occurs in only a small proportion of subjects, may be the consequence of remote infection with Q fever. On the other hand, it may merely indicate the presence in the subject of antibodies to antigens shared between *C. burnetii* and other bacteria. Users of the Australian Q fever vaccine have dealt with this finding in one of two ways:

(a) Repeat the skin test. 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 prior Q fever infection and vaccination is then contraindicated.

(b) 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. (Note: this 0.1 mL dose is different to that used in skin tests because diluted vaccine is used in the latter). If there are no adverse effects (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 8 days, ie. before the development of cell-mediated immunity to the first dose.

**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.

## Adverse events and precautions

Vaccination of subjects already immune to *C. burnetii*, as a result of prior infection, or of subjects rendered hyperimmune by repeated vaccination, may result in severe local or general adverse events. Local abscess formation may occur in some cases.[18,19] In Australia this complication has been reported at a rate of less than 1 in 30 000.

Non-immune subjects very commonly show local tenderness (48%) and erythema (33%) at the vaccination site. Local induration or oedema is uncommon (<1%). General symptoms occur in about 10% of vaccinees and may include mild influenza-like symptoms, headache (9%), fever (up to 2%), chills and minor sweating. Vaccine-associated chronic fatigue syndrome may occur very rarely.

## Contraindications

Q fever vaccine is contraindicated in the following:

- persons with a history of an illness suggestive of or proven to be Q fever;
- persons shown to be immune by serological investigation or sensitivity to the organism by skin testing;
- persons who have been previously vaccinated against Q fever;
- persons with anaphylactic sensitivity to eggs.

There is no information available on the efficacy and safety of Q fever vaccine in immunodeficient or immunosuppressed individuals.

The lower age limit for Q fever vaccine is not known, however it is not recommended for use in those aged less than 15 years.

## Use in pregnancy

Q fever vaccine contains inactivated products and inactivated bacterial vaccines are not considered to be harmful in pregnancy. However, safety of use in pregnancy has not been established. Vaccination

during pregnancy carries a risk of chance association of vaccination with complications of pregnancy not caused by vaccination. No information is available on the use of Q fever vaccine during breastfeeding.

## Conflicts with product information

The product information for Q-Vax does not include the use of the reduced dose of vaccine as in individuals who have indeterminate results for skin-testing and serology. However, this option has been used successfully, for instance, in South Australia by Q fever vaccinators [A. Milazzo, personal communication 2002].

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# 3.21 RESPIRATORY SYNCYTIAL VIRUS

## Virology

Respiratory syncytial virus (RSV) is a single stranded RNA virus of the family Paramyxovirus, genus pneumovirus. There are two subtypes, A and B.

## Clinical features

RSV has an incubation of 4 to 6 days, and causes a wide spectrum of respiratory illnesses. In infants, 25 to 40% of infections lead to pneumonia, bronchiolitis or tracheobronchitis. In adults, RSV usually causes coryzal symptoms.

## Epidemiology

RSV is the major respiratory pathogen of young children and the major cause of lower respiratory infections in infants. The peak incidence is between one and 6 months of age. It occurs worldwide, with annual epidemics in winter. RSV is transmitted by close contact with contaminated fingers or fomites, but may also be spread by coarse aerosols produced by coughing or sneezing. Attack rates in day care centres can approach 100%. Babies with chronic cardiorespiratory disease, babies born prematurely, immunocompromised hosts and the elderly are at risk of severe RSV infection. RSV also causes significant morbidity and even mortality in the elderly, due to RSV pneumonia.

## Vaccine

There are no RSV vaccines licensed in Australia, but there has been much recent research on live attenuated vaccines and subunit vaccines, which may be licensed in future.

### Passive Immunity

**RSV immunoglobulin**

Several clinical studies of immunoglobulin against RSV have been conducted overseas using hyperimmune polyclonal RSV immunoglobulin (RSVIG) derived from blood donations.[1-3] It has been shown to reduce the incidence and severity of RSV infections when given prophylactically in some babies and infants at high risk of severe infection. Benefit has been shown for babies and infants with bronchopulmonary dysplasia (BPD) and for those with prematurity without BPD.[3] RSVIG has caused severe cyanotic episodes and poor outcome after surgery in children with congenital heart disease and is contraindicated in such children.[4] RSVIG is not registered in Australia.

A humanised mouse monoclonal antibody to RSV produced by cultured cells – palivizumab (Synagis: Abbott Australia) – is now registered in Australia for prevention of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease. Its use has not been studied in children with congenital heart disease, and it should not be used for such children. This product is given by IM injection each month during periods of anticipated risk of RSV.“*The product was found to reduce the absolute risk of hospitalisation from about 10% to about 5% for both preterm and BPD babies.*”

Palivizumab is more effective and less costly than RSVIG, but its cost is still prohibitive. For infants whose gestational age was <33 weeks, who required >28 days of oxygen and who were discharged in winter, palivizumab was predicted to cost US $12 000 per hospitalisation averted, but has not been shown to prevent the need for mechanical ventilation from RSV infection or to save lives.

- **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.

### Transport, storage and handling
Palivizumab should be stored at 2 °C to 8° C. Do not freeze. Store in the original container. Do not use beyond the expiration date.

### Dosage and administration
Palivizumab is administered by IM injection preferably in the anterolateral aspect of the thigh, in a dose of 15 mg/kg once a month. The gluteal muscle should not be used routinely as an injection site because of the risk of damage to the sciatic nerve. The injection should be given using standard aseptic technique. Where possible, the first dose should be administered prior to commencement of the RSV season.

### Contraindications
Palivizumab is contraindicated in children with a history of a severe prior reaction to palivizumab or to any of its ingredients, or to other humanised monoclonal antibodies.

### Conflicts with product information
NHMRC recommends that palivizumab is contraindicated in children with congenital heart disease;

Nil

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## 3.22 RUBELLA

### Virology
Rubella is an enveloped togavirus with an RNA genome. It is related to group A arboviruses, but does not cross-react with other members of the togavirus group. It is relatively unstable, and is inactivated by extremes of heat and pH, amantadine and UV light.[1]

### Clinical features
Rubella is generally a mild infectious disease.[2] It causes a transient erythematous rash, lymphadenopathy involving 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 diagnostic of rubella.[1,2] A history of rubella should therefore

not be accepted without serological evidence of previous infection.[1] The incubation period is 14 to 23 days, and the period of infectivity is from one week before until 4 days after the onset of the rash.[2]

## Epidemiology

Rubella occurs worldwide and is spread from person to person by airborne transmission of respiratory droplets.[1] In temperate climates, the incidence is highest in late winter and early spring.[3] Rubella incidence has fallen rapidly since vaccine licensure, and there has been a shift in the age distribution of cases, with comparatively more cases seen in older age groups. Rubella is more common in males than females, as selective vaccination for females preceded universal childhood vaccination.[3] In 1992 and 1993, rubella epidemics were reported in those States where rubella was notifiable.[4] Over 3000 cases were reported again in 1993, 1994, and 1995. In 1997 this fell to 1446 cases (notification rate of 7.8/100 000), and over the 2 years 1999–2000, this fell further to 697 cases (notification rate of 1.8/100 000). This low notification rate probably reflects the high vaccine coverage achieved in the Measles Control Campaign in late 1998. There were no deaths with rubella reported as the underlying cause during 1998–2000.[3]

The rubella virus was isolated in cell culture in 1962.[1] Vaccines are prepared from strains of attenuated virus and have been approved for use in Australia since 1970. Mass vaccination of schoolgirls commenced in 1971.[5] Non-pregnant, seronegative adult women were also vaccinated. These programs were successful and there was a significant reduction in the incidence of congenital rubella from 1977.[6-8] There has also been a significant increase in the percentage of pregnant women immune to rubella (in New South Wales from 82% in 1971 to 96% in 1983).

Many adolescent and young adult males are non-immune to rubella because they did not receive MMR vaccine.[9] The MMR vaccination program for all adolescents replaced the rubella program for girls in 1993/94.[5] A recent serosurvey by the National Centre for Immunisation Research & Surveillance of Vaccine Preventable Diseases showed that only 84% of males aged 14 to 18 years (compared to 95% of females) and 89% of males aged 19 to 49 years (compared to 98% of females) were immune to rubella.[9] For this reason, adolescent and young adult males should receive MMR vaccine both for their own protection and to prevent transmission of the infection in the community.

## Rubella in pregnancy

### (i) Rubella infection in pregnancy

Maternal rubella infection in the first 8 to 10 weeks of pregnancy (counted from the first day of the last menstrual period) results in fetal damage in up to 90% of affected pregnancies, and multiple defects are common.[10-12] This group of fetal abnormalities is called congenital rubella syndrome (CRS). The risk of damage declines to about 10 to 20% by 16 weeks' gestation. After this stage of pregnancy, fetal damage is rare but has been reported up to 20 weeks. Fetal defects include mental handicap, cataract, deafness, cardiac abnormalities, retardation of intrauterine growth, and inflammatory lesions of brain, liver, lungs and bone marrow. Any combination of these defects may occur, but defects which commonly occur alone are perceptive deafness and pigmentary retinopathy, following infection after the first 8 weeks of pregnancy. Some infected infants may appear normal at birth, but defects, especially sensorineural deafness, may be detected later.[13]

### (ii) Rubella reinfection in pregnancy

Rubella reinfection can occur in individuals with both natural and vaccine-induced antibody. Occasional cases of congenital rubella syndrome after reinfection in pregnancy have been reported. However, fetal damage is very rare in cases of infection in women in whom antibody has previously been detected.[10,14-16]

### (iii) Confirmation of rubella infection in pregnant women

Because the rash is not diagnostic, and also because infection can occur with no clinical symptoms, acute rubella can only be confirmed by laboratory tests.[12,15,16]

### (iv) Investigation of pregnant women exposed to rubella

- All pregnant women with suspected rubella or exposure to rubella should be investigated serologically, irrespective of a history of prior vaccination, clinical rubella or a previous positive rubella antibody result.

- As soon as possible after the exposure to rubella, a blood sample should be taken and sent to the laboratory with the date of the last menstrual period and the date of presumed exposure (or date of onset of symptoms). If the woman has an antibody titre below the protective level (see below) or a low level of antibodies and remains asymptomatic, a second blood specimen should be collected 28 days after the exposure and tested in parallel with the first. If the woman develops symptoms, the specimen should be collected and tested as soon as possible. A third blood specimen may be required in some circumstances.
- As some patients may have more than one exposure to a person with a rubella-like illness, or because exposure may occur over a prolonged period, it is important to ascertain the dates of the first and last exposures.

**(v) Serological testing for rubella**

A number of commercial assays for testing rubella serology are available. These vary according to the method used in determining 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.[15] Antibody levels below the cut-off are likely not to be protective, particularly if the antibodies have been generated by vaccination rather than natural infection. Expert consultation and referral of sera to a reference laboratory are recommended if there is a difficulty interpreting results.

## Vaccines

Two MMR vaccines are available in Australia (see Part 3.13, 'Measles'). A monovalent vaccine for rubella is also available. A single dose of rubella vaccine produces an antibody response in over 95% of vaccinees, but antibody levels are lower than after natural infection.[12,15,16] Vaccine-induced antibody has been shown to persist for at least 16 years in the absence of endemic disease.[15-17] Protection against clinical rubella appears to be long term in those who seroconvert.[12]

**Monovalent rubella vaccine**

- **Meruvax II** – CSL Vaccines/Merck, Sharp & Dohme (live attenuated rubella virus (Wistar RA27/3 strain)); lyophilised + neomycin 25 µg, 3 mg human albumin, and sorbitol and hydrolysed gelatin as stabilisers. Single dose vial + diluent, 0.5 mL.

**For information on MMR vaccine,** see Part 3.13, 'Measles'.

## Transport, storage and handling

Rubella vaccine is a freeze-dried preparation. Store in the dried state at 2°C to 8°C (or colder). Transport freeze-dried vaccine in an insulated container with approved time-temperature monitor. If this indicates that vaccine has been exposed to temperature above 10°C do not use. Store vaccine separately to diluent and protect from light since exposure to light may inactivate vaccine. If transported with ice, diluent must be transported separately. Diluent can be stored at room temperature (15°C to 30°C) but do not freeze. Reconstituted vaccine should be injected promptly or stored in a dark place between 2°C and 8°C and must be discarded if not used within 8 hours.

## Dosage and administration

For both children and adults, the dose of MMR and monovalent rubella vaccine is 0.5 mL given by either SC or IM injection.

## Recommendations

**(i) General recommendations**

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 a sufficiently high uptake of MMR vaccine in children and adults of both sexes.

- All children should be vaccinated with MMR vaccine at the age of 12 months with a second dose at the age of 4 years. A history of rubella does not contraindicate vaccination. Individuals who are already immune to rubella will experience few, if any, side effects of vaccination.[12,15]

- Non-pregnant seronegative women of child-bearing age should be given either monovalent rubella vaccine or preferably MMR and advised not to become pregnant for 28 days after vaccination. All female immigrants, especially those from Asia, who have entered Australia after the age of routine vaccination are particularly likely to require vaccination.[4,7]
- Women should be tested for seroconversion 2 months after vaccination and revaccinated if necessary. Women who have negative or very low antibody levels after vaccination should be revaccinated. If their antibody levels remain low after a second vaccination, it is unlikely that further vaccinations will improve this.[12]
- Males, from late teenage to the age of 49, are especially likely to be non-immune to rubella (see 'Epidemiology') and should be vaccinated with 2 doses of MMR at least 4 weeks apart if they have no record of receiving the vaccine.

**(ii) Transmissibility of vaccine virus**
The vaccine virus is not transmitted from vaccinees to susceptible contacts (except rarely in the setting of breastfeeding).[1] There is therefore no risk to pregnant women from contact with recently vaccinated individuals.

**(iii) Rubella vaccination in pregnancy**
Vaccination should be avoided in early pregnancy.[1] Doctors should ascertain the date of the last menstrual period before vaccinating. However, despite active surveillance in the USA, UK and Germany, no case of vaccine-induced congenital rubella syndrome has been reported among more than 500 women inadvertently vaccinated with rubella vaccine during pregnancy, whose pregnancies continued. Based on this evidence, the vaccine cannot be considered to be teratogenic, and termination of pregnancy following vaccination is not indicated[16] (see also Part 2.3, 'Groups with special vaccination requirements', page 52).

**(iv) Rubella vaccination postpartum**
Women found to be seronegative on antenatal screening should be vaccinated after delivery and before discharge from the maternity unit. If anti-D immunoglobulin is required, the two may be given at the same time in different sites with separate syringes or at any time in relation to each other.[12,16] Anti-D immunoglobulin does not interfere with the antibody response to vaccine, but whole blood transfusion does inhibit the response in up to 50% of vaccinees.[12] In such cases, a test for antibody should be performed 2 months later, with revaccination if necessary. All women found on antenatal screening to be susceptible to rubella should be vaccinated as soon as possible after delivery and screened before the next pregnancy. Either monovalent rubella vaccine or preferably MMR can be used for this purpose.

**(v) Testing women of child-bearing age for rubella immunity**
- Every effort must be made to identify and vaccinate seronegative women and to test them for seroconversion 2 months after vaccination. All women should be informed in writing of the result of their antibody test.

- 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.[6,12] Very occasionally, errors may result in patients who are seronegative being reported as seropositive. Where possible, specimens from pregnant women should be stored until the completion of the pregnancy.

- Serological testing of non-pregnant women should be performed whenever possible before vaccination, but need not be undertaken where this might interfere with the acceptance or delivery of vaccine.[1]

**(vi) Testing health-care and child-care staff**
All health-care and child-care staff born during or since 1966, including medical, nursing, and other health professional students, either without vaccination records or seronegative upon screening, should be vaccinated both for their own protection and to avoid the risk of transmitting rubella to pregnant patients and/or colleagues.[18] Preferably, MMR should be used. Where necessary, those vaccinated can be tested for seroconversion 2 months after vaccination and revaccinated if seronegative.

## Adverse events and precautions

Mild adverse events such as fever, sore throat, lymphadenopathy, rash, arthralgia and arthritis may occur following vaccination.[1,15] Symptoms usually begin 1 to 3 weeks after vaccination and are usually transient; joint symptoms are more common in adults (12 to 20%) than in children (0.3%).[15] Thrombocytopenia, usually self-limiting, has rarely been reported after rubella vaccine.[15] Very rarely, neurological symptoms have been reported, but a causal relationship has not been established.[15]

The rubella vaccine virus may be secreted in human breast milk and transmitted to breastfed infants but where infection has occurred in an infant it has been mild.[1]

For adverse events and precautions related to MMR vaccine see Part 3.13, 'Measles'.

## Contraindications

**(i)** Rubella (and MMR) vaccine should not be given to a woman known to be pregnant, and pregnancy should be avoided for 28 days after vaccination. [19]

**(ii)** If the patient is suffering from a significant febrile illness (temperature ≥38.5°C), vaccination should be postponed until recovery is complete.

**(iii)** The vaccine should not be administered to patients receiving high-dose corticosteroid (see Part 2.3, 'Groups with special vaccination requirements') or immunosuppressive treatment, including general radiation.[1,15] It should not be given to those suffering from malignant conditions of the reticuloendothelial system (such as lymphoma, leukaemia, Hodgkin's disease), or in cases where the normal immunological mechanism may be impaired, as in hypogammaglobulinaemia.[1,15] Rubella vaccine may be given to HIV-positive individuals unless they are severely immunodeficient (see Table 2.3.1).[15]

**(iv)** Rubella (and MMR) vaccine should not be given within 3 months of an injection of immunoglobulin, other antibody-containing blood product, or whole-blood transfusion, because the expected immune response may be impaired.[12,16] It may be administered simultaneously, or at any time in relation to anti-D immunoglobulin, but at a separate site.[1,15]

**(v)** A history of a previous anaphylactic reaction to rubella vaccine or any vaccine component is a contraindication to further use. Rubella (and MMR) vaccine contains traces of neomycin and therefore an anaphylactic sensitivity to neomycin contraindicates vaccination.[1,15] Meruvax II also contains traces of gelatin, and any previous anaphylactic reaction to gelatin contraindicates the use of Meruvax II.

## Use of normal human immunoglobulin (NHIG) to prevent rubella

Post-exposure prophylaxis with NHIG does not prevent infection in non-immune contacts and is therefore of little value for protection of pregnant women exposed to rubella.[15] It may, however, prolong the incubation period, which may marginally reduce the risk to the fetus. It may also reduce the likelihood of clinical symptoms in the mother. NHIG should only be used if termination for confirmed rubella would be unacceptable under any circumstances. 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.[15] 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.[20]

## Conflicts with the product information

The product information recommends that women of child-bearing age should be advised not to become pregnant for 3 months after vaccination with rubella (or MMR vaccine), whereas NHMRC recommends 28 days.[19]

The product information recommends the vaccine be given by SC injection, but NHMRC recommends administration by either SC or IM injection.

The product information for Meruvax II states that there is no reason to revaccinate persons who were vaccinated originally when 12 months of age or older. However, NHMRC recommends routine administration of a second dose of rubella vaccine when given as MMR to children.

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# 3.23 SMALLPOX

## Virology

The smallpox or variola virus is one of the poxviruses, a group characterised by large brick-shaped virus particles, which includes the agents vaccinia, monkeypox, mousepox and cowpox. The virus is inhaled into the respiratory tract, multiplies in local lymph nodes and then seeds to the reticuloendothelial system. During the clinical prodrome the virus then circulates to the skin and mucous membranes where the cell destruction produces the characteristic vesicular lesions.

## Clinical features[1]

An incubation period of about 12 days is abruptly followed by the prodrome, a 2 to 5 day period of high fever, malaise and severe headache. Then follows the pharyngeal enanthum and, a day later, the skin rash begins as small red macules before progressing to papules, vesicles and finally pustules over the next 4 to 7 days. Death follows in about 20% of cases. The diagnosis is made by collecting vesicular fluid for examination by electron microscopy, or for detection of viral nucelic acids by amplification techniques. Diseases that are most likely to mimic smallpox in Australian populations are varicella and drug eruptions.

## Epidemiology

Smallpox, a disease only of humans, was declared eradicated in 1979 following an intense international campaign of detection and vaccination. The disease would now be of only historical interest if not for concerns that illicit laboratory stocks of the virus may exist and may be used as biological weapons.[2] In the days of endemic disease in rural areas, each case of smallpox would generate several more cases amongst family and friends attending the victim who was usually bed-bound from the onset of the prodromal illness. The epidemiology of disease spread by bioterrorists may be quite different. Patients hospitalised in the prodromal period may widely transmit the virus during coughing, as demonstrated in an outbreak in a German hospital following admission of one patient with unrecognised smallpox.[3]

## Vaccines[4]

Little is known of the origin of vaccinia virus, the poxvirus used to immunise humans against smallpox. Despite its name, which has been given generally to compounds (vaccines) which induce artificial immunity, it is not cowpox. Currently stored vaccines were grown on the skin of calves, harvested after the slaughter of the animals, purified, tested for the presence of human bacterial pathogens, freeze-dried and stored at –20°C.

In the USA, a limited supply of the vaccine 'Dryvax', last produced in 1982 by Wyeth Laboratories, Marietta, PA, is in storage. When tested recently, it still had substantial potency.[5,6]

Intradermal inoculation results in the formation of an erythematous papule within 3 to 5 days. It becomes a vesicle, then a pustule reaching a maximum size of 1 to 2 cm in 8 to 12 days, then scabs and separates by 14 to 21 days. When the procedure results in this circumscribed infection, vaccination provides long-term protection against fatal disease. Furthermore, vaccination very soon after exposure to smallpox markedly attenuates or prevents clinical disease.

## Transport, storage and handling

Freeze-dried vaccines with potency of at least $10^8$ pock-forming units per mL can be preserved indefinitely at –20°C. They are reconstituted in 50% glycerin.

## Dosage and administration

Only trained health-care workers should perform smallpox vaccination. One of several techniques can be used to place a tiny volume of the reconstituted vaccine on the skin of the lateral surface of the upper arm. Most commonly, a bifurcated needle is dipped into a multidose container and then positioned vertically over the skin, which is then punctured repeatedly with sufficient vigour to produce no more than a trace of blood at the site.

## Recommendations

The only current indication for vaccination in Australia is for workers using live vaccinia virus in recombinant gene research, in order to prevent infection at sites of accidental inoculation. No vaccine is licensed for use in Australia; however, information about sources of vaccines and their use should be obtained from the Therapeutic Goods Administration, Canberra.

Strategies for the use of the vaccine in populations threatened by bioterrorists are currently being debated. [7-9]

## Adverse events and precautions

Smallpox vaccines have well described adverse effects, which vary in frequency according to the virus present in the seed stock. They include:

- postvaccinial encephalitis, a demyelinating disease which occurs at a rate of 1 per 300 000 vaccinations;
- progressive vaccinia (vaccinia gangrenosa) at the site of inocluation, in vaccinees with prior immunodeficiency;
- eczema vaccinatum, being vaccinial skin disease at sites of prior or current eczema;
- generalised vaccinia, a self-limiting condition resulting from blood-borne dissemination of the virus to other skin sites;
- inadvertent inoculation of either the vaccinee or vaccinator in sites such as the face, eyes or hands;
- various skin rashes, usually self-limiting.

## Contraindications

The vaccine is contraindicated in subjects who are immunodeficient or who have a history of ezcema. Furthermore, individuals with eczema should live apart from recently vaccinated family members who may have skin lesions.

## Use in pregnancy

The vaccine should not be used in pregnancy.

## Vaccinia immune globulin

Vaccinia immune globulin (VIG) was used in the past to prevent or treat progressive vaccinia and eczema vaccinatum. It is currently unavailable in Australia but there is a small international supply.

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# 3.24 TETANUS

## 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).

## 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 4 to 21 days (range one day to several months). The median time of onset after injury is 7 days; 15% of cases occur within 3 days and 10% after 14 days. 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, 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 or 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 has been reported very rarely in patients who appear to have been adequately immunised and to have received booster doses of vaccine.[1,2] Clinicians should consider this diagnosis when there are appropriate symptoms and signs irrespective of the person's immunisation record.

Neonatal tetanus usually occurs as the generalised form and is usually fatal if left untreated. It develops in children born to inadequately immunised mothers, frequently after unsterile treatment of the umbilical cord stump. Its onset generally occurs during the first 2 weeks of life. Poor feeding, rigidity, and spasms are typical features of neonatal tetanus.

## Epidemiology

In Australia, tetanus is rare, occurring in older adults who have never been vaccinated or who have neglected to maintain adequate immunity through vaccination. There were 8 notified cases of tetanus during the 2 years 1999–2000, but 36 hospitalisations (July 1998–June 2000) where tetanus was the principal diagnosis. This discrepancy suggests undernotification. Over the 3 years 1998–2000, there were 4 deaths from tetanus, all of whom were aged over 50 years.[3] The case fatality rate in Australia is about 10%. Neonatal tetanus is a frequent cause of infant mortality in parts of Asia, Africa and Latin America.

Effective protection against tetanus is provided by active immunisation. 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. A completed course of vaccination provides protection for many years. One further vaccination is given to those who sustain a tetanus-prone wound (see below) and to adults ≥50 years of age.

## Vaccines

**Adsorbed diphtheria-tetanus vaccine**

- **CDT Vaccine –** CSL Vaccines (paediatric formulation diphtheria-tetanus vaccine; DT); diphtheria toxoid 30 IU and tetanus toxoid 40 IU per 0.5 mL adsorbed on to aluminium phosphate; thiomersal 0.01% w/v.

- **ADT Vaccine** – CSL Vaccines (adult formulation diphtheria-tetanus vaccine; dT); diphtheria toxoid 2 IU and tetanus toxoid 40 IU per 0.5 mL adsorbed on to aluminium phosphate; thiomersal 0.01% w/v.

**Tetanus toxoid vaccine (only to be used if diphtheria toxoid is contraindicated)**

- **Tet-Tox** – CSL Vaccines (tetanus toxoid, adsorbed); tetanus toxoid 40 IU per 0.5 mL adsorbed on to aluminium phosphate; thiomersal 0.01% w/v.

**Combination vaccines that include both tetanus and pertussis antigens –** see Part 3.16, 'Pertussis'

Tetanus vaccination protects by stimulating 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 and thereby converting it into the innocuous tetanus toxoid. Tetanus toxoid is usually adsorbed on to an adjuvant, either aluminium phosphate or aluminium hydroxide, to increase its immunogenicity. Antigens from *B. pertussis*, in combined vaccines, also act as an effective adjuvant.

Complete immunisation induces protective levels of antitoxin throughout childhood but by middle age, about 50% of vaccines have low or undetectable levels.[4,5] A single dose of tetanus toxoid produces a rapid anamnestic response in such vaccinees.[6-8]

Tetanus toxoid is available both in combination with other antigens and as a single tetanus toxoid, but because immunity to diphtheria also wanes over the years, a vaccine with a combination of tetanus and diphtheria should be used in preference to tetanus toxoid alone. (NB: Adult/adolesent formulation dTpa may be used instead of ADT, see Part 3.16, 'Pertussis'.) Tetanus toxoid should only be used alone if diphtheria toxoid is contraindicated.

## Transport, storage and handling

Transport according to general guidelines (see Part 1.10, 'Transport, storage and handling of vaccines'). Store in a refrigerator at 2°C to 8°C. Protect from light. Do not freeze. The ampoule should be shaken vigorously immediately prior to use and the vaccine injected as soon as possible.

## Dosage and administration

The dose is 0.5 mL given by IM injection into the anterolateral aspect of the thigh or the deltoid region of the arm. Accurate recording of the sites of injection of concurrently administered vaccines allows any local reactions to be attributed to the appropriate vaccine. Do not mix DTP-containing vaccines or DT vaccine with any other vaccine in the same syringe, unless specifically registered for use in this way.

## Recommendations

**(i) Vaccination in childhood**

Tetanus vaccination is part of the ARVS (see Part 1.7, 'The Australian Standard Vaccination Schedule'). Tetanus toxoid is given in combination with diphtheria toxoid and acellular pertussis as the DTPa vaccine in a primary course of vaccination at 2, 4 and 6 months of age. Boosting doses given as DTPa at 4 years of age and adult/adolescent formulation dTpa at 15 to 17 years of age are essential to maintain immunity against tetanus. By the age of 17 years, young adults should have received 5 doses

of a tetanus toxoid containing vaccine, and may have received an extra dose if they have endured an exposure-prone wound during childhood.

The removal from the ARVS of the booster dose of DTPa at 18 months of age means that the first booster dose of tetanus toxoid will now be given at age 4 years. Immunity to tetanus will not be compromised because the serological response to the primary course of vaccination is sufficient for those years. The second booster dose of tetanus toxoid, given in combination with a smaller dose of diphtheria toxoid and an adult dose of acellular pertussis vaccine (dTpa) at age 15–17 years is an important component of the new ARVS, maintaining immunity to tetanus in adults.

DT (CDT vaccine) is registered for use in children less than 8 years of age, and should only be used if there is a genuine contraindication to pertussis vaccine. For details on the management of children who have missed doses in the standard childhood vaccination schedule, see Part 1.9, 'Catch-up vaccination'.

**(ii) Vaccination of adults**
Those who have received a primary course of 3 doses as adults should receive booster doses 10 and 20 years after the primary course. Adults who have sustained injuries deemed to be tetanus-prone should receive a boosting dose of dT, if more than 5 years have elapsed since the last dose (see below). All adults who reach the age of 50 without having received a boosting dose of dT in the previous 5 years should receive a further boosting dose of dT. (NB: Adult/adolescent formulation dTpa can be used instead; see Part 3.16, 'Pertussis', page 136.) This stimulates further production of circulating tetanus antibodies in an Australian population still at risk of tetanus, especially through gardening.

**(iii) Tetanus-prone wounds**
In the event of a tetanus-prone injury (defined below) a booster dose of vaccine, given either as dT, DT (if under 8 years of age) or as tetanus toxoid, should be given if more than 5 years have elapsed since the last dose. If there is any doubt about the adequacy of prior tetanus immunisation, tetanus immunoglobulin (see below) should be given as well as tetanus toxoid (see Table 3.25.1).

Types of wounds likely to favour the growth of tetanus organisms include compound fractures, deep penetrating wounds, wounds containing foreign bodies (especially wood splinters), wounds complicated by pyogenic infections, wounds with extensive tissue damage (eg. contusions or burns) and any superficial wound obviously contaminated with soil, dust or horse manure (especially if topical disinfection is delayed more than four 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.

### General measures for treatment of tetanus-prone wounds[9-14]

**Table 3.24.1: Guide to tetanus prophylaxis in wound management**

| History of tetanus vaccination | Time since last dose | Type of Wound | DTPa, DT, dT Tet-Tox or dTpa as appropriate | Tetanus immuno-globulin* (TIG) |
|---|---|---|---|---|
| ≥3 doses | < 5 years | All wounds | NO | NO |
| ≥3 doses | 5-10 years | Clean minor wounds | NO | NO |
| ≥ 3 doses | 5-10 years | All other wounds | YES | NO |
| ≥3 doses | >10 years | All wounds | YES | NO |
| < 3 doses, or uncertain | - | Clean minor wounds | YES | NO |
| < 3 doses, or uncertain | - | All other wounds | YES | YES |

*The recommended dose for TIG is 250 IU, given by IM injection using a 21 gauge needle, as soon as practicable after the injury. If more than 24 hours has elapsed, 500 IU should be given.

Use a combination vaccine in preference to tetanus toxoid alone in order to boost protection against diphtheria. Use DTPa (or DT if pertussis is contraindicated) for children who have not reached their eighth birthday and dT for adults and for children after their eighth birthday.

Whatever the immune status of an individual with a tetanus-prone wound, local disinfection and, where appropriate, surgical treatment of tetanus-prone wounds must never be omitted. The use of antibiotics (such as penicillin or metronidazole) for preventing infection is a matter for clinical judgement.
The recommended use of booster tetanus vaccines and the use of human tetanus immunoglobulin are set out in Table 3.24.1. These should be administered as soon as possible after the injury.

**(iv) Other people at special risk**
Adults who were born in foreign countries without adequate vaccination programs may never have received primary vaccination against tetanus. Older adults may have inadequate antitoxin levels. Travellers to countries where health services are difficult to access should be adequately protected against tetanus prior to departure. They should receive a booster dose of dT if more than 10 years have elapsed since the last dose.

## Adverse events and precautions
Mild discomfort or pain at the injection site persisting for up to a few days is common. Uncommon general adverse events following tetanus toxoid include headache, lethargy, malaise, myalgia and fever. Acute anaphylactic reactions, urticaria and peripheral neuropathy rarely occur (brachial neuritis occurs in 0.001% of cases). Too frequent administration of tetanus vaccine may provoke hypersensitivity reactions.

## Contraindications
The need for further tetanus toxoid-containing vaccine should be carefully assessed if an individual has previously had a severe adverse event associated with a tetanus toxoid vaccine.

If an individual has a tetanus-prone wound and has previously had a severe adverse event following tetanus vaccination, alternative measures, including the use of human tetanus immunoglobulin, can be considered.

## Use in pregnancy
Tetanus vaccine is safe in pregnancy and breastfeeding.

## Conflicts with product information
The product information recommends routine 10-yearly tetanus boosters, whereas NHMRC no longer recommends routine 10-yearly boosters.

## Tetanus immunoglobulin
**Tetanus immunoglobulin (human) for intramuscular use**

- **Tetanus Immunoglobulin** – CSL Bioplasma (TIG); 160 mg/mL solution of immunoglobulin from selected human plasma with high concentration of antibodies to tetanus toxin 250 IU.

**(i)** TIG should be used for passive protection of individuals who have sustained a tetanus-prone wound, where the person has not received three or more doses of a tetanus toxoid-containing vaccine or where there is doubt about their tetanus vaccination status.

**(ii)** The recommended dose for TIG is 250 IU by IM injection, to be given as soon as practicable after the injury. If more than 24 hours have elapsed, 500 IU should be given. 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.

**(iii)** 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.

**(iv)** For wounds not categorised as tetanus-prone, such as clean cuts that have been treated appropriately, TIG is unnecessary.

**Tetanus immunoglobulin (human) for intravenous use**

- **Tetanus immunoglobulin** (human, for intravenous use) – CSL Bioplasma (60 mg/mL solution of immunoglobulin fraction of selected human plasma with high concentration of antibodies for tetanus toxin 4000 IU).

This product is used in the management of clinical tetanus. The recommended dose is 4000 IU 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.

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# 3.25 TUBERCULOSIS

## Bacteriology

Tuberculosis (TB) is caused by *Mycobacterium tuberculosis* complex (M.TB complex), a slow growing, aerobic, acid-fast bacillus. M.TB complex consists of *Mycobacterium tuberculosis*, *M. bovis* and *M. africanum.*[1] *M. tuberculosis* is the cause of TB in Australia, whereas *M. bovis* and *M. africanum* are rare.[2,3]

## Clinical features

As infection is usually air-borne, lung disease is the most common form of tuberculosis, accounting for 60 to 70% 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, including the meninges, bone and kidneys. Disseminated disease (miliary TB) and meningeal TB are the most serious forms, particularly in children.[4]

Most individuals infected with *M. tuberculosis* remain asymptomatic, but a small proportion develop clinical illness, sometimes many years after the original infection. Infants, the elderly and patients rendered immunodeficient by drugs or disease or as a result of adverse socio-environmental circumstances (eg. malnutrition, alcoholism) are more prone to rapidly progressive or generalised infection.[4,5]

## Epidemiology

The World Health Organization (WHO) declared tuberculosis a global emergency in 1995, and recent reports have reaffirmed the threat to human health.[6] About 1000 cases of TB are notified to Australian health authorities each year, with the lowest reported 923 cases in 1998.[2] The annual notification rate for TB over the last decade has been stable at approximately 5 to 6 cases per 100 000 population and multi-drug resistance remains rare, occurring in less than 2% of notified cases.[3,7] Tuberculosis in animals *(M. bovis*) has been virtually eradicated by screening and culling programs. In Australia, most TB (70 to 80%) occurs in migrants, particularly from Asia, Southern and Eastern European countries and the Pacific Islands. Rates of TB are also high in Indigenous people in some parts of Australia.[2] Immunocompromised patients are at high risk of developing active TB if they are infected with *M. tuberculosis.*[5] Screening programs in Australia now concentrate on those at high risk, including contacts of notified patients.

## Vaccine

- **BCG vaccine** – Aventis Pasteur (freeze-dried live vaccine prepared from an attenuated strain of *M. bovis*). When reconstituted with accompanying buffered saline diluent, vaccine contains between 8 to 32 x $10^6$ colony forming units per mL and monosodium glutamate 1.5% w/v. Reconstituted vaccine provides about 10 adult or 20 infant doses.

BCG (Bacille Calmette-Guérin) vaccine is a suspension of live attenuated *M. bovis.* Worldwide, there are many BCG vaccines available but they are all derived from the strain propagated by the Institut Pasteur and first tested in humans in 1921.[8] BCG vaccination does not prevent transmission of infection to the individual. The wide variation in protective efficacy, demonstrated in controlled trials (ranging from 0 to 80%) has been attributed to differences in vaccine strains, prevalence of (protective) local environmental mycobacteria and host factors such as age at vaccination and nutritional status. None of these hypotheses can adequately explain the variation in efficacy. However, it should be noted that BCG is highly effective in children, particularly those under 5 years of age and for whom it is primarily intended. The benefits of BCG in adolescents and adults is less certain.

Meta-analyses have found that the protective efficacy of BCG for preventing serious forms of TB in children is over 80%,[9] and the overall protective efficacy about 50%.[10,11] The only study reported in Australia demonstrated at best a protective efficacy of 30%.[12] A review of the literature reported that the effects of BCG may not persist for longer than 10 years.[13] However, the WHO does not recommend repeat vaccination.

BCG has been found to be also highly protective against leprosy.[14]

## Transport, storage and handling

Transport according to general guidelines (see Part 1.10, 'Transport, storage and handling of vaccines'). Store BCG at 2°C to 8°C or unreconstituted (freeze-dried) vaccine in a freezer at –20°C.

Protect vaccine from light (sunlight or fluorescent). Store diluent at 2°C to 8°C and do not freeze. BCG vaccine must be reconstituted using the diluent supplied. Reconstituted BCG vaccine is very unstable and should be discarded after one working session of 8 hours. Do not freeze reconstituted BCG vaccine.

## Dosage and administration

BCG vaccine is administered as a single dose by intradermal injection. BCG vaccine should only be given by specially trained medical or nursing staff who are fully conversant with the following recommended procedures.

- All individuals should receive a tuberculin test before BCG vaccination, except infants under 6 months of age. BCG should only be given to those who have less than 5 mm of induration 48 to 72 hours after a test dose of 10 tuberculin units.
- The dose of BCG is 0.1 mL for children and adults; 0.05 mL for infants under 12 months of age.
- 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.
- Protective eye-wear should be used to protect against the risk of eye splash from the intradermal injection. If an eye splash occurs, the eye should be washed with saline or water immediately.
- The site of injection of BCG vaccine is very important if the risk of keloid formation is to be minimised. The skin over the region of the insertion of the deltoid muscle into the humerus is recommended. This is just above the mid-point of the upper arm. By convention, the left upper arm is to be used wherever possible. This is to assist those who may subsequently want to find evidence of prior 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.
- The BCG injection should raise a blanched bleb of about 7 mm in diameter with the features of peau d'orange. This indicates that the injection was truly intradermal. Considerable resistance will be felt as the injection is given. If this resistance is not felt, the needle may be in the subcutaneous tissues. If that is the case, withdraw the needle and insert at a new intradermal site.
- Advise the subject of adverse events which may follow the injection.

The size of the tuberculin reaction induced by BCG usually ranges from 0 to 15 mm, but it should be noted that clinical trials have not shown a consistent relationship between the size of tuberculin reactions and the protection provided by the vaccines. For this reason, Mantoux testing of BCG vaccinees to test for a response is not routinely recommended. Because of waning hypersensitivity, most adults who were vaccinated with BCG in early childhood will have a negative tuberculin test.

### 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 in several weeks. There may be swelling and tenderness in local lymph nodes. Subjects who are given BCG despite previous tuberculosis infection will 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.

## Recommendations

**(i)** Given the low incidence of TB in Australia and the variable efficacy in adults, BCG is not used in the general population.

**(ii)** BCG is recommended for the following:

- Aboriginal neonates living in regions of high incidence;
- neonates born to patients with leprosy or TB, or a family history of leprosy;
- children under the age of 5 years who will be travelling to live in countries of high TB prevalence for longer than 3 months (WHO defines 'high-risk' countries as those with an annual incidence of TB in excess of 100 per 100 000 population – http://www.who.int/gtb/Country_info/index.htm);
- children and adolescents aged less than 16 years who continue to be exposed to an individual with active pulmonary TB, and where the child or adolescent cannot be placed on isoniazid therapy or

has completed isoniazid therapy. Children and adolescents who are currently on isoniazid therapy should not be given BCG.

**(iii)** State and Territory guidelines should be consulted for advice on vaccination of the following groups of individuals:

- health-care workers;
- children over the age of 5 years who will be travelling or living for extended periods in countries with a high prevalence of tuberculosis.

## Adverse events and precautions

Adverse events occur in about 5% of vaccinees with 2.5% being injection site abcesses and 1% lymphadenitis. About 1% of vaccinees may need medical attention as a result of the adverse event.[15] Anaphylactoid reactions have also been reported. Gross local or generalised infection can be treated with antituberculous drugs. Keloid formation can occur, but the risk is minimised if the injection is not given higher than the level of the insertion of the deltoid muscle into the humerus.

## Contraindications

The use of BCG vaccine is contraindicated in the following:

- individuals with tuberculin reactions greater than 5 mm;
- patients with HIV infection and those who are immunocompromised by use of corticosteroids, immunosuppressive drugs, radiation therapy, or malignancies involving bone marrow or lymphoid systems (because of the risk of disseminated BCG infection in these individuals);
- individuals with a high risk of HIV infection where HIV antibody status is unknown;
- individuals with significant fever;
- individuals with generalised skin diseases;
- pregnant women – BCG has never been shown to cause fetal damage, but use of live vaccines in pregnancy is not recommended;
- individuals who have previously had TB.

## The tuberculin skin test

**(i)** Hypersensitivity to tuberculin Purified Protein Derivative (PPD) follows either natural infection with either *M. tuberculosis* or with other mycobacteria that induce cross-reactivity, or BCG vaccination. The skin test is used (a) to detect latent infection in contacts of patients with TB and other potentially infected individuals, (b) as an aid to the diagnosis of TB, and (c) as a prelude to vaccination with BCG.

**(ii)** Most tuberculin testing in Australia is performed using the Mantoux technique. The PPD preparation for this test is supplied by CSL Vaccines in multidose vials containing 100 units/mL. For routine testing, 0.1 mL of PPD of 100 units/mL (ie. a dose of 10 units) is injected intradermally into the skin of the upper third of the flexor surface of the forearm, producing a peau d'orange bleb 7 to 10 mm in diameter. The reaction is examined 48 to 72 hours later, and the diameter of the palpably indurated skin is measured and recorded. In certain circumstances, 2-stage skin testing may be required. It is used to detect individuals previously infected or vaccinated with BCG who may test negative to tuberculin testing initially, but who show a strong reaction to tuberculin if the same procedure is repeated one to two weeks later. The 2-stage test is important to establish the baseline reaction when future tuberculin testing is required as part of contact tracing or monitoring of high-risk groups. For detailed advice, contact the State/Territory tuberculosis service.

**(iii)** Erythema *without* induration should be disregarded. Strongly positive reactions may be accompanied by skin necrosis, lymphangitis and regional adenitis. Patients with a history of such reactions should either be given a dose of 1 unit or not be tested.

**(iv)** The reaction to PPD may be suppressed by viral infections, live vaccines (especially MMR, but not OPV, oral typhoid or oral cholera vaccines), recent surgery, sarcoidosis, immunosuppressant drugs and immunosuppressing illnesses such as Hodgkin's disease, lymphoma and HIV infection. The reaction also wanes with increasing age, so that most adults vaccinated with BCG in childhood have negative tuberculin reactions.

**(v)** The Mantoux test may be unreliable for 4 weeks after measles infection or MMR vaccination**.**

**(vi)** The use of the Heaf gun, a multiple puncture apparatus primed with highly concentrated PPD, is not recommended.

**(vii)** Although BCG is not routinely recommended, it may be offered by some States and Territories to their health-care staff, who should be made aware that subsequent tuberculin skin testing may be difficult to interpret.

## Conflicts with product information

The product information states that BCG should not be frozen. NHMRC advises that BCG can be stored unreconstituted (freeze-dried) in a freezer at –20°C.

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# 3.26 TYPHOID

## Bacteriology

Typhoid fever is caused by the Gram-negative bacillus *Salmonella typhi,* an exclusively human pathogen.

## Clinical features

A generalised infection of non-specific onset characterised by fever, bradycardia, splenomegaly, 'rose spots' and abdominal symptoms of pain, constipation or diarrhoea. Untreated the infection has a mortality rate of 10 to 20% due to bowel perforation, haemorrhage, toxaemia and effects on remote organs.[1] Between 2 to 5% of patients may become permanent carriers in spite of treatment. The likelihood of becoming a chronic carrier increases with age, especially in females.[2]

## Epidemiology

Typhoid is spread mainly by the faecal-oral route, usually through contaminated food or drink. For travellers, the common sources are water or ice, raw vegetables, salads and shellfish. There are approximately 50 to 80 cases of typhoid reported in Australia each year,[3] and most follow travel to countries in Asia, Africa, Oceania, Central and South America and some parts of Southern Europe.[4-6] A high level of typhoid endemicity exists in Indonesia and Papua New Guinea. Occasional cases result from consumption of food prepared by long-term excretors of *S. typhi* living in Australia. Long-term carriage is an occasional feature of typhoid and therefore any individual who is an excretor should be barred from being involved in the food industry.

## Vaccines

- **Typh-Vax (Oral)** – CSL Vaccines (live attenuated typhoid vaccine containing *Salmonella typhi* strain Ty21A Berna, not less than 2 x $10^9$ viable organisms). Enteric coated capsules.

- **Typherix** – GlaxoSmithKline (purified Vi capsular polysaccharide 25 µg plus 0.5% phenol as preservative). 0.5 mL injection.

- **Typhim Vi** – Aventis Pasteur (25 µg of purified Vi capsular polysaccharide plus 0.5% phenol as preservative). 0.5 mL injection.

**Combination vaccine that includes both typhois and hepatitis A (Vivaxim)** – see Part 3.8, 'Hepatitis A'.

The live attenuated vaccine is prepared from a non-pathogenic strain of *S. typhi*, which lacks the enzyme UDP-galactose-4-epimerase and Vi capsular polysaccharide. It undergoes only a few cycles of division in the gut and is eliminated within 3 days of ingestion. The immune response includes secretory IgA.[7] The vaccine is licensed for use in individuals 6 years of age and above.

The Vi polysaccharide vaccine elicits an antibody response in more than 90% of recipients and provides 50 to 77% protection for at least 2 years. It is approved for use in individuals 2 years of age and over. In a recent study in China in middle school children, Vi vaccine was associated with 73% protection.[8]

The live attenuated vaccine and the Vi polysaccharide vaccine cause few adverse events. The advantage of using the injectable Vi vaccine is that clients may not comply with storage and dosage instructions for the oral vaccine.

A recent trial of a conjugate of the capsular polysaccharide of the Vi vaccine bound to non-toxic recombinant *Pseudomonas aeruginosa* exotoxin A (rEPA) showed 90% efficacy in children 2 to 5 years of age, which is the highest reported efficacy for any typhoid vaccine.[9] It has not been licensed yet in any country.

## Transport, storage and handling

Store all typhoid vaccines at 2°C to 8°C, protect from light and do not freeze. Transport in an insulated container with approved freeze monitor and time-temperature monitor. Discard any unused Vi vaccine within 4 hours of opening or at the end of the session.

## Dosage and administration

**Oral live attenuated vaccine**

The vaccination schedule consists of one capsule of vaccine on days 1, 3, and 5, taken one hour before food. A fourth capsule taken on day 7 will elicit an even greater and longer lasting immune response, and is recommended by some travel advisers.[10] The use of a fourth dose requires partial use of a second pack and therefore may involve the subject in considerable extra expense. However, the 4-dose regimen may be preferred for those planning to reside in an endemic area, as boosters will then be needed only every 5 years.

The capsule must be swallowed whole with water and must NOT be chewed since the organisms are destroyed by gastric acid. Do not give concurrently with antibiotics, sulphonamides or the antimalarial proguanil.

The vaccine may be administered at the same time as either OPV or yellow fever vaccine. If it is not administered at the same time as OPV, the administration of OPV should be delayed for 2 weeks after the last dose of typhoid vaccine (as oral typhoid vaccine engenders a strong mucosal interferon response, which may reduce the efficacy of OPV). If oral cholera vaccine is to be administered, there should be an interval of at least 8 hours between administration of oral cholera and oral typhoid vaccines, as the buffer administered with the live oral cholera vaccine may affect the transit of the capsules of oral typhoid vaccine through the gastrointestinal tract and interfere with immunogenicity.

**Vi polysaccharide vaccines**

Administer as a single IM dose of 0.5 mL. The dose of combined Vi polysaccharide/hepatitis A vaccine is 1 mL.

**Booster doses**

- Live attenuated vaccine – booster doses are required every 3 years when the primary vaccination has been with 3 doses. If the primary vaccination has been with 4 doses, boosters are only required every 5 years.

- Vi polysaccharide vaccine – booster doses should be given at 3-yearly intervals if at continued risk of exposure to typhoid.

## Recommendations

Typhoid vaccination is only recommended for travellers at risk, ie. those travelling to endemic countries where hygiene is poor or drinking water is unsafe. Laboratory workers may require vaccination, based on an assessment of risk. Typhoid vaccination is recommended for those persons with intimate exposure to a documented typhoid fever carrier, such as occurs with continued household contact.

## Adverse events and precautions

**Live attenuated vaccine**

These are generally mild. The following have been reported in trials: constipation, abdominal cramps, diarrhoea, nausea, vomiting, anorexia and fever.

**Polysaccharide vaccine**

Side effects are normally mild and transient. Erythema, swelling and pain at the injection site are common (10 to 20%). Systemic adverse events are much less common and include fever (3%), malaise and nausea.

## Contraindications

**Live attenuated vaccine**

The oral live vaccine should not be administered in the following circumstances:

- during intercurrent febrile illness or acute gastrointestinal infection;
- to those with a history of an anaphylactic reaction to a previous dose of the vaccine;
- to immunocompromised individuals, including those known to be infected with HIV;
- concurrently with other antibiotics, sulphonamides, or the antimalarial proguanil;
- to children aged less than 6 years, because studies of efficacy and safety have not been carried out in this group.

**Vi polysaccharide vaccines**

The injectable polysaccharide vaccines should not be administered in the following circumstances:

- any individual suffering or convalescing from an acute febrile illness;
- individuals with a history of an anaphylactic reaction to the vaccine or any vaccine components;
- children under 2 years of age.

## Use in pregnancy

There is no evidence of risk to the fetus from vaccination with the Vi polysaccharide vaccine. Studies in animals are inadequate but available data show no evidence of an increased occurrence of fetal damage with oral live attenuated vaccine. Its use in pregnancy, however, should be based on an assessment of the real risk of disease.

## Conflicts with product information

The product information for the live attenuated vaccine does not give recommendations for booster doses. The Typhim Vi product information recommends a booster dose every 2 to 3 years as an optimum schedule has not been established. The NHMRC booster recommendations are given above.

The product information does not recommend a fourth capsule of the live attenuated vaccine. NHMRC suggests that a fourth capsule can be used.

## Public health management of typhoid fever

A recent review found inconsistent approaches to the public health management of typhoid in Australia, much of which had little evidence based support.[11] The authors of this report have suggested a more rational approach to the public health response to cases of typhoid diagnosed in Australia.[11]

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# 3.27 VARICELLA-ZOSTER

## Virology

Varicella (chickenpox) is a highly contagious infection caused by the varicella-zoster virus, a member of the herpes virus family. It is a DNA virus with a lipid envelope surrounding a nucleocapsid.

## Clinical features

Varicella is usually a mild disease of short duration in healthy children. It is more severe in adults and can cause serious and even fatal illness in immunosuppressed subjects of any age. The overall case-fatality rate in Australia is approximately 3 per 100 000 cases.[1] In the USA, the fatality rate of varicella is approximately 1 per 100 000 cases among children aged 1 to 14 years; this increases to 25.2 deaths per 100 000 cases among adults aged 30 to 49 years. Immunosuppressed persons have a high risk of serious varicella infection and disseminated disease.[2]

The average incubation period is 14 to 15 days (range 10 to 21 days), followed by the appearance of a rash. The period of infectivity is from 48 hours before the onset of rash until crusting of all lesions has occurred. Acute varicella may be complicated by cerebellar ataxia (1 in 4000 cases),[3] aseptic meningitis, transverse myelitis, thrombocytopenia, encephalitis (1.8 in 10 000 cases) and pneumonia. In rare cases, it involves the viscera and joints.

Aspirin or other salicylates should not be given to children and adolescents with varicella because of the association with Reye's syndrome.

Herpes zoster (shingles) is a localised vesicular rash resulting from reactivation of latent varicella-zoster virus in a period of waning immunity. Herpes zoster is often a serious illness in older adults and immunocompromised individuals, and some may develop disseminated zoster with visceral, central nervous system and pulmonary involvement.

Congenital varicella syndrome has been reported after varicella infection in the first half of pregnancy and may result in congenital malformations, skin scarring, and other anomalies. Data from Europe indicate a higher risk when maternal infection occurs between 13 and 20 weeks of gestation compared with infection between 0 and 12 weeks (2% vs 0.4%).[4] Infants with intrauterine exposure also have a risk (0.8 to 1.7%) of developing herpes zoster in infancy with the greater risk following exposure between 25 and 36 weeks' gestation.[4] Severe neonatal varicella infection can result from perinatal maternal varicella. 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.[5]

## Epidemiology

In an unimmunised population, about 75% of children will have had varicella by the age of 12 years. Approximately 5% of cases are subclinical. There are about 240 000 cases, 1500 hospitalisations and 7 deaths each year from varicella in Australia.[1,6] The highest rates of hospitalisation occur in children under 4 years of age.[1] Zoster is uncommon before the age of 12 years (1% of cases), and most cases (81%) occur over the age of 40 years. Vaccination results in a lower rate of zoster (2.6 per 100 000) compared to natural infection (68/100 000).[7,8]

Since the introduction of varicella-zoster vaccination in the USA in 1995, active surveillance of varicella in 3 communities has shown a decline of more than 70% in reported cases.[9] This has been most marked in children aged 1 to 4 years but has also been noted in all age groups including infants and adults. Active surveillance for herpes zoster in 2 areas has shown no change in incidence [Jane Seward, personal communication, 2002]. In the period July 2000 to June 2001, vaccination coverage in children aged 19-35 months in USA was estimated at just over 70% [Jane Seward, personal communication, 2002]. In addition, a large study is being conducted in the USA to determine whether vaccination of adults previously naturally infected with varicella will prevent subsequent development of zoster. The results of this study should be available by late 2004.[10]

Two epidemiological studies from the United Kingdom suggest that exposure to varicella may help prevent herpes zoster, presumably by boosting immunity.[11,12] A study using mathematical modelling and a number of assumptions has predicted that, following the introduction of varicella-zoster vaccination, there could be a short to medium term increase in the incidence of herpes zoster with a shift in the age of cases into younger age groups (because naturally infected persons would have less opportunity to be exposed to varicella).[11,13] However, as the vaccine strain of varicella virus causes herpes zoster significantly less frequently,[8] not only varicella but also herpes zoster could ultimately be eliminated. It must also be emphasised that there is no direct proof that herpes zoster epidemiology will be altered by the introduction of varicella-zoster vaccination. Indeed, current surveillance in USA shows no change in herpes zoster incidence after 5 years of routine vaccination.

In Australia, South Australia began passive surveillance of varicella and herpes zoster from January, 2002. Other surveillance mechanisms are in place nationally (eg. hospitalisations) to track the varicella and herpes zoster disease burden following the introduction of vaccination programs.

## Vaccines

Live attenuated varicella-zoster vaccine (VZV) is presented in a freeze-dried (lyophilised) form. A single dose is sufficient for infants and children up to 13 years of age (up to the fourteenth birthday), but healthy adolescents (14 years and older) and adults require 2 doses, 1 to 2 months apart. The response to a single dose of VZV decreases progressively as age increases. The exact age at which 2 doses are needed is ill-defined. On the basis of the available data, NHMRC recommends 2 doses from the fourteenth birthday in Australia (see 'Recommendations' below).[14,15]

Overall, seroconversion occurs in 90 to 100% of those vaccinated and about 70 to 90% are protected when exposed to infection within the household. Breakthrough infection after exposure occurs at a rate of 1 to 2% a year in those vaccinated; these infections are usually mild. The duration of immunity from vaccination is not yet known and booster doses may be required. Two products are currently available in Australia. These are both derived from the Oka varicella-zoster virus strain, but have some genetic differences.[16]

- **Varilrix**– GlaxoSmithKline (lyophilised preparation of live attenuated Oka strain of varicella-zoster virus). Prepared by propagation of virus in $MRC_5$ human diploid cells. Reconstitution with diluent makes a 0.5 mL dose, containing not less than 2000 plaque forming units. The vaccine also contains amino acids 8 mg, human albumin 1 mg, lactose 32 mg, neomycin sulphate up to 25 µg, sorbitol 6 mg and mannitol 8 mg. Varilrix does not contain a preservative.[17]

- **Varivax Refrigerated** – CSL/Merck Sharp & Dohme (lyophilised preparation of live attenuated Oka/Merck strain of varicella-zoster virus). Reconstitution with diluent makes a 0.5 mL dose, containing not less than 1350 plaque forming units. Each 0.5 mL dose contains approximately 18 mg sucrose, 8.9 mg hydrolyzed gelatin, 3.6 mg urea, 2.3 mg sodium chloride, 0.36 mg monosodium glutamate, 0.33 mg of sodium phosphate dibasic, 0.057 mg of potassium phosphate

monobasic, 0.057 mg potassium chloride; residual components of MRC-5 cells and trace amounts of neomycin and fetal bovine serum from MRC-5 culture media. This product contains no preservative. [18]

## Transport, storage and handling

VZV is less stable than other commonly used live virus vaccines, and the storage temperature requirements are critical. The vaccines must be stored according to the manufacturer's instructions. The varicella-zoster vaccines available at this time have different storage requirements.

Varilrix should be stored between 2 °C and 8 °C and can be stored for 2 years from the date of manufacture. The lyophilised vaccine is not affected by freezing. The diluent should not be frozen, and can be stored in the refrigerator or at ambient temperatures. Use promptly and within 90 minutes of reconstitution.[17]

Varivax Refrigerated can be stored (before reconstitution) at 2 °C to 8 °C or colder for up to 18 months. After reconstitution, Varivax Refrigerated should be used within 30 minutes. The diluent should not be frozen but can be stored in a refrigerator or at ambient temperatures.

## Dosage and administration

Children (aged 12 months to 13 years) – a single 0.5 mL dose (see 'Conflicts with product information' and 'Recommendations').

Adolescents and adults (14 years of age and older) – two 0.5 mL doses, administered at least 1 to 2 months apart.

VZV should be administered by SC injection, preferably into the upper arm (deltoid region).

VZV can be given at the same time as other vaccines (including MMR, DTPa, hepatitis B and MenCCV), using separate syringes and injection sites. If VZV is not given simultaneously with other live virus vaccines, they should be given at least 4 weeks apart.[19]

## Recommendations

**(i) Children 12 months to 13 years of age** *(safety level II)*[15,22-24] *(effectiveness level II)*[22,23,25] *(cost-effectiveness level IV)*[20,26-32]

It is recommended that a single dose of VZV be given to:

- all children aged 18 months, unless they have already received a dose of VZV or had a clinical history of varicella;
- children aged 10-13 years, unless they have already received a dose of VZV or had a clinical history of varicella.

If parents wish to protect any non-immune child aged 12 months to 10 years, who has not received VZV or had clinical varicella, a single dose of VZV is recommended.

Note that serological testing of children 13 years of age and younger before vaccination is not warranted, as a past history of varicella correlates highly with serological evidence of immunity.[20,21] Children in this age group with a reliable history of varicella are therefore considered immune and those who do not have such a history or who have an uncertain history are considered susceptible, and should be immunised.

The immunogenicity of VZV is influenced by the age of the subject. Humoral and cellular immune responses are diminished among adolescents and adults compared with younger children.[33] In adolescents and adults, humoral immunity diminishes in a progressive manner with increasing age.[15] Data related to immunogenicity in young adolescents are limited.

Although vaccine sponsors recommend that VZV be administered in two 0.5 mL doses to adolescents aged 13 years and older, NHMRC considers the differences in seroconversion rates and geometric mean titres (GMTs) reported after a single dose of vaccine in subgroups aged 13 years compared to other children to be modest. After a single dose of one formulation of one of these products in subjects aged 10 to 12 years compared with 13 to 14 years, respective rates of seroconversion were 93% *vs.*

91%; the percentages with >5 gpELISA units were 56% *vs* 47% and GMTs were 6.6 *vs*. 3.8 gpELISA units *(effectiveness level III-2).*[34] In clincial trials, varicella subsequently developed in substantially fewer children who had post-vaccination gpELISA titres ≥5 units than those who had post-vaccination gpELISA titres of <5 units.[35] In several studies in adolescents ranging from 11 to 21 years, a single dose of this vaccine resulted in seroconversion rates exceeding 90% *(effectiveness level II).*[36] This modest reduction in immunogencity to a single dose of VZV in subjects aged 13 years compared to younger age groups is considered acceptable, taking account of programmatic issues associated with administering a second vaccine dose to subjects aged 13 years.

**(ii) Persons aged 14 years and older**

VZV is recommended for use in non-immune adolescents (14 years and older) and adults *(safety level II)*[15,37,38] *(effectiveness level II)*[15,39] *(cost effectiveness level IV).*[40-42] Lack of immunity to varicella should be based on a negative history of previous varicella infection and subsequent serological tests. These subjects require 2 doses, 1 to 2 months apart. The vaccine is especially indicated for those in the following categories:

- non-immune people in high-risk occupations (such as health-care workers *(level II evidence),* teachers and workers in child-care centres);
- non-immune women prior to pregnancy;
- non-immune parents of young children; and
- non-immune household contacts (adults and children) of immunosuppressed persons *(level III-2 evidence)* (see below).

Persons aged 14 years or older who have a reliable history of varicella should be considered immune. Many adults and adolescents who do not have a history of varicella are also immune (61% in a study of 300 adults aged 17 to 49 years in Sydney).[43] Therefore serological testing before vaccination is likely to be cost-effective for both adults and adolescents with a negative history of varicella-zoster disease. If it is more convenient, adolescents and adults can be vaccinated without testing (provided there are no contraindications), as the vaccine is well tolerated in seropositive persons.

**(iii) Post-exposure prophylaxis and outbreak control**

VZV has been shown to be effective in preventing varicella infection following exposure, in several studies *(level III-2 evidence).*[44-47] This is usually successful when given within 3 days, and up to 5 days after exposure, with earlier administration being preferable. 'Emergency' vaccination of exposed individuals during outbreaks has also been shown to stop the outbreak and prevent further expected cases (for definition of significant exposure, see 'Use of immmunoglobulin to prevent varicella' below). Two recent uncontrolled trials of the effectiveness of the Oka/Merck vaccine in post-exposure prophylaxis showed protection against moderate to severe disease, but reported some mild disease[47-49] (see also 'Conflicts with product information').

In the event of an outbreak, seek advice from local public health authorities before proceeding with vaccination of a large number of individuals (see contact details Appendix 1).

**(iv) Health-care workers (HCW)**

**The following approach is recommended for pre-exposure vaccination of a HCW:**

A HCW with a negative or uncertain history of varicella should be serotested. If found to be negative, vaccination should be offered *(level III-2 evidence).*[15,39] If a rash develops during the 6 weeks following vaccination, the HCW should be reassigned to duties that require no patient contact or placed on sick leave *(level III-2 evidence).*[50] Reassignment or leave should be only for the duration of the rash (not for 4 to 6 weeks, as per product information *(level III-2 evidence)*).[50] Note that rash resulting from vaccination may be atypical and may not be vesicular (see 'Adverse events' below). Rash is likely to occur in less than 5% of vaccinees, and to last for less than one week *(level II evidence).*[22,24]

Testing to check for seroconversion after VZV is not recommended (see 'Serotesting after vaccination' below).

**The following approach is recommended for post-exposure management of a HCW:**

- If a previously vaccinated HCW is exposed to varicella, assume immunity and report exposure. A vaccinated HCW should watch for a rash for 3 weeks after exposure and report to the nominated infection control officer should a rash develop (follow usual approach for a rash thereafter).

- If a HCW is exposed to varicella and is unimmunised or has a negative or uncertain history of varicella, offer vaccination. This is usually effective in preventing the development of varicella if given within 3 days, and up to 5 days after exposure. In situations where facilities for a rapid serotest are available, it may be possible to test prior to vaccination to identify those with pre-existing immunity. However, serotesting should not delay vaccination beyond the recommended 3 to 5 days after exposure. Vaccination in the absence of serological results can be safely carried out (provided there are no other contraindications).

- If the HCW accepts vaccination, allow to work and ask that he/she watch daily for any rash for 6 weeks after exposure. Note that the rash associated with vaccination for varicella may be atypical, maculopapular and non-vesicular. If a varicella-exposed and vaccinated HCW develops a rash following vaccination, this may be due to either wild virus or vaccine-strain varicella-zoster virus (see 'Adverse events' below). In the event of a rash after vaccination, reassign duties (no patient contact) or place on sick leave until no new lesions appear and all lesions have crusted.

- If an exposed non-immune HCW does not accept vaccination, reassign duties or place on sick leave from day 10 to day 21 from the time of first exposure.

**(v) Household contacts of immunosuppressed persons**
Vaccination of household contacts of immunosuppressed persons is strongly recommended *(level III-2 evidence).* This recommendation is based upon evidence that vaccine strain virus transmission is extremely rare and is likely to cause mild disease compared with the relatively high risk of exposure to wild type varicella-zoster virus.[50,51] If vaccinees develop a rash, they should avoid contact with immunocompromised persons for the duration of the rash. Varicella-zoster immunoglobulin (ZIG) need not be given to an immunocompromised contact of a vaccinee with a rash because the disease associated with this type of transmission (should it occur) would be expected to be mild.[5]

**(vi) Serotesting after vaccination**
Testing to check for seroconversion after VZV is not recommended given the high efficacy of the vaccine *(level II evidence).* In addition, the presence of antibodies shortly after vaccination does not ensure complete immunity to varicella [Jane Seward, personal communication, Oct 2000: Margaret Burgess, personal communication: Nov 2001], and the commercially available laboratory tests are not always sufficiently sensitive to detect low antibody levels following vaccination.

## Adverse events

Reactions are generally mild and well tolerated.[52] Fever up to 39°C has been observed in 15% of healthy children and a similar percentage of children receiving placebo. Injection site reactions (pain, redness or swelling) occur in 7–30% of vaccinees and are also well tolerated.[53] In healthy adolescents and adults, a second dose of vaccine appears to cause fewer reactions than the first.[15,37,54]

A maculopapular or sometimes papulovesicular rash may develop after vaccination (usually within 5 to 26 days). Rashes typically consist of 2 to 5 lesions and may be generalised (3 to 5%) or occur at the injection site (3 to 5%).[8] Most varicelliform rashes that occur within the first 2 weeks after vaccination are due to wild type varicella-zoster virus, with median onset 8 days after vaccination, (range 1 to 24 days), while rashes in the presence of vaccine strain occur at a median of 21 days after vaccination (range 5 to 42 days)[55] (see also 'Transmissibility of vaccine virus' below).

Fever over 39°C has been reported in 15% of healthy children within 42 days of immunisation. In adults and adolescents, fever has been reported in 10% of vaccinees.[48]

No serious adverse events were reported from prelicensure trials of VZV. Postlicensure, serious adverse events have been reported to be temporally related to vaccination at a rate of 2.9 per 100 000 doses distributed.[50] These include encephalitis, ataxia, erythema multiforme, pneumonia, thrombocytopenia, seizures, neuropathy, anaphylaxis and death. A causal relationship between VZV and many of these events has not been determined, although such a causal link is plausible for anaphylaxis and for thrombocytopenia, ataxia and encephalitis, as the latter are rare complications of natural varicella infection.[50]

Clinical trials of VZV in immunosuppressed individuals show local reactions to be no more common than in healthy vaccinees. However, general adverse events occur much more frequently in the

immunosuppressed (as high as 40% in leukaemic patients on maintenance therapy).[56] About 50% of vaccinated leukaemic patients develop a rash after the first dose, and in some of these the varicella is severe enough to warrant the use of antiviral therapy.[56]

It is not necessary to vaccinate seropositive persons, but the vaccine is well tolerated by those who are immune to varicella.

**Transmissibility of vaccine virus**
In the USA, where more than 20 million doses of VZV have been distributed, there have been only 3 reports of transmission of the vaccine-type virus from a healthy vaccinee to a healthy contact; all contact cases have been mild and associated with a rash in the vaccinee.[8,57,58] In addition, studies in immunosuppressed vaccinees suggest that they have an increased risk of spreading vaccine virus to contacts.[54,59]

**Risk of herpes zoster (shingles)**
Evidence suggests a reduced incidence of herpes zoster among healthy vaccinees, although currently there are insufficient data to assess long-term risk.[8] Herpes zoster in immunised persons may also result from previous natural varicella infection.[35]

## Contraindications
As with other vaccines, postpone vaccination in the event of an acute febrile illness.

VZV should not be given during pregnancy and vaccinees should not become pregnant for one month after vaccination. The Vaccine Adverse Events Reporting System in the USA received reports of 87 women who received Varivax before or during pregnancy; none of the exposed offspring showed evidence of congenital varicella infection.[50, 60] A non-immune pregnant household contact is not a contraindication to vaccination of another healthy child or adult in the same household, as the risk of transmission and infection of the fetus is extremely low (at present there have been no documented cases of transmission of vaccine strain virus to the fetus).

VZV is contraindicated in subjects with primary or acquired immunodeficiency states, including those immunosuppressed by AIDS, and those taking high-dose oral corticosteroids (see also Part 2.3, 'Groups with special vaccination requirements'). Vaccination with live attenuated vaccine can result in a more extensive vaccine-associated rash or disseminated infection in individuals with AIDS.[61] However, in asymptomatic or mildly symptomatic HIV-infected children, varicella vaccine may be considered after weighing the potential risks and benefits. This approach is consistent with the Advisory Committee on Immunization Practices (ACIP).[8,35] NHMRC also recommends that children who have been receiving high dose systemic steroids for 2 weeks or more may be vaccinated after steroid therapy has ceased for at least 3 months, which is also consistent with the US recommendations.[8]

VZV is contraindicated in those who have had an anaphylactic reaction to any of the vaccine components, including neomycin (in both Varivax Refrigerated and Varilix) and gelatin (in Varivax Refrigerated only).

As human immunoglobulin contains varicella antibodies, its administration may inhibit response to VZV. However, data are lacking on the use of the vaccine before or after immunoglobulin. NHMRC recommends that varicella vaccine not be given for at least 3 months after immunoglobulin administered by IM injection, or for at least 9 months after immunoglobulin administered intravenously. It also recommends that immunoglobulin should not be given for at least 3 weeks after vaccination (see also 'Conflicts with product information').

## Use in pregnancy
VZV should not be given during pregnancy and vaccinees should not become pregnant for one month after vaccination (see 'Contraindications' above).

## Conflicts with product information
Varilrix vaccine is approved for use in healthy children from 9 months of age. NHMRC recommends that this vaccine can be used in healthy children who are 12 months of age or older.

Varilrix and Varivax Refrigerated are registered for use as 2 doses of 0.5 mL (1–2 months apart) in adolescents aged 13 years and older and adults. NHMRC recommends a single dose of varicella vaccine for children up to and including 13 years of age.

In adults and adolescents where 2 doses of vaccine are required, the product information for Varilrix states that the second dose should be given at least 6 weeks after the first. NHMRC recommends that the second dose may be given 1 to 2 months after the first dose.

For both varicella-zoster vaccines, the product information states that pregnancy should be avoided for 3 months after vaccination. NHMRC recommends that pregnancy be avoided for at least one month after vaccination.

For both varicella-zoster vaccines, the product information recommends that vaccinees should avoid contact with immunosuppressed persons for up to 6 weeks following vaccination. NHMRC recommends that health-care worker vaccinees should be reassigned to duties that involve no direct patient contact or be placed on sick leave only if a rash develops, and that the period of leave or reassignment should be only for the duration of the rash (not for the 4 to 6 weeks stated in the product information; see also 'Household contacts of immunosuppressed persons').

For both varicella-zoster vaccines, the product information states that salicylates should be avoided for 6 weeks after varicella vaccination, as Reye's syndrome has been reported following the use of salicylates during natural varicella infection. At present it is not known whether Reye's syndrome occurs following the administration of salicylate after varicella vaccination, as no cases have been reported. NHMRC recommends that physicians weigh the theoretical risks associated with VZV against the known risks of the wild type virus in those children and adolescents receiving long-term salicylate therapy for conditions such as Kawasaki disease.

**Vaccination after immunoglobulin**
NHMRC recommends that VZV should not be given for at least 3 months in subjects who have received immunoglobulin by IM injection, or a blood transfusion. The product information for Varivax Refrigerated recommends delaying vaccination for 5 months after immunoglobulin or blood transfusion.

**Immunoglobulin after vaccination**
The product information for Varivax Refrigerated states that immunoglobulin should not be given for 2 months after VZV. NHMRC recommends waiting for 3 weeks after vaccination, which is consistent with US recommendations.

The product information for both varicella-zoster vaccines registered in Australia state that it is not known whether the vaccine given immediately after exposure to natural varicella infection will prevent illness. In view of the current evidence, NHMRC suggests that vaccination may be effective if given to an individual within 3 and up to 5 days after exposure.

## Use of immunoglobulin to prevent varicella

High-titre varicella-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. ZIG must be given early in the incubation period (within 96 hours of exposure). ZIG is highly efficacious, but is often in short supply.

Normal human immunoglobulin can be used for the prevention of varicella if ZIG is unavailable.

- **Zoster immunoglobulin (human)** – CSL Bioplasma (16% solution of gamma globulin fraction of human plasma from donors with high titre of varicella-zoster antibodies vials containing 200 IU Varicella-zoster antibody for IM injection).

**Recommendations**

'Significant exposure' is defined as living in the same household as a person with active varicella or herpes zoster, or direct face-to-face contact with a person with varicella or zoster for at least 5 minutes,

or being in the same room for at least one 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.

ZIG should be given to individuals in the following categories if they are significantly exposed to either varicella or zoster:

**(i)** Pregnant women who are susceptible to varicella infection. They should be tested for varicella-zoster antibodies before ZIG is given.

**(ii)** ZIG *must* be given to neonates whose mothers develop varicella from 7 or fewer days before delivery to 2 days after delivery, as the neonatal mortality without ZIG is 30% in this setting. ZIG must be given as early as possible in the incubation period – within 96 hours of exposure if possible.

**(iii)** ZIG *should* be given to neonates exposed to varicella in the first month of life, if the mother has no personal history of infection with VZV and is seronegative.

**(iv)** Premature infants (born at less than 28 weeks' gestation or with birthweight less than 1000 g) exposed to VZV while still hospitalised should be given ZIG *regardless of maternal history of varicella.*

**(v)** Patients suffering from diseases associated with cellular immune deficiency (eg. Hodgkin's disease), and those receiving immunosuppressive therapy. While it is recommended that immunosuppressed varicella contacts be tested for varicella-zoster antibody, this should not delay ZIG administration beyond 7 days after initial contact with a case.

*NB. If the immunosuppressed 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 positive. Note that varicella-zoster antibodies detected in patients who have been transfused or who have received intravenous immunoglobulin in the previous 3 months may be passively acquired and transient.*

The following dose schedule is recommended for ZIG administration

**Table 3.27.1: Zoster immunoglobulin (ZIG) dose based on weight**

| Weight of patient (kg) | Dose (IU) |
|---|---|
| 0–10 | 200 |
| 11–30 | 400 |
| over 30 | 600 |

The dose may be repeated if a second exposure occurs more than 3 weeks after the first dose. Normal human immunoglobulin can be used for the prevention of varicella if ZIG is unavailable (see Part 3.10, 'Immunoglobulin preparations').

**Conflict with product information**
The dosage of ZIG recommended in the product information differs with that in Table 3.28.1, which has been revised in order to minimise wastage of ZIG.

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# 3.28 YELLOW FEVER

## Virology

Yellow fever is caused by an arbovirus, classified as a Flavivirus, transmitted mainly by *Aedes aegypti* mosquitoes.

## Clinical features

Yellow fever is an acute viral haemorrhagic fever with an incubation period of 2 to 5 days. It ranges from a clinically indeterminate condition to an illness of sudden onset with fever, vomiting and prostration that may progress to haemorrhagic symptoms and jaundice. The case-fatality rate is about 5% in indigenous populations in endemic areas, whereas in non-indigenous individuals, or during epidemics, it may be as high as 50%.

## Epidemiology

Yellow fever infection is currently restricted to parts of Central and South America and Africa. Urban yellow fever is transmitted from person to person by the *Aedes aegypti* mosquito. In areas where *A. aegypti* has been eliminated or suppressed, urban yellow fever has disappeared. Jungle yellow fever is a zoonosis transmitted among non-human hosts (mainly monkeys) by a variety of forest mosquitoes, which may also bite and infect humans. Such infected humans may, if subsequently bitten by *A. aegypti* mosquitoes, become the source of outbreaks of the urban form of the disease.

Periodic outbreaks of urban yellow fever have occurred in some South American countries in recent years, and continue at frequent intervals in West and East Africa, in both towns and rural villages. Hundreds of cases of jungle yellow fever occur each year in South America, and epidemics involving tens of thousands of cases occur frequently in different parts of Africa.[1,2] It is believed that jungle yellow fever is greatly under-reported, and it may be active but unrecognised in forested areas of countries within the yellow fever endemic zone. To combat this disease, millions of doses of vaccine are produced annually under the control of WHO, which documents countries with recent activity.

Preventive measures against urban yellow fever include eradication of *A. aegypti* mosquitoes, protection from mosquito bites, and vaccination. Jungle yellow fever can only be prevented in humans by vaccination.

## Vaccine

- **Stamaril** – Aventis Pasteur (live attenuated yellow fever virus (17D-204 strain) freeze-dried vaccine). Each 0.5 mL dose contains not less than 1000 mouse LD50 units. The vaccine is propagated in chick embryos. It is supplied as a single dose ampoule with 0.5 mL diluent syringe.

Yellow fever vaccine is a live freeze-dried preparation of the 17D attenuated strain of yellow fever virus, a vaccine which has proven extremely safe and effective.[3,4]

## Transport, storage and handling

Protect vaccine from light and store at 2°C to 8°C. Do not freeze. Use within one hour of reconstitution.

## Dosage and administration

A single SC or IM injection of 0.5 mL of reconstituted vaccine.

## Recommendations

Yellow fever is a very infrequent cause of illness in most visitors to countries with endemic disease but travellers often need to be vaccinated to meet the regulatory requirements of either these countries or their countries of origin. Yellow fever vaccination is recommended for:

- persons 9 months of age or older travelling or living in yellow fever infected areas. The vaccine must not be given to infants aged less than 9 months because of the risk of vaccine-related encephalitis;
- those travelling outside the urban areas of countries in the yellow fever endemic areas;
- pregnant women should be considered for vaccination if travelling to high-risk areas when travel cannot be postponed and a high level of prevention against mosquito exposure is not feasible;
- laboratory personnel who might be exposed to virulent yellow fever virus.

## Adverse events

Adverse events following yellow fever vaccine are generally mild. Two to 5 % of vaccinees have mild headaches, myalgia, low-grade fevers or other minor symptoms 5 to 10 days after vaccination. Adverse events so severe as to curtail regular activities occur in less than 0.2% of cases.

Immediate hypersensitivity reactions characterised by rash, urticaria, and/or asthma, are very rare[5] with an incidence of less than 1 in 100 000 and occur principally in persons with anaphylactic sensitivity to eggs.

Surveillance in the US and case-study reports indicate that systemic adverse reactions,[6-11] including viscerotropic and neurotropic disease, may very rarely follow use of yellow fever vaccine (17-D strain), at estimated rates of 1 in 400,000 doses distributed and 1 in 8 million respectively. These adverse events appear to be more frequent in vaccinees aged 65 years and over, compared with other age groups. Travellers aged 65 years and over should therefore discuss with their provider the risks and benefits of vaccination in the context of their destination-specific risk for exposure to yellow fever virus, and their prevaccination health status. In addition, vaccinees in this age group should be carefully monitored for adverse events up to 10 days after vaccination.

Given the millions of doses that have been distributed and the rarity of reported adverse events, organ involvement by the vaccine strains (mostly as encephalitis) has been exceedingly rare. Nevertheless, recent reports of fatal infections by vaccine strains should encourage prescribers not to vaccinate travellers unnecessarily.[9-11]

## Contraindications and precautions

**(i) Hypersensitivity**

Live yellow fever vaccine is produced in chick embryos and should not be given to persons with anaphylaxis to eggs. Test doses are absolutely contraindicated for people with anaphylactic egg allergy. Generally, persons who are able to eat eggs or egg products may receive the vaccine. The vaccine is also contraindicated in those who have had a previous anaphylactic reaction to either a previous dose or to any of the vaccine components.

**(ii) Infants**

Infants under 9 months of age should not be given yellow fever vaccine.

**(iii) Adults aged 65 years and over**

Individuals in this age group are at increased risk of very rare but severe systemic adverse events compared with other age groups (see ‘Adverse events’ above). Therefore the risks of such adverse events in elderly travellers must be carefully balanced against the risk of yellow fever infection.

**(iv) Altered immune status**
Infection with yellow fever vaccine virus poses a theoretical risk to patients with impaired immunological mechanisms, such as severe combined immunodeficiency, symptomatic HIV, patients with recent bone marrow or organ transplants, leukaemia, lymphoma, and those whose immune responses are suppressed by corticosteroids, alkylating drugs, antimetabolites or radiation. Short-term (less than 2 weeks) corticosteroid therapy or intra-articular, bursal, or tendon injections with corticosteroids should not be immunosuppressive and constitute no increased hazard to recipients of yellow fever vaccine.

**(v) Administration of other vaccines on the same day**
The serological response to yellow fever vaccine is not inhibited by administration of certain other vaccines concurrently or at intervals of a few days to 4 weeks. However, with the exception of OPV, if live virus vaccines (eg. MMR) are not given concurrently with yellow fever vaccine, 4 weeks should elapse between sequential vaccinations. Although data on possible interference between yellow fever and vaccines such as typhoid, hepatitis B, plague, rabies or Japanese encephalitis are very limited, there is no plausible reason to suspect that significant interference might occur.

A prospective study of persons given yellow fever vaccine and 5 mL of commercially available immunoglobulin revealed no alteration of the immunological response to yellow fever vaccine when compared with controls.[12]

## Use in pregnancy
Although specific information is not available concerning adverse effects of yellow fever vaccine on the developing fetus, it is prudent on theoretical grounds to avoid vaccinating pregnant women, and to postpone travel to areas where yellow fever is present until after delivery. Pregnant women who must travel to areas where the risk of yellow fever is high should be vaccinated. It is believed that, under these circumstances, the small theoretical risk for mother and fetus from vaccination is far outweighed by the risk of yellow fever infection.

## Vaccination for international travel
See Part 2.2, 'Vaccination for international travel'.

## Conflicts with product information
NHMRC recommends that the vaccine not be given to children aged under 9 months. The product information states that it should not be used under 6 months of age and, in addition, that the vaccine should be used with caution between the ages of 6 and 12 months.

The product information recommends a test dose of yellow fever vaccine if there is a history of egg allergy. NHMRC states that test doses are contraindicated in people with a history of anaphylactic egg allergy.

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# Appendix 1: Contact details for Commonwealth, State and Territory Government Health Authorities and Outbreak Control

## Commonwealth Government Health Authority

Commonwealth 02 6289 1555.
Australian Childhood Immunisation Register: 1 800 653 809.

This phone number can also be used by vaccination providers to obtain information on the vaccination history of individual children.

## State and Territory Government Health Authority

| | |
|---|---|
| Australian Capital Territory Immunisation Inquiry Line | (02) 6205 2300 |
| New South Wales - contact the local Public Health Units | (look under business listing 'NSW Health- Public Health Units' in the White pages) |
| Northern Territory | (08) 8922 8044 |
| Queensland | (07) 3234 1500 |
| South Australia Immunisation Coordination Unit | (08) 8226 7177 |
| SA (24-hour) Parent Help-line (Child and Youth Health) | 1300 364 100 |
| Tasmania | The contact number for Tasmania is now "*03 6222 7724* and *1800 671 738*" |
| Victoria | and the contact number for Victoria is now *"1300 882 008".* |
| Western Australia | (08) 9321 1312 |

## Contact details for outbreak control

| | |
|---|---|
| Australian Capital Territory | 24 hour Communicable Disease Control Section: 02 6205 2155. |
| New South Wales | Contact your local Public Health Unit, number in the White Pages. |
| Northern Territory | Contact for Immunisation Handbook is 08 8922 8044. After hours Royal Darwin Hospital 08 8922 8888 for CDC on call doctor. |
| Queensland | 24 hour general enquiries: 07 3234 1155. |
| South Australia | 24 hour general enquiries line: 08 8226 7177. |
| Tasmania | 24 hour number: Hotline 1800 671 738. |
| Victoria | 24 hour contact number: 1300 651 160. |
| Western Australia | Business hours: 08 9388 4999. After hours: 08 9480 4960. |

# Appendix 2: Standards for childhood vaccination

The following is a summary of the standards for childhood vaccination which were developed in 1994 by the National Immunisation Committee in consultation with the National Immunisation Education sub-committee which consisted of representatives from professional organisations. They are intended as a guide rather than a legalistic imposition on providers, and can provide the basis for quality assurance at all levels in the health system. As such they have been endorsed by the Australian Medical Association, the Royal Australian College of General Practitioners and the Australian College of Paediatrics, and have been welcomed by a variety of other professional bodies.

| | |
|---|---|
| Standard 1 | Vaccination services are readily available. |
| Standard 2 | There are no barriers or prerequisites to vaccination services. |
| Standard 3 | NHMRC-recommended childhood vaccines are offered free, without cost to parent or guardian. |
| Standard 4 | Vaccination providers utilise all clinical encounters to assess vaccination status and, when indicated, vaccinate children. |
| Standard 5 | Providers educate parent/caregivers about vaccination. |
| Standard 6 | Providers question parent/caregivers about contraindications and, before vaccinating a child, inform them in specific terms about the benefits and risks of the vaccines their child is about to receive. |
| Standard 7 | Providers withhold vaccination only for true contraindications. |
| Standard 8 | Providers offer and administer, where possible, all vaccines for which a child is due at the one visit. |
| Standard 9 | Providers use accurate and complete recording procedures. |
| Standard 10 | Providers report adverse events following immunisation promptly, accurately and completely as set out in Part 1.6, ‘Adverse events following immunisation (AEFI)’. |
| Standard 11 | Providers adhere to appropriate procedures for vaccine cold-chain management. |
| Standard 12 | Vaccination providers maintain current and easily retrievable vaccination guidelines at all locations where vaccines are administered. |
| Standard 13 | Vaccines are administered by properly trained individuals who receive ongoing education and training on current vaccination recommendations. |

# Appendix 3: The golden rules of immunisation and the 'cold-chain'

Can be copied or made into a poster for vaccine service providers.

**General issues related to the Schedule**

1. Follow the Australian Standard Vaccination Schedule (ARVS) guidelines and the recommendations of the NHMRC at all times. All infants are now offered the first hepatitis B vaccine at birth.

2. Administer all the recommended vaccines on the ASVS at the recommended time. Reducing the intervals between doses should only be done during a 'catch-up' schedule.

3. Check and record the immunisation status of all children and adults regularly, and offer opportunistic immunisation if needed.

4. Do not defer, postpone or advise against immunisation unless a true contraindication exists.

**Prior to vaccination**

5. Ensure there are adequate trained staff, emergency equipment and drugs on site to deal with rare post-vaccination complications. It is important that the correct strength of adrenaline is kept close at hand in case of anaphylaxis.

6. Discuss the risks and benefits of immunisation and ensure that valid consent is obtained prior to immunisation.

7. Use the pre-vaccination assessment and checklist to help assess the child or adult's health status prior to vaccination.

**Administration of vaccines**

8. Administer all due vaccines on the same day, but give them in separate sites (ie. use different limbs) using separate syringes. If it is necessary to use the same limb, injection sites should be separated by at least 25mm (2.5 cm).

9. Check the expiry date of all vaccines prior to drawing up, and record the batch number in the patient's records and the Personal Health Record.

10. Draw up vaccines using sterile technique.

11. Never mix separate vaccines in the same syringe and never mix vaccines with other drugs.

12. Do not give test doses or half doses of vaccine.

13. Give all injections in children less than 12 months old in the anterolateral thigh, *not* the buttock.

14. Give single injections to children 12 months or older in the deltoid. Where multiple injections are required the anterolateral thigh may be used.

15. Give vaccines intramuscularly with the exception of oral polio vaccine (OPV), which is given orally. Note that MMR, influenza and pneumococcal vaccines can be administered either by intramuscular or subcutaneous injection. JE and varicella vaccines are administered sub-cutaneously.

16. Opened vials of OPV can be re-used until they are empty, provided that when not in use, the vial is capped, stored between 2°C and 8°C and the expiry date has not passed.

**Documentation and notification**

17. Record all vaccinations:
    - on the Australian Childhood Immunisation Register (if under 7 years of age);

- in the child's Personal Health Record folder (kept by parent/caregiver). Adults should also be given a 'take-home' record of vaccination; and
- in the child's clinical record file in your clinic or surgery.

18. Record and notify all significant adverse events following immunisation (see Part 1.6, ‘Adverse events following immunisation (AEFI)’).

**After vaccination**

19. All parents/guardians should be given pre- and post-immunisation advice as per the NHMRC guidelines.

20. Keep all vaccinated patients under observation (in the waiting area near the clinic/surgery) for at least 15 minutes after vaccination.

**Keeping vaccines potent (the 'cold-chain')**

*'Cold-chain' Management'*

21. Store, transport and maintain vaccines at a temperature between 2°C and 8°C.

22. Have a maximum/minimum thermometer in the vaccine refrigerator. The temperature needs to be read and recorded daily and kept between 2°C and 8°C. With few exceptions (see Part 1.10, ‘Transport, storage and handling of vaccines’) vaccines must not be frozen. Diluent must not be frozen.

23. Ensure there is one person responsible for the 'cold-chain' in your clinic/surgery and that other staff are aware of how to monitor and maintain the 'cold-chain'.

*Vaccine refrigeration and storage*

24. It is preferable to use a purpose-built refrigerator for storing of vaccines (see Part 1.10, ‘Transport, storage and handling of vaccines’).

25. If a purpose-built vaccine refrigerator is not available, ensure a separate vaccine refrigerator (preferably a 'frost free' type) exists solely for the storage of vaccines. Do not store food or other items in this refrigerator.

26. Store vaccine on the middle and upper shelves only and keep them away from the evaporation plate.

27. Fill lower drawers and door spaces with plastic bottles filled with salt water (label the salt water bottles).

28. Make sure your fridge is defrosted regularly and ice is not allowed to build up (not necessary for frost-free types).

29. Store vaccine in an insulated container with a sweated ice brick while defrosting the fridge. Keep vaccine away from direct contact with the ice brick.

30. Return all unused vaccine to the refrigerator immediately.

*Vaccine delivery and transport*

31. Unpack and check the 'cold-chain' monitors (heat and freeze) if they are used in your State or Territory. Store vaccines promptly.

32. Transport vaccine in an insulated container with a 'sweated' ice brick and monitor temperatures during transport.

33. During transport, ensure that vaccines do not directly contact the ice bricks. Wrap them up.

*Vaccine damage*

34. In Australia freezing is the main cause of vaccine damage in both tropical and temperate areas. *Freezing inactivates most vaccines* (see Table 1.10.1).

35. Some vaccines are damaged by exposure to light. See Table 1.10.1.

36. Always contact your State/Territory Vaccine Distribution Centre before you discard any vaccine.

**Remember – an unimmunised child is an 'at risk' child.**

**Acknowledgements**: This document is based on the Golden Rules developed by the North East Valley Division of General Practice in Melbourne, Victoria.

# Appendix 4: Commonly asked questions about vaccination

This chapter 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.

## 1. General questions

**i) How does vaccination work?**

Vaccination conveys immunity to diseases by a process called active immunity, which can be achieved by administration of either inactivated (ie. not live) or live attenuated organisms or their products. Inactivated vaccines may include the whole organism (such as oral typhoid vaccine), the toxin produced by the organism (such as tetanus and diphtheria vaccines), or specific antigens (such as Hib and pneumococcal vaccines). In some cases the antigen is conjugated (ie. chemically linked) with proteins to facilitate the immune response. Inactivated viral vaccines may include whole viruses (IPV and hepatitis A vaccines) or specific antigens (influenza and hepatitis B vaccines). Live attenuated viral vaccines include MMR, OPV, varicella-zoster and yellow fever vaccines.

Immunity can also be acquired passively by the administration of immunoglobulins. Such immunity is immediate and is dose-related and transient.

**(ii) What is the correct site for vaccination of children?**

The top, outer part of the thigh is the preferred site for injections for infants under the age of 12 months. The deltoid region of the upper arm is the preferred site for vaccination of children 12 months of age and older because it is associated with fewer local reactions and has sufficient muscle bulk to facilitate the injection.

**(iii) How many injections can be given into the same limb in a child aged under 12 months?**

Normally only one injection should be administered in each limb. However there are occasions when a child under 12 months of age may need 3 or more vaccines. In this case two injections can be given into the same leg into the vastus lateralis muscle on the same day, but the injections should be given at least 25 mm (2.5 cm) apart using separate sterile injection equipment for each vaccine administered.

**(iv) When should preterm infants be vaccinated?**

Babies born at less than 32 weeks gestation should receive their first dose of hepatitis B vaccine either at birth or at 2 months, and may require a fourth dose at 12 months of age. They should receive their doses of DTPa-hepB, Hib and OPV (or IPV) 2 months after birth as normal, unless they are very unwell. When Pedvax HIB is used in an extremely preterm baby (<28 weeks gestation or <1500 g birth weight) an additional dose should be given at 6 months of age (see Part 2.3, 'Groups with special vaccination requirements'). Additionally, extremely preterm babies with chronic lung disease should be offered 7vPCV (see Part 2.3, 'Groups with special vaccination requirements').

**(v) Do elderly people (over 65 years) who have no chronic illnesses need the influenza vaccine?**

Yes. Age is an independent risk factor for influenza. Vaccination of those aged over 65 years, regardless of the presence or absence of chronic illness, reduces all-cause mortality by up to 50% in the winter period in this age group (see Part 3.11, 'Influenza').[1,2] The healthy elderly should also receive the 23-valent pneumococcal polysaccharide vaccine (see Part 3.18, 'Pneumococcal infections').

**(vi) Should adults receive pertussis (whooping cough) vaccine boosters?**

An acellular pertussis vaccine (combined with tetanus and diphtheria antigens) is now available for adolescents and adults (dTpa, or Boostrix). This vaccine should not be given as a primary vaccination series against pertussis; further, no recommendations about additional booster doses using adult/adolescent formulation dTpa can be made at this time. A booster dose of dTpa is recommended for the following groups (unless contraindicated);

- adolescents at 15 to 17 years;
- adults working with young children;

- couples planning to have a family in the near future, and new parents as soon as possible after delivery of an infant; and
- any adult expressing an interest in receiving a booster dose of dTpa, provided a primary course of DTP has been given in the past.

Contraindications to adult/adolescent formulation dTpa include previous anaphylactic reaction to any vaccine component, and receipt of a vaccine containing either diphtheria or tetanus within the previous 5 years.

See Part 3.16, 'Pertussis' for more information.

## 2. Contraindications and precautions

**(i) What are the absolute contraindications to childhood vaccination?**

True contraindications to the childhood vaccines are extremely rare (see relevant chapters), and include only anaphylactic sensitivity to any of the particular vaccine's components, and an anaphylactic event following a previous dose of that vaccine.

NB: An anaphylactic reaction to eggs does not contraindicate MMR vaccine, as the vaccine viruses are not grown in eggs and the vaccine does not contain any egg protein[3] (see Part 3.13, 'Measles').

**(ii) What are the contraindications to further doses of pertussis-containing vaccines?**

Further doses of DTPa are contraindicated in those who have had:

- encephalopathy within 7 days of DTPa, defined as severe acute neurological illness with prolonged seizures and/or unconsciousness and/or focal signs, not due to another identified cause. Note that encephalopathy is much less likely to occur now that the acellular pertussis vaccine (DTPa) is routinely used, rather than whole-cell pertussis vaccine (DTPw).

- immediate severe allergic or anaphylactic reaction to vaccination with DTPa. In these cases CDT should be used for further vaccination. Although the pertussis component is the most likely cause of adverse events, further vaccination with diphtheria and tetanus vaccines should be undertaken under careful observation.

A previous simple febrile convulsion or pre-existing neurological disease is *not* a contraindication to pertussis-containing vaccines.

**(iii) What are the precautions to childhood vaccination?**

In general, children with immunodeficiency or on immunosuppressive therapy should not be given live vaccines (see (vii) to (ix) below).

**(iv) Should a child with an intercurrent illness be vaccinated?**

A child with a minor illness (without systemic illness and with a temperature below 38.5$^{o}$ C) may be safely vaccinated. Infants and children 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 child with a major illness or high fever ≥38.5$^{o}$ C, vaccination should be postponed until the child is 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 child. In such cases, it is advisable to defer vaccination and arrange for the child to return for vaccination when well again.

**(v) Should children with epilepsy be vaccinated?**

Yes. Stable neurological disease (such as epilepsy) is not a reason to avoid giving vaccines like pertussis (whooping cough). Pertussis vaccine is included in DTPa-combination vaccines. Children 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. Note that the fever following measles vaccine occurs 5 to 12 days after vaccination (in less than 20% of vaccinees).[4] A family history of fits or epilepsy is not a reason to avoid vaccination.

**(vi) Should children with neurological disease receive the normal vaccination schedule?**

Children with neurological disease may be at increased risk of complications of diseases such as whooping cough and measles if they attend centres where there are a number of other children. Such children are also often at increased risk of complications from diseases like measles and whooping

cough, as they can be more prone to respiratory infections and chest problems. Therefore it is important that these children be immunised, on time, as recommended in the ASVS.

**(vii) Are steroids a contraindication to vaccination?**
Live virus vaccines such as MMR, OPV, BCG and varicella-zoster vaccines, should *not* be given to children receiving high dose oral (more than 2 mg/kg/day prednisolone for more than one week) or parenteral (injected) corticosteroid therapy, or extensive topical (skin) steroid therapy for more than 2 weeks. Inactivated vaccines (eg. DTPa-hepB) may be less effective in this group but are not contraindicated. Therapy with inhaled steroids is not a contraindication to vaccination.

**(viii) Should vaccines be given to children who have problems with their immune systems?**
Children with immunodeficiency or those on immunosuppressive therapy should *not* be given live virus vaccines such as OPV, MMR, and varicella-zoster vaccines.[5] These children and their household contacts should be given inactivated poliomyelitis vaccine (IPV) instead of OPV. HIV-infected children may be given MMR vaccine provided their CD4 counts are above a certain threshold (see Table 2.3.1). The contacts of immunodeficient children can be given MMR without risk of transmission. Non-immune household contacts of immunodeficient children should be offered varicella-zoster vaccine.

With the exception of OPV (because IPV should be used instead), live virus vaccines can be given to children with leukaemia and other malignancies who are on chemotherapy 6 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 child's oncologist (see Part 2.3, 'Groups with special vaccination requirements').

**(ix) What vaccines should children with HIV infection receive?**
Children with HIV (human immunodeficiency virus) infection should have all routine inactivated vaccines on the ASVS. Inactivated poliomyelitis vaccine (IPV) should be given instead of OPV. Varicella-zoster vaccine is generally contraindicated in children with HIV, 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 can be given to children with HIV, depending on their CD4 counts (see above). Children with HIV infection should also be vaccinated against pneumococcal disease (see Table 3.18.1 and 3.18.3). Influenza vaccine is also recommended for HIV-infected children. They should *not* be given BCG, due to the risk of disseminated infection (see Part 2.3, 'Groups with special vaccination requirements').

**(x) Should chronically ill children be vaccinated?**
In general, children with chronic diseases should be vaccinated as a matter of priority because they are often more at risk from complications from the diseases. Care is needed however, in situations where the child's illness, or its treatment, may result in impaired immunity.

**(xi) Should children be vaccinated while the child's mother is pregnant?**
There is no problem with giving routine vaccinations to a child whose mother is pregnant. MMR vaccine viruses are not transmissible, and transmission of varicella-zoster vaccine virus is very rare and causes a very mild infection. Furthermore, vaccinating the child of a pregnant mother will reduce the risk of her being infected by her offspring if she is not immune. Administration of varicella-zoster vaccine to household contacts of non-immune pregnant women is safe.

**(xii) Should children with allergies be vaccinated? What precautions are required for atopic or egg-sensitive children?**
Asthma, eczema, hay fever and allergies are not contraindications to any vaccine on the childhood schedule. An important exception is anaphylactic sensitivity to eggs, characterised by generalised hives, swelling of the mouth or throat, difficulty breathing, wheeze, low blood pressure, and shock. If a person has a history of severe egg allergy, influenza, yellow fever and Q fever vaccines should *not* be given. Because MMR vaccines viruses are not cultured in eggs and the vaccine does not contain egg protein, MMR can be given safely to those with anaphylactic sensitivity to eggs.[3] Simple dislike of eggs or having diarrhoea or stomach pains after eating eggs are not reasons to avoid MMR and these

children require no special precautions. These children can also have all other routine vaccines without special precautions. [3]

## 3. Responding to questions and concerns about immunisation

Some people express concerns about immunisation. These mostly relate to whether the vaccine is safe and whether vaccines weaken the immune system of the child. Providers should listen to and acknowledge people's concerns. Providers should discuss the risks and benefits of immunisation with parents/caregivers honestly and in a non-defensive manner. Parents and adult vaccine recipients should receive accurate information on the risks from the diseases and those from vaccine side effects and adverse events (see table on back cover 'Comparison of effects of vaccines and diseases'). The following section responds to some arguments frequently raised by opponents 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.

### a) Vaccine safety

**(i) How safe are vaccines?**

Before vaccines are made available they are tested for safety and efficacy in clinical trials and then in mass 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 prior to marketing approval being granted.

After introduction into immunisation schedules there is 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 problems do occur after vaccines are registered for use. An example is rotavirus vaccine, which was licensed in the USA in August 1998. In pre-licensure trials, the vaccine appeared to be safe, but post-licensure surveillance detected a risk of intussusception associated with the vaccine. As soon as this risk was discovered, the vaccine was withdrawn from the market. Rotavirus vaccine was never released in Australia.[6]

**(ii) Can too many vaccines overload or suppress the natural immune system?**

The increase in the number of vaccines and vaccine doses given to children has led to concerns about the possible adverse effects of the aggregate vaccine exposure, especially on the developing immune system. In day-to-day life, all children and adults confront enormous numbers of antigens (substances that provoke a reaction from the immune system) 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 2 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 antigens.[7]

**(iii) Do vaccines cause disease?**

Some studies have suggested a link between immunisations and certain medical conditions, such as asthma, multiple sclerosis, and diabetes. The allegations of a link are often made for a disease of unknown cause. The existence of a link between vaccination and the diseases does not necessarily imply causation, and 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 autism?[6]**

In 1993, Wakefield et al (Royal Free Hospital, London) suggested an association between both the natural and vaccine types of measles virus and inflammatory bowel disease (IBD) based on a study of 25 children with Crohn's disease. In 1998 researchers from the same group reported the occurrence of an apparently new syndrome of an unusual type of IBD in association with developmental disorders such as autism.[8] The researchers suggested that MMR vaccine caused 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.

This study had several weaknesses. First, finding out whether or not MMR causes autism is best determined by comparing the incidence of autism in vaccinated versus unvaccinated children. However, the researcher included only vaccinated children. Second, the author claimed that gastrointestinal inflammation contributes to autism – however, in several of the cases the behavioural problems appeared before the onset of bowel disease.[9] Furthermore, the association between vaccine and autism was primarily based on parental recall, and parents are more likely to have linked changes in behaviour with memorable events such as vaccination. The Royal Free Hospital study was conducted on a very selective group of patients, all referred to the hospital for gastrointestinal ailments, and such a case series analysis is unable to determine causal links.

In 2002 Uhlmann, Wakefield and others published a further study showing a higher rate of measles virus in the bowel of autistic children with bowel symptoms, compared to a group of children without autism.[10] The validity of this study is difficult to assess because the study does not report key information on the characteristics and the method of selection of the cases and controls, and on laboratory methods. For example, the vaccination status of the children in the study is not known. There was no attempt to distinguish between wild-type measles virus and vaccine strain virus – nor was there any mention of whether the laboratory personnel performing the tests were aware of the immunisation status of the children whose specimens they tested.[9]

The onset of autism and MMR vaccination may coincidentally appear associated in time because the average age at which parents report concerns about child development is 18 to 19 months, and over 90% of children receive MMR vaccine before their second birthday in the UK.[11] More thorough, large epidemiological studies have found no evidence of an association.[12-15]

- **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.[16]

- **Does hepatitis B vaccine cause multiple sclerosis?**

There is no evidence that hepatitis B vaccine causes multiple sclerosis (MS). Concerns about hepatitis B vaccination arose from France, after a few reports of a possible link between hepatitis B vaccine and MS. However, when the French data were examined closely, the rate of MS in vaccinated people was not significantly different from the expected population rate. With millions of vaccinations administered worldwide, it is likely that surveillance systems in some countries will receive some reports of MS, which seem to be related in time to vaccinations. As with all such reports, however, they only suggest the possibility of an association. Subsequent studies have found no increase in incidence of MS, or even relapse of MS, after hepatitis B vaccination.[17-21]

- **Do some vaccines cause 'Mad Cow Disease'?**

Variant Creutzfeld-Jakob disease (vCJD) is considered to be the human equivalent of bovine spongiform encephalopathy (BSE, also known as 'mad cow disease'). There is no evidence that any case of vCJD has resulted from the administration of any vaccine product, despite millions of doses of vaccine being administered worldwide. Concerns about the risk of transmission of this disease arose because the production of some vaccines requires bovine derivatives such as fetal bovine serum, and there is thus a theoretical risk of transmitting BSE via some vaccines. In Australia, the Therapeutic Goods Administration has confirmed that the vaccines available in this country contain bovine materials preferentially sourced from BSE-free areas, and that they undergo appropriate purification treatment. Therefore, although some vaccines carry a theoretical risk of transmissible spongiform encephalopathies, this risk is infinitesimally small (estimated at less than one in a billion).[22] The benefits of vaccination are considered to far outweigh any theoretical risk of BSE transmission.[23]

- **Is there a link between vaccination and Sudden Infant Death Syndrome (SIDS)?**

Despite extensive studies, there is no evidence that vaccination causes SIDS (cot death). Deaths do occasionally occur shortly after vaccination but the relationship is simply a chance association, since SIDS tends to happen in babies of 2 to 6 months of age whether they are vaccinated or not. Many studies have conclusively shown that SIDS is not caused by immunisation. In addition, some studies have found a lower rate of SIDS in immunised children.[24-26]

- **Does immunisation cause diabetes?**

In 1997, a study from Finland suggested a link between Hib vaccination and type 1 diabetes.[27] However, subsequent reanalysis of the data did not support such a link. The conclusion that there is no causal link between any of the childhood vaccines and diabetes has also been supported by a subsequent review of the literature, and the conclusions of two workshops held in the USA in 1998.[6,28-30]

- **Does influenza vaccine cause 'flu?**

Influenza vaccine is included on the vaccination schedule for adults over the age of 65 years and is recommended for other groups at risk of complications of the 'flu. Although some believe that the vaccine causes influenza, this is not possible as it is not a live virus vaccine. As some people experience adverse events such as a mild fever after the vaccine, it is understandable that they may confuse these symptoms with actually having the 'flu.

## b) Vaccine content

### (i) Why are there additives in some vaccines?

Additives may be necessary either as part of the production process of some vaccines, as preservatives, or to help boost the body's immune response to the vaccine (an adjuvant). These may include formaldehyde, thiomersal and aluminium.

### (ii) Formaldehyde

Formaldehyde is used during the manufacture of tetanus vaccine (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.

### (iii) Thiomersal

Thiomersal (or thimerosal) is a compound which is partly composed of mercury. 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 seafoods) and other environmental sources are also possible sources of mercury. Vaccines used in the past, such as DTP, contained only 25 µg thiomersal per dose.

Mercury causes poisoning after it reaches a certain level in the body. Whether on not it reaches a toxic level depends on the amount of mercury consumed and the persons body weight; individuals with very low body weight are usually more susceptible to poisoning 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.

In response to this theoretical concern, all vaccines on the current ASVS for children under the age of 5 years are now either free of thiomersal, or contain a reduced (trace) amount of thiomersal. Hepatitis B containing vaccines which do not contain any thiomersal include preservative-free paediatric formulation of H-B-Vax II (which is recommended for administration in newborns and infants), and the infant and childhood vaccines, such as Infanrix Hep B, Comvax and Twinrix Junior (360/60).

People sometimes ask why thiomersal was removed from vaccines if it did not cause adverse health effects in children. There were two main reasons; first, it was an attempt to reduce to a minimum the amount of mercury given, in any form, to very small premature babies with low birth weight in whom there was a theoretical risk. Second, the intent was to reduce total exposure to mercury in babies and young children in a world where other environmental sources may be more difficult to eliminate.[31-33]

### (iv) 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 immunisation by keeping antigens near the injection site so that they can be readily accessed by cells responsible for inducing an immue 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 is 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.[34,35]

### (c) The need for immunisation

**(i) Isn't natural immunity better than immunity from vaccination?**
While vaccine-induced immunity may diminish with time, 'natural' immunity, acquired by catching the disease is usually lifelong. The problem is that the wild or 'natural' disease has a high 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. It is important to remember that vaccines are many times safer than the diseases they prevent.

**(ii) Diseases like measles, polio, whooping cough and diphtheria have already disappeared from most parts of Australia. Why do we need to keep vaccinating children against these diseases?**
These diseases are much less common now, but the bacteria and viruses that cause them are still present. The potential problem 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 big 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. So 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.

**(iii) Why do some children get the disease despite being vaccinated?**
This is possible, since no vaccine is 100% effective. 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 vaccines differ. For example, if 100 children are vaccinated with MMR, 5 to 10 of the 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 (lung infection) or encephalitis (inflammation of the brain).

**(iv) What about homeopathic 'immunisation'?**
Homeopathic 'immunisation' has not been proven to give protection against infectious diseases; only conventional immunisation produces a measurable immune response. The Council of the Faculty of Homeopathy, London, have 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".[36] The Executive Director of the Australian Natural Therapies Association has stated that no properly qualified natural therapist would recommend homeopathic 'immunisation' as an alternative to conventional immunisation.

## Where can I get more information about vaccination?

More information about vaccination can be found in the following publications published by the Commonwealth Department of Health and Ageing:

- Understanding Childhood Immunisation
- Immunisation Myths: Responding to Arguments Against Immunisation
- Immunise Australia web site http://www.health.gov.au/pubhlth/immunise/publications.htm.

Also check with your local State or Territory public health unit or your doctor, local council, maternal child health nurse, or public health vaccination clinic for more information (see Appendix 1).

**Other web sites on immunisation:**
(Note that inclusion on this list does not necessarily indicate endorsement of the organisation producing these web sites);

http://www.health.gov.au
http://www.cdc.gov/nip
http://www.who.int/vaccines/
http://www.immunize.org
http://www.cdc.gov/mmwr/
http://www.ncirs.usyd.edu.au

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# Appendix 5: Definitions of adverse events following immunisation

**Notify any events that the reporter considers serious and may be related to the vaccine or vaccines.**

**Abscess**
Occurrence of a fluctuant or draining fluid-filled lesion at the site of injection with or without fever.
(a) Bacterial: Purulent collection.
(b) Sterile abscess: No evidence of bacterial infection.

**Acute flaccid paralysis** [diagnosis must be made by a physician]
Acute onset of flaccid paralysis of one or more limbs following any vaccine.

**Allergic reaction (generalised)**
A non-anaphylactic, generalised reaction characterised by one or more symptoms or signs of skin and/or gastro-intestinal tract involvement WITHOUT respiratory or cardiovascular involvement. (NB. See also 'Anaphylaxis').

**Anaphylaxis**
A rapidly evolving generalised multi-system allergic reaction characterised by one or more symptoms or signs of respiratory and/or cardiovascular involvement AND involvement of other systems such as the skin or GI tract.
(a) Respiratory: Difficulty/noisy breathing, swelling of the tongue, swelling/tightness in throat, difficulty talking/hoarse voice, wheeze or persistent cough.
(b) Cardiac: loss of consciousness, collapse, pale and floppy (babies), hypotension.

**Arthralgia**
Joint pain without redness or swelling.

**Arthritis**
Joint pain together with redness and/or swelling.

**Brachial neuritis**
Pain in arm causing weakness of limb on side of vaccination. Usually described in adults following diphtheria-tetanus vaccines.

**Death**
Any death of a vaccine recipient temporally linked to vaccination, where no other clear cause of death can be established.

**Disseminated BCG**
Disseminated infection occurring after BCG vaccination and confirmed by isolation of *Mycobacterium bovis* BCG strain.

**Encephalopathy** [diagnosis must be made by a physician]
Encephalopathy is an acute onset of major neurological illness temporally linked with vaccination and characterised by any 2 or more of the following 3 conditions:
(a) seizures;
(b) severe alteration in level of consciousness or mental status (behaviour and/or personality) lasting for one day or more; and/or
(c) focal neurological signs which persist for one day or more.

**Encephalitis** [diagnosis must be made by a physician]
Encephalitis is characterised by the above-mentioned symptoms and signs of cerebral inflammation and, in many cases, CSF pleocytosis and/or virus isolation.

**Extensive limb swelling**

Swelling and/or redness over a substantial area, involving at least half the circumference of the limb, and the joints both above and below the injection site, commencing within 48 hours of vaccination and resolving completely without sequelae.

**Fever**
Only very high fever should be reported, eg. over 40.5°C

**Guillain-Barré Syndrome (GBS)** [diagnosis must be made by a physician]
Acute onset of rapidly progressive, ascending, symmetrical flaccid paralysis, without fever at onset of paralysis and with or without sensory loss. Cases are diagnosed by cerebrospinal fluid (CSF) investigation showing dissociation between cellular count and protein content.

**Hypotonic–hyporesponsive episode (shock, collapse)**
Episode of pallor, limpness and unresponsiveness occurring 1 to 48 hours following vaccination. The episode is transient and self-limiting.

**Local reaction (severe)**
Redness and/or swelling centred at the site of injection and one or more of the following:
(a) swelling beyond the nearest joint;
(b) pain, redness and swelling of more than 3 days duration, and/or
(c) requires hospitalisation.
(See also under 'Extensive limb swelling')

**Lymphadenitis (includes suppurative lymphadenitis)**
Occurrence of either:
(a) at least one lymph node, 1.5 cm in diameter or larger; or
(b) a draining sinus over a lymph node.
May be caused by BCG on the same side as vaccination (mostly axillary); or by the rubella component of MMR (usually occipital or post-auricular).

**Meningitis** [diagnosis must be made by a physician]
Acute onset of major illness with fever and often neck stiffness/positive meningeal signs (Kernig, Brudzinski). Symptoms may be subtle or similar to those of encephalitis. CSF pleocytosis is usual.

**Nodule**
Injection site nodules are fibrous remnants of the body's interaction with the vaccine components in the muscle.

**Orchitis**
Swelling with pain and/or tenderness of testes.

**Osteitis**
Inflammation of the bone due to BCG vaccination.

**Osteomyelitis**
Proven bacterial infection of bone.

**Parotitis**
Swelling and/or tenderness of parotid gland or glands.

**Rash**
Severe or unusual rash.

**Screaming (persistent)**
Inconsolable, continuous crying lasting at least 3 hours, accompanied by high-pitched screaming.

**Seizure**
A seizure lasting from several minutes to more than 15 minutes and not accompanied by focal neurological signs or symptoms.
(a) febrile seizures: with fever ≥38.5°C

(b) afebrile seizures: without fever
(c) syncopal seizures: syncope followed by seizure(s).

**Sepsis**
Acute onset of severe, generalised illness due to bacterial infection and confirmed by positive blood culture.

**Subacute sclerosing panencephalitis** [diagnosis must be made by a physician]
Degenerative CNS condition with laboratory confirmation of abnormal serum and CSF measles antibodies.

**Thrombocytopenia**
Platelet count <50 x $10^9$/L.

**Toxic-shock syndrome** [diagnosis must be made by a physician]
Abrupt onset of fever, vomiting, watery diarrhoea and shock within a few hours of vaccination (note that toxic shock syndrome may be due to causes other than vaccination).

**Vaccine-associated paralytic poliomyelitis**
See "acute flaccid paralysis".

**Other severe or unusual events**
Any unusual event that does not fit into any of the categories listed above, but is of medical or epidemiological interest should be reported with a detailed description of the clinical features.

Report by telephone to State or Territory Health Department or notify by the blue card to ADRAC (see Part 1.6, 'Adverse events following immunisation (AEFI)').

Note: the Brighton Collaboration is an international group considering definitions of adverse events following immunisation. Their web site is: http://www.brightoncollaboration.org.

# Appendix 6: Glossary of technical terms to assist parents

**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.

**ADT** = Adult diphtheria and tetanus. Trade name for diphtheria-tetanus vaccine made by CSL for use in adults (dT).

**Adjuvant** = a preparation which may be added to a vaccine to improve the immune response to the vaccine.

**Anaphylaxis** = a sudden and severe allergic reaction, which results in a serious fall in blood pressure and may cause unconsciousness and death if not treated immediately.

**Attenuation** = the process of modifying a virus or bacteria so as 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.

**BCG** = Bacillus of Calmette Guérin, a vaccine that protects against tuberculosis.

**Carrier** = a person who has an infection which may still be active and may spread to others; the carrier state may last for years; examples of infections that can result in the carrier state are hepatitis B and typhoid.

**CDT** = Child diphtheria and tetanus. Trade name for diphtheria-tetanus vaccine made by CSL for use in children (DT).

**Conjugate** = some vaccines (eg. pneumococcal conjugate vaccine) are made from the chemical linking (conjugation) of the bacterial polysaccharide cell coat with a protein carrier, in order to improve the immune response to the vaccine.

**Contraindication** = a reason why a vaccine or drug should not be given.

**Corticosteroid** = a drug used to reduce inflammation and other immune responses.

**dT** =Diphtheria-tetanus vaccine for use in adults (ADT).

**DT** = diphtheria-tetanus vaccine for use in children (CDT).

**DTP** = a vaccine that protects against diphtheria, tetanus and pertussis (whooping cough). The recently released DTPa contains an acellular pertussis component, made of refined pertussis extracts instead of whole cells, which causes fewer adverse events such as fever, pain and swelling at the injection site than the older whole-cell vaccine, DTPw.

**dTpa =** adult/adolescent formulation diphtheria-tetanus-acellular pertussis vaccine

**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.

**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.

**Febrile** = related to a fever, as in febrile illness and febrile convulsions.

**HAV** = abbreviation for hepatitis A virus, the cause of infectious hepatitis, a common food-borne infection in travellers in developing countries.

**HBsAg** = hepatitis B surface antigen; a marker in the blood that indicates that the person is a carrier of active hepatitis B virus infection.

**HBV** = abbreviation for hepatitis B virus, a virus that is spread in various ways including blood-to-blood contact through sharing injection equipment and by sexual intercourse.

**Hepatitis** = an inflammation of the liver; can be caused by viral infections.

**Hib** = *Haemophilus influenzae* type b; a bacterium that causes meningitis and other serious infections in young children.

**HIV** = human immunodeficiency virus, or the AIDS virus; people with HIV infection have weakened immunity and need special programs of vaccination to protect them against other infections.

**Hypotonic-hyporesponsive episode (HHE**) = a rare reaction which may follow some hours after DTP vaccination; the child becomes pale, limp and unresponsive; the condition may last from a few minutes to hours but causes no long-term serious problems.

**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.

**Immunoglobulin** = a protein extract from blood, sometimes called 'antibody', which 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; this time 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 injection** = an injection into the surface layers of the skin; this is used for the administration of 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.

**IPV** = inactivated poliomyelitis vaccine; an injectable vaccine formerly known as Salk vaccine.

**JE** = Japanese encephalitis; a viral encephalitis.

**Jaundice** = yellow skin colour that may result from severe hepatitis.

**MMR** = measles-mumps-rubella vaccine.

**OPV** = oral poliomyelitis vaccine; also known as Sabin vaccine.

**Pandemic influenza** = results when a new sub-type 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 which is given to minimise reactions to vaccination; it works in the same way as aspirin, but aspirin should never be given to children.

**Pertussis** = whooping cough, an illness caused by a bacterium, *Bordetella pertussis*.

**Polysaccharide** = a group of complex carbohydrates (sugars) which make up the cell coating of bacteria.

**Polyvalent vaccine** = a combination vaccine which protects against more than one disease; examples are DTP and MMR.

**PRP-OMP** = a type of Hib vaccine.

**PRP-T** = a type of Hib vaccine.

**Rubella** = a viral illness, also known as German measles.

**Subcutaneous (SC) injection** = an injection into the tissue between the skin and the underlying muscle.

**Triple Antigen** = another name for DTP vaccine.

**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 infection.

**Varicella** = chickenpox, an infection caused by the varicella-zoster virus.

**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 7: List of commonly used abbreviations

| | |
|---|---|
| ABL | Australian bat lyssavirus |
| ACIP | Advisory Committee on Immunization Practices |
| ACIR | Australian Childhood Immunisation Register |
| AEFI | adverse event following immunisation |
| AFP | acute flaccid paralysis |
| AIDS | acquired immunodeficiency syndrome |
| ARVS | Australian Standard Vaccination Schedule |
| ATAGI | Australian Technical Advisory Group on Immunisation |
| anti-HBs | hepatitis B surface antibody |
| BCG | Bacillus of Calmette-Guerin |
| BSE | bovine spongiform encephalopathy |
| CCM | cold chain monitor |
| cm | centimetre |
| CSF | cerebrospinal fluid |
| dT | diphtheria-tetanus vaccine for use in adults (ADT) |
| DT | diphtheria-tetanus vaccine for use in children (CDT) |
| DTPa | diphtheria-tetanus-acellular pertussis vaccine |
| dTpa | adult/adolescent formulation diptheria-tetanus-acellular pertussis vaccine |
| ELISA/EIA | Enzyme linked immunosorbent assay |
| GVHD | graft versus host disease |
| HAV | hepatitis A virus |
| HBIG | hepatitis B immunoglobulin |
| HBV | hepatitis B virus |
| HBsAg | hepatitis B surface antigen |
| HHE | hypotonic-hyporesponsive episode |
| Hib | *Haemophilus influenzae* type b |
| HIV | human immunodeficiency virus |
| HRIG | human rabies immunoglobulin |
| IM | intramuscular |
| IPD | invasive pneumococcal disease |
| IPV | inactivated poliomyelitis vaccine |
| IU | international units |
| IV | intravenous |
| JE | Japanese encephalitis |
| kg | kilogram |
| ng | nanogram |
| µg | microgram |
| mg | milligram |
| mm | millimetre |
| 4vMenPV | meningococcal polysaccharide vaccine (tetravalent) |
| MenCCV | meningococcal C conjugate vaccine |
| MMR | mumps-measles-rubella |
| MS | multiple sclerosis |
| NHIG | normal human immunoglobulin |
| NHMRC | National Health and Medical Research Council |
| OMP | outer membrane protein |
| OPV | oral poliomyelitis vaccine |
| PI | product information |
| 7vPCV | 7-valent pneumococcal conjugate vaccine |
| PPD | purified protein derivative |
| 23vPPV | 23-valent pneumococcal polysaccharide vaccine |
| PRP | polyribosylribitol phosphate |
| SC | subcutaneous |
| SIDS | sudden infant death syndrome |
| TB | tuberculosis |
| TGA | Therapeutic Goods Administration |
| TIG | Tetanus immunoglobulin |
| VAPP | Vaccine-associated paralytic poliomyelitis |
| vCJD | variant Creutzfeld-Jakob disease |
| WHO | World Health Organization |
| ZIG | Zoster immunoglobulin |

# Appendix 8: NHMRC hierarchies of study design and levels of evidence

| Study design | Level of evidence |
|---|---|
| Systematic review of all relevant randomised controlled trials (RCT) | I |
| Properly designed RCT | II |
| Well-designed pseudo-randomised controlled trial (eg. alternate allocation) | III-1 |
| Comparative studies (or systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group | III-2 |
| Comparative studies with a historical control, two or more single arm studies or interrupted time series without a parallel control group | III-3 |
| Case series, post-test or pre-test/post-test, with no control group | IV |

The level of evidence indicates the study design used by the investigators to assess the effectiveness of an intervention. The level assigned to a study reflects the degree to which bias has been eliminated by the study design.[1]

1. National Health and Medical Research Council. How to use the evidence: assessment and application of scientific evidence. Canberra: AusInfo; 2000.

# Appendix 9: Dates when childhood vaccines became available in Australia free of charge* in the public and private sectors[1]

| Vaccine | Public sector | | Private sector† | |
|---|---|---|---|---|
| | Australia | Exceptions | Australia | Exceptions |
| OPV | 1966 | | 1994 | Qld (? 1998) |
| | | | | NSW 1966 |
| | | | | Tas 1966 |
| DTPw | 1953 | | 1994 | WA 1988 |
| Rubella | 1971 | | | |
| (adolescent girls) | | | | |
| MMR | 1989 | | 1994 | NSW 1989 |
| (infant dose) | | | | Qld 1989 |
| MMR | 1994 | SA 1996 | 1994 | WA 1993 |
| (adolescent dose) | | | | SA 1996 |
| ADT | 1982 | | 1994 | WA 1988 |
| CDT | 1975 | | 1994 | WA 1988 |
| Hib vaccines | 1993 April | | 1993 April | |
| (infants born from Feb 1993) | | | | |
| Hib vaccines | 1993 July | WA 1993 Jan | 1993 July | WA 1993 Jan |
| (all infants aged <5 years) | | NT 1993 April | | NT 1994 |
| DTPa boosters | 1997 Sept | Tas 1997 Oct | 1997 Sept | Tas 1997 Oct |
| (infants aged 18 months and 4-5 years) | | Qld 1997 Dec | | Qld 1997 Dec |
| DTPa | 1999 Feb | NT 1997 Aug | 1999 Feb | NT 1997 Aug |
| (infants aged 2, 4 and 6 months) | | SA 1997 Aug | | SA 1997 Aug |
| | | Tas 1999 Feb | | Tas 1999 Feb |
| | | Qld 1999 April | | Qld 1999 April |
| Hep B | 1987 | NT 1988 Jan | Not funded by | NSW 1987 |
| (at-risk infants) | | SA 1996 | the C'wealth | |
| Hep B | 1998 Jan | Qld 1998 March | ?1998 | Qld 1998 March |
| (adolescent dose) | | Tas 1998 March | | Tas 1998 March |
| | | NT 1998 April | | NT 1998 April |
| | | NSW 1999 | | NSW 1999 |
| | | SA 1999 | | |
| Hep B | 2000 May | NT 1990 Aug | 2000 May | NT 1994 |
| (universal infant dose) | | | | |

* Vaccines on the current National Immunisation Program became free of charge in the public and private sector in all jurisdictions in 1999/2000.

† All scheduled childhood vaccines became free in the private sector in the Australian Capital Territory in 1993 (except for MMR vaccine which became free in the private sector in 1994) and in the Northern Territory in 1994.

1. McIntyre P, Gidding H, Gilmour R, et al. Vaccine preventable diseases and vaccination coverage in Australia, 1999-2000. *Communicable Diseases Intelligence* 2002;26:S111.

# Parent Advice Sheet – Commonly observed adverse events following immunisation and what to do about them

The following information can be photocopied and given to parents as post-vaccination advice.

All the common adverse events following immunisation are usually mild and transient and treatment is not usually required. If the adverse event following immunisation is severe or persistent, or if you are worried about yourself or your child's condition, see your doctor or immunisation clinic nurse as soon as possible or go to a hospital.

| **Commonly observed adverse events (conditions) following specific vaccines used in the Australian Standard Vaccination Schedule (ASVS)** | | | | |
|---|---|---|---|---|
| **HepB** | **DTPa-containing vaccines & dTpa** | **Hib** | **IPV & IPV-containing vaccines** | **OPV** |
| • Localized pain, redness & swelling at injection site<br>• Occasionally injection site nodule – may last many weeks (no treatment needed)<br>• Low grade temperature (fever) | • Irritable, crying, unsettled and generally unhappy<br>• Drowsiness or tiredness<br>• Localized pain, redness & swelling at injection site<br>• Occasionally injection site nodule – may last many weeks (no treatment needed)<br>• Low grade temperature (fever) | • Localized pain, redness & swelling at injection site<br>• Occasionally injection site nodule – may last many weeks (no treatment needed)<br>• Low grade temperature (fever) | • Muscle aches<br>• Localized pain, redness & swelling at injection site<br>• Occasionally injection site nodule – may last many weeks (no treatment needed)<br>• Low grade temperature (fever) | • Occasional diarrhoea (no treatment usually needed but parent or carer must wash hands carefully after changing nappies) |
| **MMR** | **MenCCV** | **7vPCV** | **dT (ADT)** | **VZV** |

| | | | | |
|---|---|---|---|---|
| • Occasionally injection site nodule – may last many weeks (no treatment needed)<br>Seen 7 to 10 days after vaccination:<br>• Low grade temperature (fever) lasting 2-3 days, faint red rash (not infectious), head cold and/or runny nose, cough and/or puffy eyes<br>• Drowsiness or tiredness<br>• Swelling of salivary glands | • Irritable, crying, unsettled and generally unhappy<br>• Loss of appetite<br>• Headache (usually observed in adolescent/adults)<br>• Localized pain, redness & swelling at injection site<br>• Occasionally injection site nodule – may last many weeks (no treatment needed)<br>• Low grade temperature (fever) | • Localized pain, redness & swelling at injection site<br>• Occasionally injection site nodule – may last many weeks (no treatment needed)<br>• Low grade temperature (fever) | • Localized pain, redness & swelling at injection site<br>• Occasionally injection site nodule – may last many weeks (no treatment needed) | • Localized pain, redness & swelling at injection site<br>• Occasionally injection site nodule – may last many weeks (no treatment needed)<br>• Low grade temperature (fever)<br>Seen 5-26 days after vaccination:<br>• Pustular rash (2-5 lesions) usually at injection site which occasional covers other parts of the body |
| **Influenza** | **23vPPV** | | | |
| • Drowsiness or tiredness<br>• Muscle aches<br>• Localized pain, redness & swelling at injection site<br>• Occasionally injection site nodule – may last many weeks (no treatment needed) | • Localized pain, redness & swelling at injection site<br>• Occasionally injection site nodule – may last many weeks (no treatment needed)<br>• Low grade temperature (fever) | | | |

| | |
|---|---|
| • Low grade temperature (fever) | |

**Key to table:**

| | |
|---|---|
| DTPa | Diphtheria-tetanus-pertussis (acellular) infant/child formulation |
| dTpa | Adult/adolescent formulation diphtheria-tetanus-pertussis (acellular) vaccine |
| dT or ADT | Adult diphtheria-tetanus vaccine |
| hepB | hepatitis B vaccine |
| Hib | *Haemophilus influenzae* type b (Hib) vaccine PRP-OMP, PRP-T, HbOC (as monovalent or in combination) |
| Influenza | Influenza vaccine |
| IPV | Inactivated poliomyelitis vaccine (usually in combination with other vaccine and given as injection) |
| 7vPCV | 7-valent pneumococcal conjugate vaccine |
| 23vPPV | 23-valent pneumococcal polysaccharide vaccine |
| MenCCV | Meningococcal C conjugate vaccine |
| MMR | measles-mumps-rubella vaccine |
| OPV | oral poliomyelitis vaccine |
| VZV | varicella-zoster vaccine (both Varivax Refrigerated and Varilrix, unless stated otherwise) |
| NA | not applicable |

#### What to do to manage injection site discomfort

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 may persist for some weeks or months. This should not be of concern and requires no treatment,

### Managing fever after immunisation

Give extra fluids to drink. Do not overdress the baby if hot. Although the routine use of paracetamol at the time of vaccination is no longer necessary, it may be required if, for example, an infant or child has a high fever following vaccination. The dose of paracetamol is 15 mg/kg of paracetamol liquid, up to a maximum daily dose of 90 mg/kg/day.

**Reference:** see Part 1.6, ‘Adverse events following immunisation (AEFI)’ for more information.

**BACK COVER- Comparison of effects of vaccines and diseases**

| Disease | Effects of disease | Side effects of vaccination |
|---|---|---|
| Diphtheria - contagious bacteria spread by droplets; causes severe throat and breathing difficulties. | About 1 in 15 patients dies. The bacteria release a toxin, which can produce nerve paralysis and heart failure. | DTPa vaccine- about 1 in 10 has local inflammation or fever. Serious adverse events are very rare, and much less common than with DTPw. |
| Hepatitis B - virus spread mainly by blood, sexual contact or from mother to newborn baby, causes acute hepatitis or chronic carriage. | About 1 in 4 chronic carriers will develop cirrhosis or liver cancer. | About 1 in 15 to 1 in 100 will have pain and fever. Anaphylaxis occurs in about 1 in 600 000. |
| Hib - contagious bacteria spread by droplets; causes meningitis, epiglottitis (respiratory obstruction), septicaemia, osteomyelitis. | About 1 in 20 meningitis patients dies and about 1 in 4 survivors has permanent brain or nerve damage. About 1 in 100 epiglottitis patients die. | About 1 in 20 has discomfort or local inflammation. About 1 in 50 has fever. |
| Influenza - contagious virus spread by droplets; causes fever, muscle and joint pains, pneumonia. | Causes increased hospitalisation in the elderly. High-risk groups include the elderly, diabetics, and alcoholics. | About 1 in 10 has local reactions. Guillain-Barré syndrome occurs in about 1 in 1 million. |
| Measles - highly infectious virus spread by droplets; causes fever, cough, rash. | 1 in 25 children with measles develops pneumonia and 1 in 2000 develops encephalitis (brain inflammation). For every 10 children who develop measles encephalitis, 1 dies and 4 have permanent brain damage. About 1 in 25 000 develops SSPE (brain degeneration) which is always fatal. | About 1 in 10 has discomfort, local inflammation or fever. About 1 in 100 develops a rash which is non-infectious. 1 in 1 million recipients may develop encephalitis (inflammation of the brain). |
| Meningococcal infections - bacteria spread by respiratory droplets. Cause sepsis (infection of the blood stream) and meningitis (infection of the tissues surrounding the brain). | About 1 in 10 patients dies.<br>Of those that survive, 1 in 30 has severe skin scarring or loss of limbs, and 1 in 30 has severe brain damage. | Polysaccharide vaccine: Local reactions common. Mild fever, headache, malaise in 1 in 30.<br>Conjugate vaccine: About 1 in 10 has local inflammation, fever, irritability, anorexia or headaches. |
| Mumps - contagious virus spread by saliva; causes swollen neck and salivary glands, fever. | 1 in 200 children develops encephalitis. I in 5 males past puberty develop inflammation of the testes. Occasionally mumps causes infertility or deafness. | 1 in 100 vaccine recipients may develop swelling of the salivary glands. 1 in 3 million recipients develops mild encephalitis. |
| Pertussis- contagious bacteria spread by droplets; causes whooping cough and vomiting, lasting up to 3 months. | About 1 in 200 whooping cough patients under the age of 6 months dies from pneumonia or brain damage | As for DTPa vaccine (see diphtheria). |
| Pneumococcal infections - bacteria spread by droplets; cause fever, pneumonia, septicaemia, meningitis | About 1 in 10 meningitis patients dies | Polysaccharide vaccine: Less than 1 in 20 has pain or local reaction.<br>Conjugate vaccine: About 1 in 10 has local reaction or fever. |
| Polio - contagious virus spread by faeces and saliva; causes fever, headache, vomiting and may progress to paralysis.. | While many infections cause no symptoms, about 1 in 20 hospitalised patients dies and 1 in 2 patients who survive is permanently paralysed. | OPV: Less than 1 in 100 recipients develops diarrhoea, headache and/or muscle pains. 1 in 2.5 million recipients or close contacts develops paralysis.<br>IPV: Local redness (1 in 3), pain (1 in 7) and swelling (1 in 10) common. Up to 1 in 10 has fever, crying, and decreased appetite. |
| Rubella - contagious virus spread by droplets; causes fever, rash, swollen glands, but causes severe malformations in babies of infected pregnant women. | About 5 in 10 patients develop a rash and painful swollen glands; 5 in 10 adolescents and adults have painful joints; 1 in 3000 develops thrombocytopenia (bruising or bleeding); 1 in 6000 develops inflammation of the brain; 9 in 10 babies infected during the first 10 weeks after conception will have a major congenital abnormality (such as deafness, blindness or heart defects). | About 1 in 10 has discomfort, local inflammation, or fever. About 1 in 20 has swollen glands, stiff neck, or joint pains. About 1 in 100 has a rash, which is non-infectious. Thrombocytopenia (bruising or bleeding) occurs after a first dose of MMR at a rate of about 1 in 30 500. |
| Tetanus -caused by toxin of bacteria in soil; causes painful muscle spasms, convulsions, lockjaw. | About 1 in 10 patients dies. The risk is greatest for the very young or old. | As for DTPa vaccine (see diphtheria). |
| Varicella (chickenpox) - caused by highly contagious virus; causes low-grade fever and vesicular rash.<br>Reactivation of the virus later in life causes herpes zoster (shingles). | 1 in 5000 patients develop encephalitis (brain inflammation). About 3 in 100 000 patients die.<br>Infection during pregnancy can result in congenital malformations in the baby. Onset of infection in the mother from 5 days before to 2 days after delivery 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. A mild varicella-like rash may develop in 3-5 per hundred recipients. |