PART 3: VACCINES LISTED BY DISEASE

3.1 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 2 recognised human cases of ABL infection, it has to be assumed that ABL has the same clinical features as rabies. The incubation period of rabies is usually 3 to 8 weeks, but can range from as short as a week to, on rare occasions, several years. The risk of rabies is higher, and the incubation period shorter, after severe and multiple wounds proximate to the central nervous system (such as on the head and neck) and in richly innervated sites (such as the fingers).

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, Japan, Papua New Guinea and Pacific Island nations 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, the licking of open wounds or saliva contact with intact mucous membranes are very rare.[2,3] Cases have been recorded after exposure to aerosols in a laboratory and in caves infested with rabid bats, and cases have been reported following tissue transplantation from donors who died with undiagnosed rabies.[1]

Although rabies in travellers is rare, such cases – always fatal – continue to be reported in the medical literature.[4,5] Travellers to rabies-endemic regions should be advised of the risk and to avoid close contact with either wild or domestic animals; this is particularly important for children. They should be advised about pre-travel (ie. pre-exposure) rabies vaccination (or, if appropriate, booster doses), and they should be advised on what to do should they be either bitten or scratched by an animal while abroad.

In Australia, 2 cases of a fatal rabies-like illness caused by ABL have been reported, one in 1996 and the other in 1998.[6] 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 several 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** – Sanofi Pasteur Pty Ltd. Each 1.0 mL monodose vial of lyophilised vaccine contains at least 2.5 IU inactivated rabies virus; 100–150 µg neomycin; ≤70 mg human serum albumin; trace of phenol red (indicator). 1.0 mL distilled water as diluent.
- **Rabipur Inactivated Rabies Virus Vaccine –** CSL Biotherapies/Novartis Vaccines. Each 1.0 mL monodose vial of lyophilised vaccine contains at least 2.5 IU inactivated rabies virus; trace amounts of neomycin, chlortetracycline and amphotericin B; may contain trace amounts of bovine gelatin. May contain traces of egg protein. 1.0 mL distilled water as diluent.

The Mérieux vaccine is a lyophilised, stabilised suspension of inactivated Wistar rabies virus that has been cultured on human diploid cells and then inactivated by beta-propiolactone. This human diploid cell vaccine (HDCV) is coloured off-white, but after reconstitution with the diluent it turns a pinkish colour due to the presence of phenol red. The vaccine does not contain a preservative.

Rabipur is a lyophilised, stabilised suspension of inactivated Flurey LEP rabies virus that has been cultured on purified chick embryo cells and then inactivated by beta-propiolactone. This purified chick embryo cell vaccine (PCECV) does not contain a preservative.

The above two vaccines, and other tissue culture vaccines, are interchangeable.

Rabies immunoglobulin

- **Imogam Rabies** – Sanofi Pasteur Pty Ltd (human rabies immunoglobulin). Each 1.0 mL contains IgG class human rabies antibodies with a minimum titre of 150 IU; 22.5 mg glycine; 1 mg sodium chloride. It is supplied in 2 mL and 10 mL vials.

Human rabies immunoglobulin (HRIG) is prepared by cold ethanol fractionation from the plasma of hyperimmunised human donors.

Transport, storage and handling

Transport according to *National Vaccine Storage Guidelines: Strive for 5*.[7] Rabies vaccine, diluent and HRIG should be transported and stored at +2°C to +8°C. Do not freeze. Reconstituted vaccine should be used immediately after reconstituting. The HRIG should be used immediately once the vial is opened.

Dosage and administration

NB. The doses of rabies vaccines are the same for both children and adults.

(i) Pre-exposure prophylaxis

The dose of rabies vaccine for pre-exposure prophylaxis is 1.0 mL by IM injection, on days 0, 7 and 28. (HDCV can also be given by the subcutaneous (SC) route.)

(ii) Post-exposure treatment

The dose of rabies vaccine for post-exposure treatment is 1.0 mL by IM injection, on days 0, 3, 7, 14 and 28–30. (HDCV can also be given by the SC route.) The dose of HRIG is 20 IU/kg body mass by infiltration around the wounds; the remainder of the dose should be administered 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 rabies.[8] Although data on the effectiveness of rabies vaccine as prophylaxis against ABL infection are limited, the available animal data[9] and clinical experience support its use. Pre-exposure prophylaxis simplifies the management of a subsequent exposure because fewer doses of vaccine are needed and because HRIG is not required. (Rabies immunoglobulin is often difficult, or even impossible, to obtain in many developing countries.)

Pre-exposure prophylaxis with rabies vaccine is 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),
- expatriates and travellers who will be spending prolonged periods (ie. more than a month) in rabies-endemic areas. (NB. This time interval, of more than a month, is arbitrary, and rabies has occurred in travellers following shorter periods of travel),[5]
- people working with mammals in rabies-endemic areas, and
- research laboratory personnel working with live lyssaviruses.

Pre-exposure prophylaxis for both ABL infection and rabies, for all ages, consists of a total of 3 IM (IM or SC if HDCV is used) injections of 1 mL of rabies vaccine, the second given 7 days after the first, and the third given 28 days after the first. Although the third dose can be given at 21 days,[1] there are no data to support the use of an even more accelerated schedule for those with limited time before travel to a rabies endemic area.

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, people with impaired immunity 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 are recommended for immunised people who have ongoing exposure to either ABL or rabies. People who work with live lyssaviruses in research laboratories should have rabies antibody titres measured every 6 months. If the titre is reported as inadequate (<0.5 IU/mL), they should have a booster dose. Others with 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 (ID) rabies vaccination for the prevention of ABL infection. Therefore, *ID pre-exposure administration of rabies vaccine should not be used for pre-exposure prophylaxis of ABL.*

Antibody titres are lower and wane more rapidly after ID compared to either IM or SC administration of rabies vaccine, and there may be a slow initial immune

response following exposure to rabies virus in those given ID rabies vaccine.[10] For these 2 reasons, *it is strongly recommended that the IM (IM or SC if HDCV is used) route be used for pre-exposure prophylaxis.*

However, the cost of IM (IM or SC if HDCV is used) rabies vaccination may be prohibitive for some travellers. In this circumstance, ID 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 ID technique,
- it must not be administered to anyone known to have impaired immunity,
- 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 ID vaccine.

The use of the ID route for rabies vaccination is the practitioner's own responsibility, as rabies vaccines are not licensed for use via this route in Australia. The ID 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 rabies exposures. Although data on the effectiveness of rabies vaccine and HRIG as post-exposure treatment against ABL infection are limited, the available animal data[9] and clinical experience support its use. 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 as soon as is practicable.[8] Both HRIG and rabies vaccine are available for post-exposure treatment from the relevant State/Territory health authorities (see Appendix 1, *Contact details for Australian, State and Territory Government health authorities and communicable disease control*).

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, the time lapsed since the exposure, the species of bat involved, and even if the bat was apparently normal in appearance and behaviour. (Although ABL is more likely to be found in bats that either appear unwell or are behaving abnormally,[11] 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 others at risk of exposure, be kept and arrangements promptly made 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 begin as soon as is practicable. Where a bat is tested at a reference laboratory and later found to be negative for ABL, then post-exposure treatment for individuals exposed to that bat can be discontinued.

The relevant State/Territory health authority should be contacted about any animal bite or scratch sustained in a rabies-endemic area. Dogs and monkeys comprise the usual exposures in Asia, Africa and Central and South America, but exposures to other mammals must also be assessed for potential rabies transmission. If a traveller presents >10 days after being bitten or scratched by either a dog or cat in an endemic country, and it can be reliably ascertained that the animal has remained healthy (>10 days after the exposure), post-exposure treatment is not required;[8,12] otherwise, a complete course of treatment should be administered, even if there has been a considerable delay in reporting the incident.

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).

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 (IM or SC if HDCV is used) injection; and (ii) HRIG (see below).

The volume of rabies 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 as soon as is practicable (day 0), and subsequent doses are given on days 3, 7, 14 and 28–30; deviations of a few days from this schedule are probably unimportant.[8] 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 <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 have impaired immunity. In such cases, the antibody titre should be measured 2 to 3 weeks after the dose given at 28–30 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.[13] 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 (see below).

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 vaccination course. 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. If the wounds are severe and the calculated volume of HRIG is inadequate for complete infiltration of all wounds (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;[8] such exposures are probably high-risk exposures because of the extensive nerve supply to the fingers and hand. 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 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.

Table 3.1.1: Summary of Australian bat lyssavirus and rabies post-exposure treatment for non-immune individuals

Treatment	Immediate (Day 0)	Follow-up
Local treatment	Thorough wound cleansing	
Rabies vaccine	1.0 mL	1.0 mL on days 3, 7, 14, 28–30
Human rabies immunoglobulin (150 IU/mL)	20 IU/kg – no later than 7 days after the first rabies vaccine dose	Do not give later than 7 days after the first rabies vaccine dose

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 (IM or SC if HDCV is used) 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 travelling abroad who are exposed to a potentially rabid animal may be given post-exposure treatment with vaccines not available in Australia. However, it is very likely that they will receive a cell culture derived vaccine, all of which (including both vaccines available in Australia) are considered interchangeable.[14]

Therefore, if a person has received a cell culture-derived vaccine abroad, the standard post-exposure treatment regimen should be continued in Australia with either HDCV or PCECV. If the post-exposure treatment was started overseas but HRIG was not given, and the person presents in Australia within 7 days of commencing post-exposure treatment, HRIG should be given as soon as is practicable (and within 7 days of the first rabies vaccine). If the person presents in Australia 8 days or more after commencing post-exposure treatment, then HRIG should be withheld.

Contraindications

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

A person with an anaphylactic sensitivity to eggs, or to egg proteins, should not receive PCECV; HDCV should be used instead.

Adverse events

Cell culture-derived vaccines are generally well tolerated. In a large study, the following adverse events were reported after administration of HDCV to adults: sore arm (15 to 25% very common), headache (5 to 8% common), malaise, nausea or both (2 to 5% common); and allergic oedema (0.1% uncommon).[14] Similar adverse event profiles have been reported for the PCECV; these reactions occur at the same rates in children.[14]

Although anaphylactic reactions are rare (approximately 1 per 10 000 vaccinations) following administration of HDCV, approximately 6% (common) of people receiving booster doses may experience allergic reactions.[14] 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.[14] NB. HDCV contains human albumin, whereas PCECV does not.

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 simple analgesics.

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.

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).

Use in 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.[15]

Variations from product information

Neither of the product information sheets (of the 2 vaccines available in Australia) mentions that they can be used for both pre-exposure prophylaxis and post-exposure treatment for ABL exposures.

The HDCV 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 a further dose should be offered to a person with impaired immunity who has an inadequate antibody level 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).

Rabies in Indonesia

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. Therefore, post-exposure treatment following animal bites sustained in Bali is currently not warranted, but obviously this situation could change.

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

References

Full reference list available on the electronic *Handbook* or website http://immunise.health.gov.au.

3.2 CHOLERA

Bacteriology

Vibrio cholerae is a motile, curved Gram-negative bacillus and differences in the O antigens have led to the description of more than 150 serogroups, only two of which have been found to cause cholera. Cholera is caused by enterotoxin producing *V. cholerae* of serogroups O1 and O139 (sometimes referred to as the 'Bengal' strain). Serogroup O1 includes 2 biotypes (classical and El Tor), each of which includes organisms of Inaba, Ogawa and Hikojima serotypes. The ability of *V. cholerae* to persist in water is determined by the temperature, pH, salinity and availability of nutrients; it can survive under unfavourable conditions in a viable dormant state.[1] Transmission predominantly occurs when people ingest faecally contaminated food or water.

Clinical features

Cholera is an acute bacterial infection that is generally characterised by the sudden onset of painless, profuse, watery diarrhoea. If untreated, more than half the severe cases will die. Mild cases also occur, as does subclinical infection.[1]

The cholera toxin does not produce intestinal inflammation. The cholera toxin induces secretion of increased amounts of electrolytes into the intestinal lumen, resulting in mild to severe dehydration and, in some cases, metabolic acidosis.

Epidemiology

Cases of cholera in Australia (about 2 to 6 cases a year) almost always occur in individuals who have been infected in endemic areas of Asia, Africa, the Middle East, South America or parts of Oceania.[2-4] The disease is usually transmitted via food and water contaminated with human excreta. Shellfish obtained from contaminated waters have also been responsible for outbreaks.[1]

In 1977, a locally acquired case led to the discovery of *V. cholerae* in some rivers of the Queensland coast.[5] Because of this, health workers should be aware that sporadic cases of cholera may, on rare occasions, follow contact with estuarine waters.

As the incubation period of the disease may extend up to 5 days, surveillance of household contacts or those exposed to a possible common source should be maintained for 5 days from the date of last exposure. Stool cultures (cultured using specific media) may be taken from close contacts if required. Food handlers should not be allowed to return to work until 2 consecutive stool samples, taken at least 24 hours apart, are negative. Contacts should also be advised to maintain high standards of personal hygiene to avoid becoming infected. Cases should be reported immediately to the public health authorities (for contact details, refer

to Appendix 1, *Contact details for Australian, State and Territory Government health authorities and communicable disease control*).

Vaccines

- **Dukoral** – Sanofi Pasteur Pty Ltd (inactivated whole-cell *V. cholerae* O1 in combination with a recombinant cholera toxin B subunit (rCTB)). Each 3.0 mL liquid vaccine dose vial contains heat and formalin inactivated Inaba, Ogawa, classic and El Tor strains of *V. cholerae* O1, 2.5 x 10^{10} vibrios of each, combined with 1.0 mg rCTB. The buffer consists of a sachet of effervescent granules of anhydrous sodium carbonate, sodium bicarbonate, anhydrous citric acid, sodium citrate, saccharin sodium and raspberry flavour.

Trials of the safety, immunogenicity and efficacy of oral vaccines, both killed and live attenuated, have been carried out in the United States, Bangladesh, Thailand, Indonesia, Chile, Peru and Switzerland.[6-12]

Trials of the inactivated vibrio combined with rCTB vaccine have been done mainly in Bangladesh and Peru.[9,13-16] In Bangladesh, a 2-dose regimen showed protective efficacy of 44% in children 2 to 6 years of age and 76% in adults at the end of 1 year, and 33% and 60%, respectively, after 2 years. The studies in Peru showed an overall efficacy of 61% in 2–65-year-olds. A recent study undertaken during a mass oral cholera vaccination program in Mozambique concluded that 1 or more doses of the inactivated oral cholera vaccine was 78% protective.[17]

To date, there is no vaccine marketed to protect against infection with *V. cholerae* O139. A killed oral whole cell cholera bivalent vaccine (against both serogroups O1 and O139) is currently being evaluated in Vietnam.[18,19]

A study in short-term Finnish tourists[20] showed that the inactivated oral cholera vaccine also provided a 60% reduction in diarrhoea caused by heat-labile toxin producing enterotoxigenic *E. coli* (LT-ETEC). A study in Bangladesh, an endemic area, showed 67% protection against LT-ETEC for 3 months only.[21] It can be expected that the inactivated vaccine will reduce the proportion of travellers' diarrhoea that is caused by LT-ETEC. Approximately 30 to 40% of travellers to developing countries contract travellers' diarrhoea, with an average of 20% of cases caused by LT-ETEC; hence, the 60% efficacy of the oral inactivated vaccine against LT-ETEC could be expected to prevent around 10 to 12% of travellers' diarrhoea.[22] However, in Australia this vaccine is only registered for the prevention of cholera.

Transport, storage and handling

Transport according to *National Vaccine Storage Guidelines: Strive for 5*.[23] Store in a refrigerator at +2°C to +8°C. Do not freeze. Protect from light.

Dosage and administration

For adults and children over the age of 6 years, Dukoral is administered orally after dissolving the buffer granules in 150 mL of water and adding the vaccine to the solution. Two doses are required, given a minimum of 1 week and up to 6 weeks apart. If the second dose is not administered within 6 weeks, re-start the vaccination.

For children aged 2–6 years, Dukoral is administered orally after dissolving the buffer granules in 150 mL of water. Half the solution is then poured away and the entire content of the vaccine vial is mixed with the remaining 75 mL. Children aged 2–6 years should receive 3 doses of the vaccine. Doses are to be administered with a minimum interval of 1 week between doses up to a maximum interval of 6 weeks. If an interval of more than 6 weeks occurs between any of the doses, re-start the vaccination.

Food and drink should be avoided for 1 hour before and 1 hour after administration of the inactivated cholera vaccine, as it is acid labile.

The inactivated oral cholera vaccine can be given at the same time as other travel vaccines. However, there should be an interval of at least 8 hours between the administration of the inactivated oral cholera and oral typhoid vaccines, as the buffer in the cholera vaccine may affect the transit of the capsules of oral typhoid vaccine through the gastrointestinal tract.

Adults and children >6 years of age should receive a single booster dose after 2 years and children 2–6 years of age should receive a booster dose 6 months after completion of the primary course.

Recommendations

Despite the endemicity of cholera in some countries often visited by Australians, routine cholera vaccination is not recommended as the risk to travellers is very low. Careful and sensible selection of food and water is of far greater importance to the traveller than vaccination.

Immunisation should be considered for people at increased risk of diarrhoeal disease, such as those with achlorhydria, and for people at increased risk of severe or complicated diarrhoeal disease, such as those with poorly controlled or otherwise complicated diabetes, inflammatory bowel disease, HIV/AIDS or other conditions resulting in impaired immunity, or significant cardiovascular disease. It could also be considered for humanitarian disaster workers.

Vaccination against cholera is not an official requirement for entry into any foreign country.

Contraindications

The only contraindications to the use of cholera vaccine are:

- anaphylaxis following a previous dose of the vaccine,
- anaphylaxis following any component of the vaccine,
- inactivated oral cholera vaccine is *not* recommended for children <2 years of age.

Precautions

- Postpone administration during either an acute febrile illness or acute gastrointestinal illness with persistent diarrhoea or vomiting, until recovered.
- Although the vaccine is not contraindicated in immune impaired individuals, including HIV-infected individuals, data on effectiveness in this population is limited.
- There should be an interval of at least 8 hours between the administration of the inactivated oral cholera and oral typhoid vaccines, as the buffer in the cholera vaccine may affect the transit of the capsules of oral typhoid vaccine through the gastrointestinal tract.

Adverse events

The inactivated oral vaccine is uncommonly (<1%) associated with mild gastrointestinal disturbances.

Use in pregnancy

There is inadequate information on the use of inactivated oral cholera vaccines during pregnancy and breastfeeding.[24]

Variations from product information

None.

References

Full reference list available on the electronic *Handbook* or website http://immunise.health.gov.au.

3.3 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 or, less commonly, on damaged skin, 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 respiratory droplets or by direct contact with skin lesions or articles soiled by infected individuals. Pharyngeal diphtheria is characterised by an inflammatory exudate which forms a greyish or green membrane in the upper respiratory tract 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.[1] 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.[2] The current epidemiology of diphtheria in Australia is similar to that in other developed countries. Almost all recent cases in the United Kingdom and the United States have been associated with imported infections.[3] Hence, there is still the possibility of an imported case occurring in Australia, particularly from developing countries, as occurred in 2001 when a case, acquired in East Timor, was notified in Australia.[4] There is now little possibility of acquiring natural immunity or boosting declining immunity with subclinical infection. It is therefore important for Australians to retain high levels of immunity through high vaccination coverage.

Disruption of vaccination programs following the collapse of the Soviet Union resulted in the re-emergence of diphtheria throughout the Newly Independent States. From 1991 to 1996, there were more than 140 000 cases and more than 4000 deaths.[5] Cases also occurred in neighbouring European countries and in visitors to the area. Mass vaccination eventually brought the epidemic under control.[6,7] This experience illustrates the importance of maintaining high levels of vaccination coverage against diphtheria.

Vaccines

Diphtheria toxoid is available in Australia only in combination with tetanus and other antigens.

The acronym DTPa, using capital letters, signifies child formulations of diphtheria, tetanus and acellular pertussis-containing vaccines. The acronym dTpa is used for adolescent/adult formulations which contain substantially lesser amounts of diphtheria toxoid and pertussis antigens (see formulations).

Formulations for children aged <8 years

- **Infanrix hexa** – GlaxoSmithKline (DTPa-hepB-IPV-Hib; diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliomyelitis vaccine-*Haemophilus influenzae* type b (Hib)). The vaccine consists of *both* a 0.5 mL pre-filled syringe containing 30 IU diphtheria toxoid, 40 IU tetanus toxoid, 25 µg pertussis toxoid (PT), 25 µg filamentous haemagglutinin (FHA), 8 µg pertactin (PRN), 10 µg recombinant HBsAg, 40 D-antigen units inactivated polioviruses type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett) adsorbed onto aluminium hydroxide/phosphate; phenoxyethanol as preservative; traces of formaldehyde, polymyxin and neomycin *and* a vial containing a lyophilised pellet of 10 µg purified Hib capsular polysaccharide (PRP) conjugated to 20–40 µg tetanus toxoid. The vaccine *must be reconstituted* by adding the entire contents of the syringe to the vial and shaking until the pellet is completely dissolved. May also contain yeast proteins.
- **Infanrix-IPV** – GlaxoSmithKline (DTPa-IPV; diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis vaccine). Each 0.5 mL pre-filled syringe contains 30 IU diphtheria toxoid, 40 IU tetanus toxoid, 25 µg PT, 25 µg FHA, 8 µg PRN, 40 D-antigen units inactivated polioviruses type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett) adsorbed onto aluminium hydroxide; phenoxyethanol as preservative; traces of formaldehyde, polymyxin and neomycin.
- **Infanrix Penta** – GlaxoSmithKline (DTPa-hepB-IPV; diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliomyelitis vaccine). Each 0.5 mL pre-filled syringe contains 30 IU diphtheria toxoid, 40 IU tetanus toxoid, 25 µg PT, 25 µg FHA, 8 µg PRN, 10 µg recombinant HBsAg, 40 D-antigen units inactivated polioviruses type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett) adsorbed onto aluminium hydroxide/phosphate; phenoxyethanol as preservative; traces of formaldehyde, polymyxin and neomycin. May also contain yeast proteins.

Formulations for people aged ≥8 years

Adsorbed diphtheria-tetanus vaccine

- **ADT Booster –** Statens Serum Institut/CSL Biotherapies (dT; diphtheria-tetanus, adult formulation). Each 0.5 mL pre-filled syringe or monodose vial contains ≥2 IU diphtheria toxoid and ≥20 IU tetanus toxoid adsorbed onto 0.5 mg aluminium hydroxide.

Combination vaccines

- **Adacel** – Sanofi Pasteur Pty Ltd (dTpa; diphtheria-tetanus-acellular pertussis). Each 0.5 mL monodose vial contains ≥2 IU diphtheria toxoid, ≥20 IU tetanus toxoid, 2.5 µg PT, 5 µg FHA, 3 µg PRN, 5 µg pertussis fimbriae (FIM) 2+3; 1.5 mg aluminium phosphate; phenoxyethanol as preservative; traces of formaldehyde.
- **Adacel Polio** – Sanofi Pasteur Pty Ltd (dTpa; diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis vaccine). Each 0.5 mL monodose vial contains ≥2 IU diphtheria toxoid, ≥20 IU tetanus toxoid, 2.5 µg PT, 5 µg FHA, 3 µg PRN, 5 µg FIM 2+3, 40 D-antigen units inactivated polioviruses type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett); 1.5 mg aluminium phosphate; phenoxyethanol as preservative; traces of formaldehyde, polymyxin, neomycin and streptomycin.
- **Boostrix** – GlaxoSmithKline (dTpa; diphtheria-tetanus-acellular pertussis). Each 0.5 mL monodose vial or pre-filled syringe contains ≥2 IU diphtheria toxoid, ≥20 IU tetanus toxoid, 8 µg PT, 8 µg FHA, 2.5 µg PRN, adsorbed onto 0.5 mg aluminium hydroxide/phosphate; 2.5 mg phenoxyethanol as preservative. May contain traces of formaldehyde.
- **Boostrix-IPV** – GlaxoSmithKline (dTpa-IPV; diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis vaccine). Each 0.5 mL pre-filled syringe contains ≥2 IU diphtheria toxoid, ≥20 IU tetanus toxoid, 8 µg PT, 8 µg FHA, 2.5 µg PRN, 40 D-antigen units inactivated polioviruses type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett) adsorbed onto aluminium hydroxide/phosphate; traces of formaldehyde, polymyxin and neomycin.

Diphtheria vaccination stimulates the production of antitoxin, which protects against the toxin produced by the organism. The immunogen is prepared by treating a cell-free preparation of toxin with formaldehyde, thereby converting it into the innocuous diphtheria toxoid. Diphtheria toxoid is usually adsorbed onto an adjuvant, either aluminium phosphate or aluminium hydroxide, to increase

its immunogenicity. Antigens from *Bordetella pertussis*, in combination vaccines, also act as an effective adjuvant.

Circulating levels of antitoxin are closely related to protection from diphtheria. Antitoxin levels of <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.[8] Complete immunisation induces protective levels of antitoxin lasting throughout childhood but, by middle age, at least 50% of vaccinees have levels <0.1 IU.[9-11] This has been confirmed in Australia by a recent national serosurvey.[12] Single low doses of toxoid in previously immunised adults induce protective levels within 6 weeks.[13]

Production of DT (CDT vaccine), registered for use in children <8 years of age, ceased in June 2005.

ADT Booster can be used for the booster dose of dT in people aged ≥8 years or, if necessary, for the primary dT course (see 'Variations from product information').

Transport, storage and handling

Transport according to *National Vaccine Storage Guidelines: Strive for 5*.[14] Store at +2°C to +8°C. Protect from light. Do not freeze.

Dosage and administration

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

Do not mix DTPa-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

The recommended primary course of vaccination is at 2, 4 and 6 months of age. A booster dose of DTPa is given at 4 years of age. Immunity to diphtheria will not be compromised before the booster dose, as the serological response to the primary course of vaccination is usually sufficient for those years. A second booster, using the adolescent/adult formulation, dTpa, at 12–17 years of age, is essential for maintaining immunity to diphtheria in adults. Vaccination against diphtheria is part of the National Immunisation Program (NIP) schedule, diphtheria toxoid being given in combination with tetanus toxoid and acellular pertussis as DTPa vaccine. Before the 8th birthday, DTPa-containing vaccines should be given, as they contain a larger dose of diphtheria toxoid. After the 8th birthday, smaller doses of toxoid (dT or adolescent/adult formulation dTpa) should be given. Dose reduction is necessary because of the increased incidence of local and systemic reactions to diphtheria toxoid in older children and adults.

For details on the management of children who have missed doses in the NIP schedule, see Section 1.3.5, *Catch-up*.

(ii) Vaccination of adults

Individuals who have not received any diphtheria vaccines are also likely to have missed tetanus vaccination. Three doses of dT should be received at minimum intervals of 4 weeks, followed by booster doses at 10 and 20 years after the primary course. It is prudent to give the first of these doses as dTpa, to also provide boosting to natural immunity from exposure to pertussis, which is almost universal in unvaccinated adults. In the event that dT vaccine is *not* available, dTpa can be used for all primary doses. This is not recommended routinely because there are no data on the safety, immunogenicity or efficacy of dTpa in multiple doses for primary vaccination.

All adults who reach the age of 50 years without having received a booster dose of dT in the previous 10 years should receive a further booster dose of dT, or preferably dTpa, if this has not been given previously, to also provide protection against pertussis.

(iii) Other people at special risk

Diphtheria can be a significant risk for travellers to some countries (particularly southeast Asia, the Newly Independent States of the former Soviet Union, Baltic countries or eastern European countries). Travellers to high-risk countries should receive a booster dose of dT (or dTpa) if they have not received one in the previous 10 years.

Contraindications

The only absolute contraindications to diphtheria vaccine are:

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

Adverse events

Mild discomfort or pain at the injection site persisting for up to a few days is common. Uncommon general adverse events following dT vaccine include headache, lethargy, malaise, myalgia and fever. Acute anaphylactic reactions, urticaria and peripheral neuropathy very rarely occur (brachial neuritis occurs in 0.001% of cases). (For specific adverse events following combination vaccines containing both diphtheria and pertussis antigens, see Chapter 3.14, *Pertussis*).

The public health management of diphtheria cases

A suspected case of diphtheria is of considerable public health importance, and should be notified immediately to the State/Territory public health authorities, who will advise on further management. In general, contacts of a proven or presumptive diphtheria case will require vaccination (either primary or booster, depending on vaccination status), and appropriate prophylactic antibiotics.[15]

Diphtheria antitoxin and penicillin should be given immediately to suspected cases. Do not wait for bacteriological confirmation of the disease. Diphtheria antitoxin derived 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, and 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. Expert advice should be sought with respect to antitoxin dose and special arrangements made if hypersensitivity is suspected. This can be coordinated through the relevant State/Territory health authority (see Appendix 1, *Contact details for Australian, State and Territory Government health authorities and communicable disease control*).

- **Diphtheria antitoxin** – This is currently available only through the Special Access Scheme.

Use in pregnancy

Refer to Chapter 2.3, *Groups with special vaccination requirements*, Table 2.3.1 *Vaccinations in pregnancy*.

Variations from product information

The product information for both Infanrix hexa and Infanrix Penta states that these vaccines may be given as a booster dose at 18 months of age. NHMRC recommends that a booster dose of DTPa (or DTPa-containing vaccines) is not necessary at 18 months of age. However, DTPa-containing vaccine may be used for catch-up of the primary schedule in children <8 years of age.

The product information for Infanrix-IPV states that this vaccine may be used as a booster dose for children ≤6 years of age who have previously been vaccinated against diphtheria, tetanus, pertussis and poliomyelitis. NHMRC recommends that booster doses of DTPa and IPV be given at 4 years of age; however, this product may be used for catch-up of the primary schedule or as a booster in children <8 years of age.

The product information for ADT Booster states that this vaccine is indicated for a booster dose only in children aged ≥5 years and adults who have previously received at least 3 doses of diphtheria and tetanus vaccines. NHMRC recommends that, where a dT vaccine is required for any person ≥8 years of age, ADT Booster can be used, including for primary immunisation against diphtheria and tetanus.

The product information for adolescent/adult formulations of dTpa-containing vaccines states that these vaccines are indicated for booster doses only. NHMRC recommends that, where dT is unavailable for the primary course, dTpa can be used.

The product information for Adacel and Boostrix (adolescent/adult formulations of dTpa) states that these vaccines are recommended for use in those aged >10 years. However, NHMRC recommends that they may be used in people aged ≥8 years. The product information also states that dTpa should not be given within 5 years of a tetanus toxoid-containing vaccine. However, NHMRC recommends that dTpa vaccines can be administered at any time following receipt of a diphtheria and tetanus toxoid-containing vaccine.

References

Full reference list available on the electronic *Handbook* or website http://immunise.health.gov.au.

3.4 *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 known as non-typable (NT). Six capsular types (a to f) have been described and, before the introduction of vaccination against *Haemophilus influenzae* type b (Hib), almost all *H. influenzae* isolates from sterile sites (blood, cerebrospinal fluid, joint or pleural fluid) were of the b capsular type.

Before Hib immunisation, invasive disease caused by Hib rarely occurred after the age of 5 years. This was because the prevalence of antibody to Hib progressively increased from the age of 2 years, thought to be related to exposure to Hib (or cross-reacting organisms) colonising the nasopharynx or other sites. Children <2 years of age are usually unable to mount an antibody response to the type b capsular polysaccharide, even after invasive disease.[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 <6 years of age every year, and a total of 10 to 15 deaths.[3] Hib meningitis accounted for approximately 60% of all invasive Hib disease, most cases occurring in children <18 months of age. 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.[4] Hib epiglottitis was a more common disease presentation than

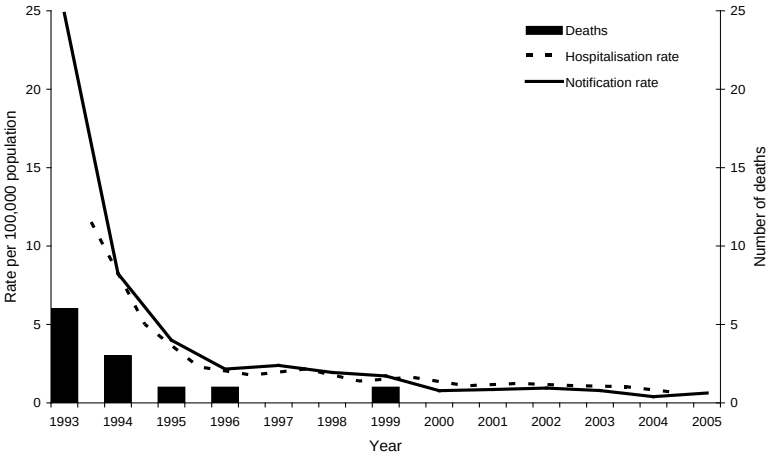
in many other countries,[5] and usually occurred in children >18 months of age. Other manifestations such as cellulitis, septic arthritis and pneumonia occurred at a similar age to meningitis.[6]

The incidence of Hib disease in Aboriginal and Torres Strait Islander children, especially those in remote and rural areas, was considerably higher than in non-Indigenous children.[7] Most importantly, the onset of Hib disease in this population was at a much younger age, manifesting mostly as meningitis, with epiglottitis being rare. Rates of death and long-term morbidity following Hib meningitis were similar to those observed in non-Indigenous children.[7]

(ii) After the introduction of 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 an average of 30 cases per year between 1999 and 2002, with approximately 15 cases per year currently reported in Australia (see Figure 3.4.1).[8] This reduction has been particularly marked in Indigenous children.[9] Similar impressive reductions in Hib disease have been seen in other countries with routine childhood vaccination.[5,10] 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.[11,12]

Figure 3.4.1: *Haemophilus influenzae* type b (Hib) notifications, presumed Hib hospitalisations and deaths* of children aged 0 to 4 years from Hib, Australia 1993 to 2005†[8]



* Hospitalisations and deaths include those for *Haemophilus* meningitis for the period up to 30 June 2005 (hospitalisations) and 31 December 2004 (deaths).

† Notifications where the month of diagnosis was between July 1993 and December 2005; hospitalisations where the month of admission was between 1 July 1993 and 30 June 2005; deaths where the date of death was recorded between January 1993 and December 2004.

Vaccines

The first generation Hib vaccines, consisting of purified polysaccharide (PRP) from the Hib capsule, were not effective in children <18 months of age. A review of the efficacy data for the second generation Hib vaccines, which consist of PRP chemically linked ('conjugated') to a variety of carrier proteins, found 3 of the 4 Hib vaccines to be immunogenic against invasive Hib disease, PRP-OMP, PRP-T and HbOC.[13] The fourth vaccine, PRP-D, was not found to be highly protective in high-risk populations, such as Indigenous children.[13]

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) (COMVAX, Liquid PedvaxHIB) gives protective PRP antibody responses after the first dose, and requires only 2 doses to complete the primary course. For this reason, its main application worldwide has been in populations with a high incidence of early onset disease.[5] Vaccines using other protein carriers such as tetanus (PRP-T) (Hiberix, Infanrix hexa) and diphtheria (HbOC) toxoids do not achieve protective PRP antibody levels until at least a second dose has been given, and

require 3 doses to complete primary immunisation. No or minimal immunologic interference has been observed when children are vaccinated with 7vPCV and Infanrix hexa at the same immunisation visit.[14,15]

Many Hib combination vaccines containing acellular pertussis are known to produce lower Hib antibody responses than similar formulations containing whole-cell pertussis.[16] When administered according to the United Kingdom's schedule as 3 primary doses at 2, 3 and 4 months of age without a booster, their use has been associated with an increased risk of vaccine failure.[17] In other European countries that routinely give a fourth dose around the time of the 1st birthday, as is included in the Australian schedule, no loss of effectiveness has been observed.[18,19]

- **Liquid PedvaxHIB** – CSL Biotherapies/Merck & Co Inc (PRP-OMP). Each 0.5 mL monodose vial contains 7.5 µg PRP conjugated to 125 µg meningococcal protein; liquid formulation with 35 µg borax and 225 µg aluminium hydroxide.
- **Hiberix** – GlaxoSmithKline (PRP-T). Each 0.5 mL monodose lyophilised vaccine contains 10 µg PRP conjugated to 30 µg tetanus toxoid (with a lactose stabiliser) for reconstitution with 0.9% saline.

Combination vaccines that include Hib

- **COMVAX** – CSL Biotherapies/Merck & Co Inc (Hib (PRP-OMP)-hepatitis B). Each 0.5 mL monodose vial contains 7.5 µg PRP conjugated to 125 µg meningococcal protein, 5 µg hepatitis B surface antigen; 225 µg aluminium hydroxide; 35 µg borax. May contain yeast proteins.
- **Infanrix hexa** – GlaxoSmithKline (DTPa-hepB-IPV-Hib; diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliomyelitis vaccine-*Haemophilus influenzae* type b (Hib)). The vaccine consists of *both* a 0.5 mL pre-filled syringe containing 30 IU diphtheria toxoid, 40 IU tetanus toxoid, 25 µg pertussis toxoid (PT), 25 µg filamentous haemagglutinin (FHA), 8 µg pertactin (PRN), 10 µg recombinant HBsAg, 40 D-antigen units inactivated polioviruses type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett) adsorbed onto aluminium hydroxide/phosphate; phenoxyethanol as preservative; traces of formaldehyde, polymyxin and neomycin *and* a vial containing a lyophilised pellet of 10 µg purified Hib capsular polysaccharide (PRP) conjugated to 20–40 µg tetanus toxoid. The vaccine *must be reconstituted* by adding the entire contents of the syringe to the vial and shaking until the pellet is completely dissolved. May also contain yeast proteins.

Transport, storage and handling

Transport according to *National Vaccine Storage Guidelines: Strive for 5*.[20] Store conjugate Hib vaccines at +2°C to +8°C. Do not freeze.

Dosage and administration

The dose of Hib vaccine is 0.5 mL to be given by IM injection. Conjugate Hib vaccines may be administered in separate sites on the same day as any of the other childhood vaccines such as the 7-valent pneumococcal conjugate (7vPCV), meningococcal serogroup C conjugate (MenCCV), hepatitis B, DTPa-containing and monovalent IPV (or IPV-containing) vaccines.

Recommendations

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

Immunisation using PRP-OMP (COMVAX or Liquid PedvaxHIB) requires 2 primary doses at 2 and 4 months, followed by a booster at 12 months of age. If PRP-T (Infanrix hexa or Hiberix) is used, 3 primary doses at 2, 4 and 6 months are needed, with a booster at 12 months of age.

(ii) Indigenous children living in the Northern Territory, Queensland, South Australia and Western Australia

Many Indigenous populations experienced high Hib attack rates associated with early peak disease onset before the introduction of Hib immunisation. While vaccination has reduced the overall incidence of invasive Hib infection in these vulnerable groups, increased disease risk during the first year of life remains. It is therefore important that Aboriginal and Torres Strait Islander children in jurisdictions (the Northern Territory, Queensland, South Australia and Western Australia) where such different patterns of Hib disease remain evident continue to receive PRP-OMP, because of the early antibody response seen with this vaccine.[7] In Alaskan natives, who experienced similar pre-vaccination attack rate profiles, re-emergence of Hib disease was observed when the Hib vaccine in use was changed from PRP-OMP to HbOC.[21]

(iii) Non-Indigenous children and Indigenous children living in Australian Capital Territory, New South Wales, Tasmania and Victoria

Any licensed Hib vaccine may be used in these children as the period of significant risk does not begin until after 6 months of age. Although there are limited data on the epidemiology of Hib disease before vaccination in Indigenous children in south-eastern Australia, available data since vaccination commenced in 1993 suggest that the epidemiology in these children does not differ substantially from that in non-Indigenous children living in these areas (NCIRS data, unpublished).

(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.[22] 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.[23] 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 >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 Section 1.3.5, *Catch-up*.

(v) Vaccine failures

Children who have developed confirmed Hib disease after 2 or more doses of PRP-OMP or 3 or more doses of PRP-T may warrant immunological investigation. Consultation with an immunologist with paediatric expertise is recommended.

(vi) Preterm babies

Preterm babies can be immunised at the normal age, without correction for prematurity[24] (see Section 2.3.2, *Vaccination of women planning pregnancy, pregnant or breastfeeding women, and preterm infants*). Extremely preterm babies (<28 weeks' gestation or <1500 g birth weight) who are vaccinated with PRP-OMP should be given an extra dose at 6 months of age, resulting in a 4-dose schedule at 2, 4, 6 and 12 months of age.[25] When other Hib vaccines, including Infanrix hexa, are used, no change in the usual schedule is required. Preterm babies have been shown to produce good antibody responses to all the antigens in Infanrix hexa following administration at 2, 4 and 6 months of age, although the responses to hepatitis B and Hib are not quite as high as in term babies.

(vii) Splenectomy

Hib is an uncommon cause of post-splenectomy sepsis in adults and children. Children >2 years of age who have received all scheduled doses of Hib vaccine do not require a booster dose after splenectomy. A single dose of Hib vaccine is recommended for other splenectomised individuals who were not vaccinated in infancy or are incompletely vaccinated. The vaccine should be given 2 weeks before a planned splenectomy. Subsequent booster doses of Hib vaccine are not required.[26] For other recommendations for asplenic or splenectomised individuals, see Section 2.3.3, *Vaccination of individuals with impaired immunity due to disease or treatment*.

(viii) Allogeneic and autologous haematopoietic stem cell transplant (HSCT) recipients

These patients should also be considered for Hib vaccination post transplant. The Hib conjugate vaccine should be administered to recipients at 12, 14, and 24 months after HSCT. See Section 2.3.3, *Vaccination of individuals with impaired immunity due to disease or treatment*.

Contraindications

The only contraindications to any of the Hib vaccines are:

- anaphylaxis following a previous dose of any of the vaccines, or
- anaphylaxis following any component of the vaccine.

Adverse events

Swelling and redness at the injection site after the first dose are common and have been reported in up to 5% of vaccinated children. Fever in up to 2% (common) has also been reported. These adverse events usually appear within 3 to 4 hours and resolve completely within 24 hours. The incidence of these adverse events declines with subsequent doses, so it is recommended that the course of vaccination be completed regardless.

The public health management of contacts of a child with invasive Hib disease

Healthcare workers should be guided by public health authorities in the public health management of cases of invasive Hib disease.

Household

As the incidence of invasive Hib disease is now very low, rifampicin chemoprophylaxis is no longer routinely indicated *unless* the household contains either:

- an infant <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, *everybody in the household* should receive rifampicin prophylaxis after 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.

Childcare facilities

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 <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 a case.

Use in pregnancy

Refer to Chapter 2.3, *Groups with special vaccination requirements*, Table 2.3.1 *Vaccinations in pregnancy*.

Variations from product information

The product information for Hib vaccines recommends the vaccine for use in children aged 2 months to 5 years. NHMRC recommends administration of Hib vaccine to older people with asplenia or following either allogeneic or autologous haematopoietic stem cell transplantation.

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

The product information for Infanrix hexa states that this vaccine may be given as a booster dose at 18 months of age. NHMRC recommends that a booster dose of DTPa (or DTPa-containing vaccines) is not necessary at 18 month of age. However, DTPa-containing vaccine may be used for catch-up of the primary schedule in children <8 years of age.

References

Full reference list available on the electronic *Handbook* or website http://immunise.health.gov.au.

3.5 HEPATITIS A

Virology

Hepatitis A is an acute infection of the liver caused by a hepatovirus, the hepatitis A virus (HAV).[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.

Clinical features

Hepatitis A is an infection of humans; there is no animal reservoir. HAV is predominantly transmitted by the faecal-oral route. The infecting dose is unknown but it is presumed to be low. The incubation period of hepatitis A is 15 to 50 days, with a mean of about 30 days.[1] HAV is excreted in faeces for up to 2 weeks before the onset of illness and for at least 1 week afterwards.[1]

In young children, HAV usually causes either an asymptomatic infection or a very mild illness without jaundice. 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 2 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.[2] 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] Serum anti-HAV IgG indicates past infection (or possibly immunisation) and therefore immunity; it probably persists for life.

Epidemiology

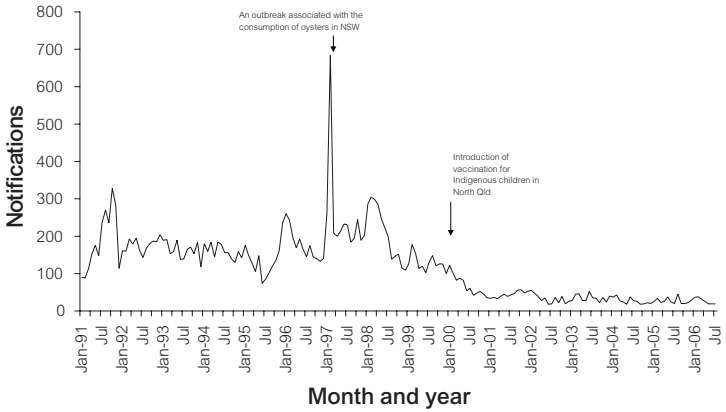
Hepatitis A was a considerable public health problem in Australia in the 1990s. During this time numerous outbreaks occurred in child day-care centres and preschools,[3] communities of men who have sex with men,[4] schools and residential facilities for the intellectually disabled,[5] and communities of injecting drug users.[4] A very large outbreak of hepatitis A associated with the consumption of raw oysters occurred in New South Wales in 1997 (see Figure 3.5.1).[6]

However, there has been a marked decline in notifications of hepatitis A in Australia in recent years (see Figure 3.5.1). This is probably a consequence of

the liberal use of hepatitis A vaccine among travellers, and those at increased risk because of lifestyle or occupation. A hepatitis A vaccination program for Indigenous children in north Queensland that began in 1999 has also contributed substantially to the decline in notifications.[7]

Nevertheless, Indigenous Australian children remain at considerably greater risk, not only of acquiring hepatitis A but also for being hospitalised with the infection, compared to non-Indigenous children.[8] This is particularly true for Indigenous children residing in other regions of Queensland, the Northern Territory, South Australia and Western Australia.

Figure 3.5.1: Notifications of hepatitis A in Australia, 1991 to 2006



Vaccines

- **Avaxim** – Sanofi Pasteur Pty Ltd (formaldehyde inactivated hepatitis A virus (GBM strain)). Each 0.5 mL pre-filled syringe contains 160 ELISA units of hepatitis A virus (HAV) antigens inactivated by formaldehyde; 0.3 mg aluminium hydroxide; 2.5 µL phenoxyethanol; 12.5 µg formaldehyde; trace of neomycin.
- **Havrix Junior** – GlaxoSmithKline (formaldehyde inactivated hepatitis A virus (HM175 strain)). Each 0.5 mL monodose vial or pre-filled syringe contains 720 ELISA units of HAV antigens; 0.25 mg as aluminium hydroxide; 0.5% w/v phenoxyethanol; traces of formaldehyde and neomycin.
- **Havrix 1440** – GlaxoSmithKline (formaldehyde inactivated hepatitis A virus (HM175 strain)). Each 1.0 mL monodose vial or pre-filled syringe contains 1440 ELISA units of HAV antigens; 0.5 mg aluminium hydroxide; 0.5% w/v phenoxyethanol; traces of formaldehyde and neomycin.

- **Twinrix Junior (360/10)** – GlaxoSmithKline (formaldehyde inactivated hepatitis A virus (HM175 strain) and recombinant hepatitis B vaccine). Each 0.5 mL monodose vial or pre-filled syringe contains 360 ELISA units of HAV antigens, 10 µg recombinant DNA hepatitis B surface antigen protein; 0.225 mg aluminium phosphate/hydroxide; 0.5% w/v phenoxyethanol; traces of formaldehyde and neomycin. May contain yeast proteins.
- **Twinrix (720/20)** – GlaxoSmithKline (formaldehyde inactivated hepatitis A virus (HM175 strain) and recombinant hepatitis B vaccine). Each 1.0 mL monodose vial or syringe contains 720 ELISA units of HAV antigens, 20 µg recombinant DNA hepatitis B surface antigen protein; 0.45 mg aluminium phosphate/hydroxide; 0.5% w/v phenoxyethanol; traces of formaldehyde and neomycin. May contain yeast proteins.
- **VAQTA Paediatric/Adolescent formulation** – CSL Biotherapies/Merck & Co Inc (formaldehyde inactivated hepatitis A virus (CR326F strain)). Each 0.5 mL monodose vial contains approximately 25 units (U) of hepatitis A virus protein; 0.225 mg aluminium hydroxide; 35 µg borax; trace of formaldehyde.
- **VAQTA Adult formulation** – CSL Biotherapies/Merck & Co Inc (formaldehyde inactivated hepatitis A virus (CR326F strain)). Each 1.0 mL monodose vial contains approximately 50 units (U) of hepatitis A virus protein; aluminium 0.45 mg as aluminium hydroxide; 70 µg borax; trace of formaldehyde.
- **Vivaxim** – Sanofi Pasteur Pty Ltd (inactivated hepatitis A virus and typhoid Vi capsular polysaccharide). Supplied in a unique dual-chamber syringe which enables the 2 vaccines to be mixed just before administration. Each 1.0 mL dose of mixed vaccine contains 160 ELISA units of inactivated hepatitis A virus antigens, 25 µg purified typhoid capsular polysaccharide; 0.3 mg aluminium hydroxide; 2.5 µL phenoxyethanol; formaldehyde; traces of neomycin 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 onto aluminium hydroxide adjuvant. Although the vaccines are prepared from differing strains of HAV, there is only one known serotype; immunity induced by a particular strain probably provides protection against all strains.[1]

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, the 'equivalent' vaccines of the different manufacturers are interchangeable.

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, serological testing to assess immunity after vaccination against hepatitis A is neither necessary nor appropriate.* Likewise, it is also inappropriate to undertake testing if an individual cannot recall if he/she has been vaccinated against hepatitis A in the past; if no vaccination records are available, vaccination should be advised.

Hepatitis A vaccines are highly immunogenic in both children and adults, with virtually universal seroconversion 4 weeks after vaccination.[1] Two randomised clinical trials conducted in the early 1990s showed that the vaccines have a very high protective efficacy, approaching 100%.[9,10] This finding is supported by the apparent eradication of hepatitis A from Indigenous communities in north Queensland since the introduction of the vaccination program in the region.[7]

The duration of immunity and, therefore, protection following vaccination is not certain. However, vaccine-induced anti-HAV probably persists for many years. There is no current evidence that booster doses are required; in healthy individuals, it is quite possible that they will never be required.[11]

Transport, storage and handling

Transport according to *National Vaccine Storage Guidelines: Strive for 5*.[12] Hepatitis A vaccines should be transported and stored at +2°C to +8°C. Do not freeze.

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 3.5.1.

Table 3.5.1: Recommended dosages and schedules for use of the inactivated hepatitis A vaccines

Vaccine	Vaccinee's age (years)	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– <16	720 EIA U	0.5	0, 6 to 12 mo
Havrix 1440	≥16	1440 EIA U	1.0	0, 6 to 12 mo
VAQTA Paediatric/ Adolescent	1– <18	25 U	0.5	0, 6 to 18 mo
VAQTA Adult	≥18	50 U	1.0	0, 6 to 18 mo
Combination hepatitis A/hepatitis B vaccines				
Twinrix Junior (360/10)	1– <16	360 EIA U	0.5	0, 1, 6 mo
Twinrix (720/20)	≥16	720 EIA U	1.0	0, 1, 6 mo
Twinrix (720/20)*	1– <16	720 EIA U	1.0	0, 6 to 12 mo
Twinrix (720/20)†	≥16	720 EIA U	1.0	0, 7, 21 days, 12 mo
Combination hepatitis A/typhoid vaccine				
Vivaxim	≥16	160 EIA U	1.0 (mixed vaccine)	0; a single dose of monovalent adult formulation hepatitis A vaccine should be given at 6 to 36 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 be used only if there is very limited time before departure to either moderately or highly endemic regions.

Recommendations

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

- those born before 1950,
- those who spent their early childhood in endemic areas, and
- those with an unexplained previous episode of hepatitis or jaundice. (NB. Such a previous episode cannot be assumed to be hepatitis A.)

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

(i) Hepatitis A vaccination is recommended for:

- **all travellers to, and all expatriates living in, moderately to highly endemic areas (including all developing countries)**

A single dose of a monovalent hepatitis A vaccine provides protective levels of anti-HAV for at least a year;[1] the second dose is recommended to increase the duration of protection. As they do not contain live viruses, hepatitis A vaccines can be administered either simultaneously with, or within a month of, all other vaccines relevant to international travel.[13]

There is no place for the routine use of normal human immunoglobulin to prevent hepatitis A in travellers. It should only be given (at the same time as hepatitis A vaccine) to those, such as aid-workers about to be deployed in emergency refugee camps, who will be living in very inadequate circumstances. Otherwise, it is only recommended for contacts of hepatitis A cases (see 'The public health management of contacts of hepatitis A cases' below).

- **Aboriginal and Torres Strait Islander children residing in the Northern Territory, Queensland, South Australia and Western Australia**

Hepatitis A vaccination for these children should commence in the second year of life. State/Territory health authorities should be contacted about the local hepatitis A vaccination schedules, including catch-up.

- **those whose occupation may put them at risk of acquiring hepatitis A**

This includes those who live or work in rural and remote Indigenous communities, child day-care and preschool personnel, carers of people with intellectual disabilities, healthcare workers who regularly provide care for Aboriginal and Torres Strait Islander children, plumbers or sewage workers, and sex workers.

- **those whose lifestyle may put them at risk of acquiring hepatitis A**

This includes men who have sex with men, and injecting drug users.

- **people with intellectual disabilities**
- **people chronically infected with either hepatitis B or hepatitis C viruses**
- **patients with chronic liver disease**

Hepatitis A vaccination is recommended for patients with chronic liver disease of any aetiology. Those with chronic liver disease of mild to moderate severity mount a satisfactory immune response following vaccination, but those with end-stage liver disease do not respond as well, and liver transplant recipients may not respond at all.[14,15] Nevertheless, all those with chronic liver disease should be vaccinated, preferably as early in the course of the disease as possible.

(ii) Combined hepatitis A/hepatitis B vaccines

Combined hepatitis A/hepatitis B vaccines should be considered for:

- 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.[16] This consists of a single dose on each of days 0, 7 and 21. It is important that a fourth dose be given as a booster 12 months after the first dose to ensure longer-term protection.
- medical, dental and nursing undergraduate students,
- men who have sex with men,
- sex industry workers,
- injecting drug users,
- patients with chronic liver disease,
- solid organ transplant recipients (see Table 2.3.2 *Recommendations for vaccinations for solid organ transplant (SOT) recipients*),
- people with intellectual disabilities and their carers.

NB. Twinrix (720/20) can be administered in a 2-dose regimen in people 1 to 15 years of age (see Table 3.5.1). However, this regimen should not be used in those who require prompt protection against hepatitis B; for example, if there is close contact with a known hepatitis B carrier.

Combined hepatitis A/hepatitis B vaccines can be administered simultaneously with, or within a month of, all other vaccines relevant to international travel.

(iii) Combined hepatitis A/typhoid vaccine

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

A single dose of a monovalent adult formulation hepatitis A vaccine 6 to 36 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 a monovalent adult formulation hepatitis A vaccine. This may be given 6 to 36 months after primary vaccination.

Contraindications

The only contraindications to any of the hepatitis A vaccines are:

- anaphylaxis following a previous dose of any of the hepatitis A vaccines, or
- anaphylaxis following any component of the vaccine.

Combination vaccines containing the hepatitis B component are contraindicated where there is a history of anaphylaxis to yeast.

Adverse events

The most common adverse events following administration of hepatitis A vaccines are mild local events of a short duration, probably caused by the aluminium hydroxide adjuvant. About 15% (very common) of adults report headache and approximately 5% (common) report malaise or fatigue following vaccination.[17] Up to 20% (very common) 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.[17]

Hepatitis A vaccines do not affect liver enzyme levels. They can be safely given to HIV-infected people, and do not adversely affect either the HIV load or CD4 cell count.[18]

The public health management of contacts of hepatitis A cases

Normal human immunoglobulin (NHIG) can be used to prevent secondary cases in close contacts of hepatitis A cases. (NB. A hepatitis A IgM positive test in an adult without either clinical or epidemiological features of hepatitis A should be considered as a false-positive result.[19] In this circumstance, no interventions are necessary for the close contacts.)

NHIG should be administered to close contacts within 2 weeks (of the last exposure to the cases) in the doses given in Table 3.5.2; NHIG may not be effective if given >2 weeks after the exposure.[17] 'Close contacts' are those who have had contact with a case during the 2 weeks before, up until 1 week after, the onset of jaundice, and usually include only household and/or sexual contacts (but in some circumstances may include close occupational exposure).

Table 3.5.2: Recommended doses of normal human immunoglobulin (NHIG) to be given as a single intramuscular injection to close contacts of hepatitis A cases

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

Although 1 study suggests that hepatitis A vaccine may be effective in preventing secondary cases of hepatitis A in close contacts,[20] there is currently insufficient evidence to be able to recommend it for this purpose.

Further public health considerations

If a person with hepatitis A was a food-handler by occupation while infectious, a review of the food-handling procedures in the food establishment should be undertaken and the staff at the establishment reminded of standard food and personal hygiene practices.[17] If the review identifies issues which raise the possibility of transmission of HAV, NHIG should be administered to the other food-handlers in the establishment. State/Territory public health authorities should determine the need for recall of customers of the establishment for NHIG. A food-handler with hepatitis A should be excluded from work until at least 1 week after the onset of jaundice.

A single case of hepatitis A associated with a day-care or preschool facility (ie. a case in an attendee child, a staff member or a household contact of an attendee or staff member) does not require any mass intervention.[3] However, the supervisor of the facility should be contacted to:

- explore the possibility of within-centre transmission by the case (eg. faecal accidents, other hygiene control concerns), and
- determine if there could be other cases associated with the facility. In particular, it should be ascertained whether an attendee child arrived from an endemic region overseas about a month before the case's onset, and whether any other children at the facility have recently been vaguely unwell with a change in bowel motions.

Should there be any concerns about the potential for further transmission of hepatitis A virus within the facility, mass interventions (as per 2 or more cases below) may be considered. The supervisor should be reminded of the relevant infection control practices that should be in place at all times at the facility, and that hepatitis A vaccine is routinely recommended for day-care and preschool staff (unless they have either had hepatitis A in the past or been vaccinated previously). A useful reference is 'Staying Healthy in Child Care' available at http://www.nhmrc.gov.au/publications/synopses/ch43syn.htm.

Two or more cases of hepatitis A (associated with the same day-care or preschool facility) that occur in different households are strongly suggestive that transmission of HAV is occurring within that facility.[3] These cases may be in attendee children or staff or household contacts of an attendee or staff member. As soon as transmission of HAV is recognised within a day-care or preschool facility, NHIG should be offered to children and susceptible staff in the relevant age groups (or classes) at that facility. Parents and staff need to be reminded that live virus vaccines, MMR and varicella vaccines in particular, should not be administered within 3 months of receiving IM NHIG.[3]

Use in pregnancy

Refer to Chapter 2.3, *Groups with special vaccination requirements*, Table 2.3.1 *Vaccinations in pregnancy*.

Variations from product information

None.

References

Full reference list available on the electronic *Handbook* or website http://immunise.health.gov.au.

3.6 HEPATITIS B

Virology

Hepatitis B virus (HBV) contains partially double-stranded DNA. The outer surface of the virus is glycolipid which contains the hepatitis B surface antigen (HBsAg). Other important antigenic components are hepatitis B core antigen (HBcAg), and hepatitis B e antigen (HBeAg). HBcAg is not detectable in serum, but can be detected in liver tissue in 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 and HBV DNA are positive.[1]

Clinical features

In approximately 30 to 50% of adults, infection causes symptomatic acute hepatitis, but in young children, particularly those <1 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 usually to 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, and the passage of dark-coloured urine and light-coloured stools. Jaundice may be preceded by an acute febrile illness with arthralgia or arthritis and rash, most typical of hepatitis B. During recovery, malaise and fatigue may persist for many weeks. Fulminant hepatitis occurs in approximately 1% of acute cases.[1,2]

Following acute infection, 1 to 10% of those infected as adults[2,3] and up to 90% of those infected as neonates[1,2] remain persistently infected for many years (see Figure 3.6.1). Chronically infected carriers of HBV are identified by the long-term presence (longer than 6 months) of circulating HBsAg.[4]

Figure 3.6.1: The influence of age of infection with the hepatitis B virus on the likelihood of becoming a hepatitis B carrier

(Modified and used with permission from: Edmunds WJ, Medley GF, Nokes DJ, Hall AJ, Whittle HC. The influence of age on the development of the hepatitis B carrier state. *Proceedings. The Royal Society Biological Sciences.*1993;253:197-201.)

Carriers of HBV are capable of transmitting the disease, though 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 more than 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 some Australian Aboriginal populations, and greater than 10% in many sub-Saharan African, southeast Asian and Pacific island populations.[5-7] First-generation immigrants usually retain the carrier rate of their country of origin, but subsequent generations show a declining carrier rate irrespective of vaccination.[5]

Transmission of hepatitis B may result from percutaneous inoculation or mucosal contact with blood or sexual secretions from an HBsAg-positive individual. Screening of blood and organ donors has virtually eliminated the risk of transmission of hepatitis B through blood transfusion and organ transplants.[8,9] Saliva may also contain levels of virus which are likely to be infective only if inoculated directly into tissue (ocular or mucous membranes). Transmission by inadvertent parenteral inoculation, such as by toothbrush, razor etc., through close personal contact in households in which 1 or more carriers or other infected individuals reside, is a low but significant risk.

Routes of transmission include:

- sharing injecting equipment (such as occurs in injecting drug use),
- needle-stick injury, and other types of parenteral inoculation,

- sexual contact (including heterosexual or homosexual intercourse, although the latter has a higher risk),
- transmission from infected mother to neonate (vertical transmission), usually occurring at or around the time of birth,
- child-to-child (horizontal) transmission, usually through contact between open sores or wounds,
- breastfeeding,[10]
- nosocomial transmission in overseas healthcare facilities if infection control procedures are unsatisfactory.

Australian vaccination policy

The initial strategy for the control of hepatitis B in Australia commenced in 1988, targeting groups at particular risk of infection for vaccination at birth. In addition to vaccine, hepatitis B immunoglobulin (HBIG) was given if the mother was a hepatitis B carrier. In 1990, universal infant vaccination commenced in the Northern Territory. 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, with the first dose given at birth, 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 1.0 mL monodose vial contains 20 µg recombinant hepatitis B surface antigen (HBsAg) protein, adsorbed onto 0.5 mg aluminium hydroxide. **Paediatric formulation** – Each 0.5 mL monodose vial contains 10 µg HBsAg protein, adsorbed onto 0.25 mg aluminium hydroxide. Both formulations contain traces of yeast proteins and thiomersal (<2 µg/mL). Both are available in packs of 10.
- **H-B-VAX II** – CSL Biotherapies/Merck & Co Inc (recombinant DNA hepatitis B vaccine). **Adult formulation preservative free** – Each 1.0 mL pre-filled syringe or vial contains 10 µg recombinant HBsAg protein, adsorbed onto 0.5 mg aluminium hydroxide. May contain yeast proteins. **Paediatric formulation preservative free –** Each 0.5 mL pre-filled syringe or vial contains 5 µg recombinant HBsAg protein, adsorbed onto 0.25 mg aluminium hydroxide. May contain yeast proteins. Both are available in packs of 10. **Dialysis formulation preservative free –** Each 1.0 mL vial contains 40 µg recombinant HBsAg protein, adsorbed onto 0.5 mg aluminium hydroxide. May contain yeast proteins. Available as single pack only.

Combination vaccines that include both DTPa and hepatitis B

- **Infanrix hexa** – GlaxoSmithKline (DTPa-hepB-IPV-Hib; diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliomyelitis vaccine-*Haemophilus influenzae* type b (Hib)). The vaccine consists of *both* a 0.5 mL pre-filled syringe containing 30 IU diphtheria toxoid, 40 IU tetanus toxoid, 25 µg pertussis toxoid (PT), 25 µg filamentous haemagglutinin (FHA), 8 µg pertactin (PRN), 10 µg recombinant HBsAg, 40 D-antigen units inactivated polioviruses type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett) adsorbed onto aluminium hydroxide/phosphate; phenoxyethanol as preservative; traces of formaldehyde, polymyxin and neomycin *and* a vial containing a lyophilised pellet of 10 µg purified Hib capsular polysaccharide (PRP) conjugated to 20–40 µg tetanus toxoid. The vaccine *must be reconstituted* by adding the entire contents of the syringe to the vial and shaking until the pellet is completely dissolved. May also contain yeast proteins.
- **Infanrix Penta** – GlaxoSmithKline (DTPa-hepB-IPV; diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliomyelitis vaccine). Each 0.5 mL pre-filled syringe contains 30 IU diphtheria toxoid, 40 IU tetanus toxoid, 25 µg PT, 25 µg FHA, 8 µg PRN, 10 µg recombinant HBsAg, 40 D-antigen units inactivated polioviruses type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett) adsorbed onto aluminium hydroxide/phosphate; phenoxyethanol as preservative; traces of formaldehyde, polymyxin and neomycin. May also contain yeast proteins.

Other combination vaccines that include hepatitis B

- **COMVAX** – CSL Biotherapies/Merck & Co Inc (Hib (PRP-OMP)-hepatitis B). Each 0.5 mL monodose vial contains 7.5 µg PRP conjugated to 125 µg meningococcal protein, 5 µg hepatitis B surface antigen; 225 µg aluminium hydroxide; 35 µg borax. May contain yeast proteins.
- **Twinrix Junior (360/10)** – GlaxoSmithKline (formaldehyde inactivated hepatitis A virus (HM175 strain) and recombinant hepatitis B vaccine). Each 0.5 mL monodose vial or pre-filled syringe contains 360 ELISA units of HAV antigens, 10 µg recombinant DNA hepatitis B surface antigen protein; 0.225 mg aluminium phosphate/hydroxide; 0.5% w/v phenoxyethanol; traces of formaldehyde and neomycin. May contain yeast proteins.
- **Twinrix (720/20)** – GlaxoSmithKline (formaldehyde inactivated hepatitis A virus (HM175 strain) and recombinant hepatitis B vaccine). Each 1.0 mL monodose vial or syringe contains 720 ELISA units of HAV antigens, 20 µg recombinant DNA hepatitis B surface antigen protein; 0.45 mg aluminium phosphate/hydroxide; 0.5% w/v phenoxyethanol; traces of formaldehyde and neomycin. May contain yeast proteins.

Hepatitis B vaccines are prepared using recombinant technology. After purification, the HBsAg protein is adsorbed onto elemental aluminium (as hydroxide and/or phosphate). 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 to newborns and infants.[11] Engerix-B paediatric formulation contains a trace amount of thiomersal (<2 µg/mL). All other infant and childhood hepatitis B-containing combination vaccines, such as Infanrix Penta, Infanrix hexa, COMVAX and Twinrix Junior (360/10), are thiomersal-free.

Transport, storage and handling

Transport according to *National Vaccine Storage Guidelines: Strive for 5*.[12] Store at +2°C to +8°C. Do not freeze.

Dosage and administration

Monovalent hepatitis B vaccines are white, slightly opalescent liquids. Any visible change in the product, such as an amorphous flocculent or a granular precipitate may indicate incorrect storage conditions.

(i) Administer by deep IM injection.

(ii) 3-dose regimen

For children and young adults <20 years of age, a total of 3 doses of 0.5 mL of paediatric formulation is recommended. The optimal interval is 1 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.[13,14] The *minimum interval* between the second and third doses is 2 months.

(iii) For adults ≥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). The *minimum interval* between the second and third doses is 2 months.

This induces protective levels of neutralising antibody against hepatitis B virus in more than 90% of adults. The frequency of seroconversion increases progressively from approximately 35% after the first injection to more than 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

A randomised controlled trial, involving 1026 adolescents, demonstrated that adolescents 11–15 years of age who received 2 doses of the adult formulation at 0 and 4–6 months, developed similar protective antibody levels to those vaccinated using the paediatric formulations in the standard 3-dose regimen administered at 0, 1 and 6–12 months.[15]

An open label comparative study in adults found increased compliance among those receiving a 2-dose schedule (86%) over those who completed the 3-dose schedule (18%). Antibody responses were found to be similar among the 2 groups.[16]

A 2-dose schedule used in the 11–15 years age group will improve compliance and provide comparable immunogenicity to that of a 3-dose paediatric schedule. Adolescents (11–15 years of age) can be vaccinated with H-B-VAX II 10 µg (adult formulation) or Engerix-B 20 µg (adult formulation) in a 2-dose regimen of 0 and 4–6 months (H-B-VAX II) or 0 and 6 months (Engerix-B). In older adolescents up to the age of 19 years, in whom compliance with a 3-dose paediatric dosing schedule is in doubt, a 2-dose schedule using an adult formulation may also be used in order to improve protection.

When protection is required against both hepatitis A and hepatitis B in children 1–15 years of age, administration of Twinrix (720/20) in a 2-dose regimen at 0 and 6–12 months results in protective antibody levels for both hepatitis A and hepatitis B (see Table 3.6.1).

Table 3.6.1: Hepatitis B and hepatitis A/hepatitis B combination vaccination schedules

Vaccine	Age	Dose (HBsAg protein)	Volume	Schedule (mo=months)
Monovalent hepatitis B vaccines				
Engerix-B (paediatric)	<20 years	10 µg	0.5 mL	0, 1, 6 mo (3-dose schedule)
Engerix-B (adult)	11–15 years	20 µg	1.0 mL	0, 6 mo (2-dose schedule)
Engerix-B (adult)	≥20 years	20 µg	1.0 mL	0, 1, 6 mo (3-dose schedule)
H-B-VAX II (paediatric)	<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)
H-B-VAX II (adult)	≥20 years	10 µg	1.0 mL	0, 1, 6 mo (3-dose schedule)
H-B-VAX II (dialysis formulation)	≥20 years	40 µg	1.0 mL	0, 1, 6 mo (3-dose schedule)
Combination hepatitis A/B vaccines				
Twinrix (720/20)*	1– <16 years	20 µg	1.0 mL	0, 6–12 mo (2-dose schedule)
Twinrix Junior (360/10)	1– <16 years	10 µg	0.5 mL	0, 1, 6 mo (3-dose schedule)
Twinrix (720/20)	≥16 years	20 µg	1.0 mL	0, 1, 6 mo (3-dose 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.

(v) Accelerated schedule

Engerix-B formulations (paediatric and adult) and Twinrix (720/20) are registered for use in accelerated schedules. Accelerated schedules should only be used if there is very limited time before departure to endemic regions (see Table 3.6.2).

Table 3.6.2: Accelerated hepatitis B vaccination schedules*

Vaccine	Age	Dose (HBsAg protein)	Volume	Schedule (mo=months)
Engerix-B (paediatric)	<20 years	10 µg	0.5 mL	0, 1, 2, 12 mo
Engerix-B (adult)	≥20 years	20 µg	1.0 mL	0, 1, 2, 12 mo or 0, 7, 21 days, 12 mo
Twinrix (720/20)	≥16 years	20 µg	1.0 mL	0, 7, 21 days, 12 mo

* As higher seroprotective rates are seen after the 0, 1, 2 month schedule, it is recommended that the 0, 7, 21 days schedule be used only in adults and only in exceptional circumstances. In both schedules, a booster dose at 12 months is recommended for long-term protection.

Recommendations

(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, DTPa-hepB-IPV-Hib or Hib (PRP-OMP)-hepB) at 2, 4 and either 6 or 12 months, is 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, reporting, communication or appropriate response), but also to prevent horizontal transmission in the first months of life from a carrier among household or other close contacts.[17] 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.[18-20]

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 (preterm or term) of carrier mothers must be given a birth dose of hepatitis B vaccine *and* HBIG.

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. It also has benefits of enabling appropriate follow-up and management of a carrier, identification of the immune status of other household members, and protection of those who are susceptible to HBV infection. Infants born to HBsAg positive mothers should be given HBIG and a dose of 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 after birth.

The first dose of monovalent hepatitis B vaccine should be given at the same time as HBIG, but in the opposite anterolateral thigh, as soon as possible – preferably within 24 hours of birth, and definitely within 7 days. This regimen results in seroconversion rates of more than 90% in neonates, despite concurrent administration of HBIG. If concurrent administration is not possible, vaccination should not be delayed beyond 7 days after birth as (providing it is given early) vaccine alone has been shown to be effective in preventing carriage.[21] 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.

Preterm babies

Preterm babies do not respond as well to hepatitis B-containing vaccines as term babies.[22-25] Thus, for babies at <32 weeks' gestation or <2000 g birth weight, it is recommended to give vaccine at 0, 2, 4 and 6 months of age and either:

(a) measure anti-HBs at 7 months of age and give a booster at 12 months of age if antibody titre is <10 mIU/mL, or

(b) give a booster at 12 months of age without measuring the antibody titre.

(ii) Adolescents

Vaccination of 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 authority for further information (see Appendix 1, *Contact details for Australian, State and Territory Government health authorities and communicable disease control*).

(iii) Adults 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 of acute and chronic hepatitis B carriers**

There is a low, but definite, risk of transmission from a person with acute or chronic hepatitis B. This can be reduced by avoiding contact with blood or other body fluids and not sharing household items which can penetrate skin (such as combs, nail brushes, toothbrushes and razors).

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, family members may have been exposed by the time the risk is recognised. Testing before planned vaccination is recommended for such families, as well as for members of families who have migrated from high prevalence countries.

- **Sexual contacts**

Susceptible (anti-HBc and 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 within 14 days of the last sexual contact. Susceptible 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 immunity. The combined hepatitis A/hepatitis B vaccine may be appropriate for men who have sex with men, if they are not immune to either disease, as they are at increased risk of both.

- **Haemodialysis patients, HIV-positive individuals and other adults with impaired immunity**

Dialysis patients, HIV-positive individuals and other adults with impaired immunity should be given a larger than usual dose of hepatitis B vaccine. Adults should be given either (i) 1 mL of normal adult formulation in each arm on each occasion (double dose), or (ii) a single dose of dialysis formulation vaccine on each occasion, at 0, 1 and 6 months. HIV-positive children should receive 3 doses using an adult formulation.

- ***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 have an elevated risk of hepatitis B virus infection, and 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.[26]

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

Vaccination of carers, staff and susceptible residents is recommended in both residential and non-residential care of people 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**

If seronegative for hepatitis B, such individuals should be vaccinated before transplantation 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.

- **Healthcare workers, ambulance personnel, dentists, embalmers, tattooists 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,[27] embalming, or in the handling of human blood or tissue, be vaccinated. In addition, standard precautions against exposure to blood or body fluids should be used as a matter of routine.

- **Others at risk**
    - Police, members of the armed forces and emergency services staff should be vaccinated if they are assigned to duties which may involve exposure.
    - Funeral workers and other workers who have regular contact with human tissue, blood or body fluids and/or used needles or syringes.
    - People travelling to regions of intermediate or high endemicity, either long-term or for frequent short terms, should be vaccinated.

- Staff of child day-care centres will normally be at minimal risk of hepatitis B. If advice on risk is sought, the enquiry should be directed to the local public health authority.
- Contact sports generally carry a low risk of hepatitis B infection. Vaccination is nevertheless encouraged.
- As the risk in Australian schools is very low,[28] vaccination of classroom contacts is seldom indicated. Nevertheless, vaccination of all children and adolescents should be encouraged.
- Sex industry workers.

(iv) Serological confirmation of post-vaccination immunity

Post-vaccination serological testing 4 to 8 weeks after completion of the primary course is recommended only for those in the following categories:

- those at significant occupational risk (eg. healthcare workers whose work involves frequent exposure to blood and body fluids),
- those at risk of severe or complicated disease (eg. people with impaired immunity, and individuals 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),
- sexual partners and household contacts of recently notified hepatitis B carriers.[29]

Anti-HBs and HBsAg levels should be measured in infants born to known HBsAg/HBeAg positive carrier mothers 3 to 12 months after completing the primary vaccine course. If anti-HBs levels are adequate and HBsAg is negative, then children are considered to be protected.[29]

(v) Non-responders to primary vaccination

If adequate anti-HBs levels (≥10 mIU/mL) are not reached after 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. These can be given as either a fourth double dose or a further 3 doses at monthly intervals, with further testing at least 4 weeks after the last dose.

There is limited evidence from several trials that HBsAg negative healthcare workers, who are non-responders to a primary course of vaccination and subsequent intramuscular booster schedule, as above, may respond to 5µg of Engerix-B (0.25 mL of the adult formulation) administered intradermally at fortnightly intervals (up to 4 doses) with anti-HBs levels measured before each dose to assess for seroconversion.[30-32] Persistent non-responders should be informed that they are not protected and should minimise exposures, and about the need for HBIG within 72 hours of parenteral exposure to HBV (see Table 3.6.3 *Post-exposure prophylaxis for non-immune individuals exposed to an HBsAg positive person*).

Individuals who are at significant occupational risk who have a documented history of a primary course of hepatitis B vaccine, but it is not known whether they ever seroconverted, and they now have an antiHBs level <10 mIU/mL, should be given a single booster dose of vaccine and have their anti-HBs level checked 4 weeks later. If the anti-HBs level is <10 mIU/mL, regard the individual as a non-responder, give 2 further doses of hepatitis B vaccine at monthly intervals, and re-test for anti-HBs levels at least 4 weeks after the last dose.

(vi) Booster doses

Although vaccine-induced antibody levels decline with time and may become undetectable, 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* healthcare workers and dentists.[33-39] However, booster doses are recommended for individuals with impaired immunity, 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.[33]

(vii) 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 age-appropriate formulation may be used as there is no reason to believe that use of a different brand will compromise immunogenicity or safety.

(viii) 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 and HBsAg 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 weighing up to 30 kg (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, depending on age) as soon as possible, but within 7 days of exposure. Two further doses of vaccine should be given, 1 and 6 months after the first dose.

For previously vaccinated people exposed to either an HBsAg positive source or a source whose hepatitis B status cannot be determined, post-exposure prophylaxis is not necessary if there was a documented protective response (anti-HBs level ≥10 mIU/mL) at any time after vaccination. If the response to previous vaccination is unknown, the anti-HBs level should be determined as quickly as possible. If the anti-HBs level is <10 IU/mL and HBsAg is negative, HBIG and vaccine should be administered as above.

In most instances, it is advisable to offer a course of hepatitis B vaccine to a non-immune healthcare worker sustaining a needle-stick injury or other potential hepatitis B exposure, since the injury or exposure itself is evidence that they work in an area with a significant risk of exposure.

Table 3.6.3: Post-exposure prophylaxis for non-immune individuals exposed to an HBsAg positive person

Type of exposure	Hepatitis B immunoglobulin		Vaccine	
Perinatal (exposure of babies during and after birth)	100 IU by IM injection	Single dose 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 at 2, 4, and either 6 or 12 months of age
Percutaneous/ ocular or mucous membrane	400 IU by IM injection 100 IU if body weight <30 kg	Single dose within 72 hours	0.5 mL or 1 mL by IM injection depending on age	Within 7 days* and at 1 and 6 months after first dose
Sexual	400 IU by IM injection	Single dose within 14 days of sexual contact	0.5 mL or 1mL by IM injection depending on age	Within 14 days* and at 1 and 6 months after first dose

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

Contraindications

The only absolute contraindications to hepatitis B vaccine are:

- anaphylaxis following a previous dose of hepatitis B vaccine, or
- anaphylaxis following any component of the vaccine.

Adverse events

- Adverse events after hepatitis B vaccination are transient and minor, and include soreness at the injection site (5%, common), fever (usually low grade, 2–3%, common), nausea, dizziness, malaise, myalgia and arthralgia. Fever can be expected in neonates immunised with hepatitis B vaccine (0.6–3.7%, common).
- 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.[40,41] There have been a few reports of generalised

febrile reactions attributed to yeast allergy, and exceptional instances of polyarteritis nodosa have been reported.

- The World Health Organization Global Advisory Committee on Vaccine Safety states that "multiple studies and review panels have concluded that there is no link between MS [multiple sclerosis] and hepatitis B vaccination".[42]
- The vaccine produces neither therapeutic effects nor adverse events in hepatitis B virus carriers. It is safe in those already immune to hepatitis B.

Use in pregnancy

Refer to Chapter 2.3, *Groups with special vaccination requirements*, Table 2.3.1 *Vaccinations in pregnancy*.

Variations from product information

The product information for both Infanrix hexa and Infanrix Penta states that these vaccines may be given as a booster dose at 18 months of age. NHMRC recommends that a booster dose of DTPa (or DTPa-containing vaccines) is not necessary at 18 month of age. However, DTPa-containing vaccine may be used for catch-up of the primary schedule in children <8 years of age.

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 healthcare workers who are exposed to the blood of HbsAg positive individuals through occupational exposure. Requests should be directed to the Australian Red Cross Blood Service in your State/Territory (see Chapter 3.8, *Immunoglobulin preparations* 'Availability of immunoglobulins').

HBIG is given by IM injection.

- **Hepatitis B Immunoglobulin-VF** – CSL Bioplasma (160 mg/mL immunoglobulin (IgG) prepared from human plasma containing high levels of antibody to surface antigen of the hepatitis B virus). 100 IU and 400 IU ampoules, with the actual volume stated on the label on the vial.

References

Full reference list available on the electronic *Handbook* or website http://immunise.health.gov.au.

3.7 HUMAN PAPILLOMAVIRUS

Virology and HPV classification

Human papillomaviruses (HPVs) are small, non-enveloped viruses that have circular double-stranded DNA. HPVs infect and replicate within cutaneous and mucosal epithelial tissues, most commonly involving the skin or anogenital tract. HPVs are designated as specific types according to sequence variation in the major genes.

There are 40 distinct HPV genotypes that affect the genital tract; of these, 15 genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82) are designated as 'high-risk' as they are causally associated with the development of cervical cancer. HPV genotypes 16 and 18 are the causative agents in 70 to 80% of all cervical cancers. HPV genotypes 6 and 11 are among the HPV genotypes designated as 'low-risk' (for cancer), and are associated with 90% of genital warts and 100% of recurrent respiratory papillomatosis (RRP) cases.[1,2]

High-risk genital HPV genotypes are associated with a spectrum of other anogenital diseases, including vulval, vaginal, penile and anal cancers, and their precursors. In addition, genital HPV genotypes are associated with extragenital diseases, including some squamous cell carcinomas of the head and neck (high-risk HPV types) and recurrent respiratory papillomatosis (HPV types 6 and 11).

Persistent HPV infection is a necessary precursor of cervical cancer, but is not sufficient in itself to cause the disease.[3] For pre-cancerous lesions to form and progress to cancer, the crucial event appears to be HPV DNA integration into the host cell genome, which interferes with the expression and regulation of proteins responsible for normal cell growth and repair.[4] Malignancy due to build-up of sufficient mutations for cellular transformation usually requires 10 to 20 years, but has been reported to occur in under 2 years.[5]

Clinical features

HPV infection is often subclinical but, dependent upon the infecting HPV genotype, may result in lesions that include cutaneous warts, genital warts, cervical and other anogenital tract dysplasias and cancers, and respiratory papillomatosis. Most genital HPV infections are cleared (no longer detectable) within 12 to 24 months (the median duration for high-risk genotypes is 7 to 10 months).[6-9] In a minority of infections, estimated at 3 to 10%, the virus persists.[10]

Epidemiology

HPV infection

Transmission of HPV occurs through contact with infected skin or mucosal surfaces, primarily via sexual contact for the genital HPV genotypes. Transmission may rarely occur by other mechanisms, such as laryngeal infection of infants during birth.[11] There is a high probability of transmission following sexual exposure to a person with a productive HPV infection, estimated to be 50 to 80%, after unprotected sexual intercourse.[12-14] However, sexually active adolescents and young adults may remain naïve to all 4 vaccine HPV genotypes or be infected with a non-vaccine HPV genotype.

HPV infection rates vary greatly between geographic regions, but it is estimated that up to 79% of women worldwide will be infected with at least one genital type of HPV at some point in their lives.[15,16] HPV infection rates are highest among young women, usually peaking soon after the age when most young women become sexually active.[17] Australian data show that, among women currently aged 16–19 years, the median age of first intercourse is 16 years.[18]

Although comprehensive risk-prediction models for HPV exposure are not available, an increasing number of lifetime sex partners is consistently found to be associated with HPV acquisition.[19-24] A US population-based study of women aged 18–25 years found genital HPV infection in 14.3% of women with one lifetime sex partner, 22.3% with 2 lifetime sex partners, and 31.5% with more than 3 lifetime partners.[25] Australian women aged 16–19 years report a median number of 2 lifetime sexual partners, women aged 20–29 years a median of 4.3 lifetime sexual partners, and those aged 30–39 years a median of 4.7 lifetime sexual partners.[26] Although its sensitivity is somewhat limited, HPV seroprevalence measured using serum anti-HPV antibody levels can be used to estimate cumulative lifetime exposure to specific types of HPV infection.[27] In a study of women in Finland, Dillner et al (1996) described a linear increase in the risk of HPV16 seropositivity of 4% for every additional sex partner, ranging from 4% for 1 lifetime partner to 35% among those with 6 or more partners.[24] Similarly, HPV18 seroprevalence was observed to increase linearly at the rate of 3% per partner from 4% for 1 lifetime partner up to 24% for 6 or more partners. In the US, population data indicate that 25% of women aged 20–29 years are seropositive for HPV16.[28] An increasing number of sexual contacts on the part of their male partner is also associated with HPV acquisition in women.[29]

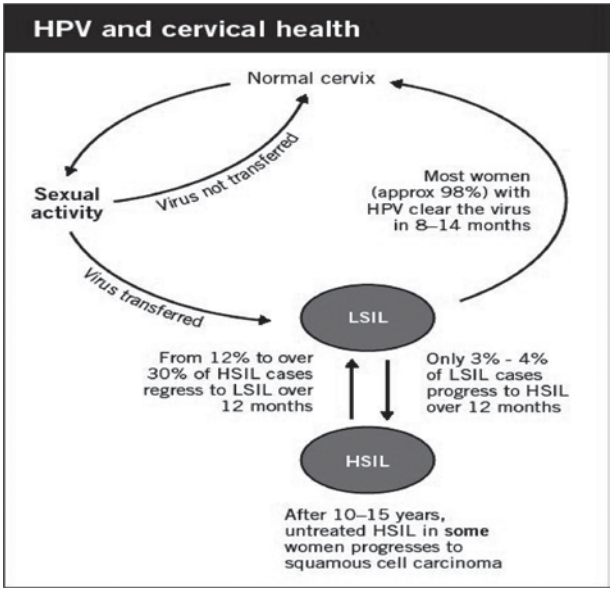
Cervical abnormalities

Cervical infection with HPV causes a range of pathological responses depending on the genotype of HPV. These range from no reaction, carriage of HPV without cytological changes, to a variety of cellular changes in the cervix. Histologically, the cervical abnormalities have been referred to as cervical intraepithelial neoplasia (CIN), with 3 grades of severity: CIN1 (mild dysplasia), CIN2 (moderate dysplasia) and CIN3 (severe dysplasia/carcinoma in situ). CIN3 and AIS (adenocarcinoma in situ) are immediate precursors of cervical cancer. CIN2 represents a mix of low-grade and high-grade lesions (and hence it is treated as a high-grade lesion). Cytologically, under the Australian Modified Bethesda System, the term Low-grade Squamous Intraepithelial Lesion (LSIL) encompasses changes thought to be due to HPV and mild dysplasia, and the term High-grade Squamous Intraepithelial Lesion (HSIL) encompasses the former categories of moderate dysplasia, severe dysplasia and carcinoma in situ. Guidelines for the interpretation and treatment of screen-detected cervical abnormalities are published by the NHMRC.[12]

Every year in Australia, approximately 90 000 women have an LSIL detected and 15 000 women have an HSIL detected through Pap screening.[12] The incidence of both lesions peaks in women aged 20–24 years. In addition, there are approximately 20 000 hospital admissions per year for cervical dysplasia and carcinoma in situ. This is an underestimate of the burden of disease, as the investigation and management of cervical lesions are mostly carried out as outpatient procedures, either in the private or public sector. For procedures in the private sector, Medicare has processed, over the past 10 years, claims for an average of approximately 104 000 examinations of the lower genital tract by colposcopy and 14 600 combined colposcopy procedures per year. As well as physical side effects and complications from treatment for cervical abnormalities, there is consistent evidence that receipt of an abnormal Pap smear result, and the subsequent investigation and management, is associated with a considerable psychosocial burden.[30-35]

It was originally thought that there was an inevitable progression from low-grade abnormalities to high-grade abnormalities to cervical cancer. It is now recognised that LSIL cytology is a manifestation of acute HPV infection, and that most LSIL regresses over time.[12] The absolute risk of cancer associated with a high-grade abnormality is difficult to determine from available observational data, but is estimated at less than 1% per year.[36] Figure 3.7.1 summarises the dynamic relationship between HPV infection and cervical health.

Figure 3.7.1: The dynamic relationship between HPV infection and cervical health



(Figure courtesy of the Australian Government Department of Health and Ageing.)

Cervical cancer

Cancer of the uterine cervix is the second most common cause of cancer among women worldwide.[37] However, Australia has one of the lowest mortality rates from cervical cancer in the world.[38] In 2002, the age standardised incidence rate in Australia was 6.8 per 100 000 and, in 2004, the mortality rate was 1.9 per 100 000, with an estimated 750 cases, 1800 hospitalisations and 250 deaths each year from cervical cancer.[39] This low incidence can be attributed to the success of the National Cervical Screening Program, with cervical cancer in Australia now occurring predominantly in unscreened or under-screened women. The largest decline in cervical cancers has been observed for those of squamous origin, with the incidence of adenocarcinomas being essentially unchanged. This has been attributed to sampling difficulties in obtaining cells from the area where adenocarcinoma arises, problems in pathological interpretation, and variations in clinical investigation and treatment.[12]

Other anogenital cancers

High-risk HPV types (predominantly types 16 and 18) are also implicated in 50 to 90% of other anogenital cancers in both women and men, including cancers of the vulva, vagina, anus, and penis, although these types have almost no role in

causing non-malignant lesions (see below). In Australia in 2001, there were 252 vulvar cancers (2.6 per 100 000), 62 vaginal cancers (0.6 per 100 000) and 225 anal cancers (1.2 per 100 000) diagnosed.[40]

Non-malignant lesions

Genital warts are a common manifestation of HPV type 6 and 11 infection. Genital warts can cause significant psychological morbidity. In Australia, 4.0% of men and 4.4% of women aged 16–59 years report ever being diagnosed with genital warts.[41] These prevalence estimates translate into approximately 36 000 cases in Australia. The cumulative lifetime risk of genital warts has been estimated at 10%.[42,43] Peak attack rates occur in young women aged 15–24 years.[44] An analysis of data from the BEACH cross-sectional survey of national GP activity found that, between April 2000 and March 2003, consultations for genital warts in women aged 12–49 years occurred at a rate of 0.17 per 100 encounters.[45] Severe morbidity from genital warts, as measured by hospitalisation, is uncommon and peaks in women 20–24 years of age (26 per 100 000) (AIHW National Hospital Morbidity Database 2006). Morbidity not causing hospitalisation includes recurrence and a range of local complications. Worldwide, the best epidemiological data on genital wart incidence comes from the United Kingdom.[2]

Exposure to HPV types 6 and 11 at birth can also cause recurrent respiratory papillomatosis in children. This relatively rare disease, with an estimated incidence of 4 per 100 000 children,[46,47] is characterised by repeated growth of warts in the respiratory tract requiring repeated surgery. Adults can also develop recurrent respiratory papillomatosis.

Type-specific HPV epidemiology

Worldwide, approximately 50% of cervical cancers contain HPV16 DNA and 16% contain HPV18 DNA.[48,49] Among cervical adenocarcinomas, 70% contain HPV 16 or 18 DNA, with HPV18 being relatively more common (37.7%) than HPV16 (31.3%).[48] HPV16 has been detected in 48% of HSILs, 19% of LSILs and 2% of cytologically normal women. HPV18 has been detected in 7% of HSILs, 6% of LSILs and 0.7% of cytologically normal women.[50-52] The low-risk HPV types 6 and 11 have been detected in 6.2% and 3.2% of LSILs respectively and each type in 0.1% of cytologically normal women.[51,52]

Australian studies indicate that the 5 most frequent HPV genotypes identified in 553 cervical cancers were HPV16 (60%), HPV18 (20%), HPV45 (5%), and HPV39 and HPV73 (2.3% each).[53-57] Best available Australian data indicate that HPV16 and HPV18 are, respectively, responsible for approximately 60%/20% of cervical cancers and 37%/8% of high-grade cervical abnormalities.[53,54]

Vaccines

HPV vaccines have been developed using recombinant DNA technology based on virus-like particles (VLPs), which are not infectious and do not have any cancer-causing potential.

There are 2 HPV vaccines registered for use in Australia. The bivalent vaccine, 2vHPV vaccine (CERVARIX), contains VLPs of HPV genotypes 16 and 18, and is administered as a 3-dose schedule at 0, 1 and 6 months. The quadrivalent vaccine, 4vHPV vaccine (GARDASIL), is administered at 0, 2 and 6 months and contains VLPs of HPV genotypes 16, 18, 6 and 11.

- **CERVARIX** – GlaxoSmithKline (human papillomavirus vaccine – recombinant protein particulate (VLP) vaccine containing the major capsid (L1) protein of HPV types 16 and 18). Each 0.5 mL monodose pre-filled syringe or vial contains 20 µg each of HPV types 16 and 18 adjuvanted with AS04 (AS04 is comprised of 500 µg aluminium hydroxide and 50 µg of 3-O-desacyl-4'-monophosphoryl lipid A [MPL]); 4.4 mg sodium chloride; 624 µg sodium dihydrogen phosphate dihydrate.
- **GARDASIL** – CSL Biotherapies/Merck & Co Inc (human papillomavirus vaccine – recombinant protein particulate (VLP) vaccine containing the major capsid (L1) protein of HPV types 6, 11, 16 and 18). Each 0.5 mL monodose pre-filled syringe or vial contains 20, 40, 40 and 20 µg of HPV types 6, 11, 16 and 18, respectively, adsorbed onto 225 µg aluminium hydroxyphosphate sulphate; 9.65 mg of sodium chloride; 780 µg of L-histidine; 50 µg of polysorbate 80; 35 µg of sodium borate. May also contain yeast proteins.

It is important to note that HPV vaccines are prophylactic vaccines (ie. designed to prevent initial HPV infection). In women who are already infected with HPV types covered by the vaccines before vaccination (ie. HPV DNA positive), the vaccines do not treat infection or prevent disease caused by that type.[58]

In women HPV DNA negative and HPV seronegative for relevant types, both vaccines are highly effective at preventing persistent type-specific infection and related cervical disease (~90–100%).[59-62] The 4vHPV vaccine also has established efficacy against external genital lesions (warts, and vulval and vaginal dysplasias) in women. Vaccine efficacy against external genital lesions related to HPV 6, 11, 16 or 18 in women who were naïve to vaccine types at the beginning of the trials and who received 3 doses was 99% (95% CI: 95–100%).

Compared to HPV DNA negative and HPV seronegative women, vaccine efficacy (VE) in women who received vaccine regardless of HPV status at baseline and may, therefore, have had previous infection, was much lower. Against HPV16/18-related CIN2/3 or worse, VE was 44% (95% CI: 31–55%) at a mean of 3 years follow-up[63] and against high-grade CIN caused by any HPV type it

was 18% (95% CI: 7–29%).[63] However, vaccine efficacy is expected to be higher over a longer duration of follow-up, as the proportion of disease due to incident infection (where vaccination has an effect) increases compared to the proportion of disease due to infection/disease at baseline (which is not affected by the vaccine). These data reflect the reduced impact of vaccinating women in whom a proportion will already have been infected with HPV, eg. older women who are/have been sexually active. Vaccine efficacy estimates in populations including women already infected with HPV at baseline have not yet been published for 2vHPV vaccine, but a similarly reduced impact, compared with an HPV naïve population, can be anticipated.

It is possible that HPV vaccines may provide some protective efficacy against disease due to types closely related to types 16 and 18, in particular HPV31 and HPV45, but published data supporting this hypothesis are currently limited to infection endpoints only and are imprecise.[60,64-66]

When given as a 3-dose series, HPV vaccines elicit neutralising antibody titres many times higher than those observed following natural infection.[67-69] Antibody responses peak at month 7 (1 month after dose 3) at titres between 7 and 150 times greater than following natural infection, depending upon the HPV type and vaccine.[59,62,70,71] Following an initial decline, they appear to plateau at 18 to 24 months, remaining stable for at least 5 years at levels above or at least equivalent to those seen following natural infection.[58,60,62,70] It should be noted that there is no standard serological assay for detecting HPV antibodies and no protective titre has been established. Therefore, absolute titres achieved (as reported in the randomised trials) are not directly comparable between 2vHPV and 4vHPV vaccines. Similarly, differences in methodologies and the populations examined make direct comparisons of published 4vHPV and 2vHPV vaccine efficacy estimates difficult.

Overall, seroconversion occurs in 99 to 100% of those vaccinated.[58,60,61] The duration of immunity after vaccination is not yet known (but is of at least 5 years' duration); hence, it is possible that booster doses may be required in the future.[58,60,62]

There are currently no clinical efficacy data available in males or in pre-adolescent females (as collection of genital specimens is not appropriate). Antibody response to both 4vHPV and 2vHPV vaccination has been evaluated in pre-adolescent and adolescent females (9–15 years of age and 10–14 years of age, respectively). In males, antibody response has only been studied for 4vHPV, and only in the age group 9–15 years, through immunological bridging studies.[72,73] Young males and females administered 4vHPV vaccine and females aged 10–14 years administered 2vHPV vaccine produce antibody responses that are at least 2-fold higher compared to women in whom clinical efficacy has been demonstrated. The peak antibody levels achieved following vaccination decrease with age. Immunobridging studies for older women (aged >26 – ≤45 years) administered the 2vHPV demonstrate antibody titres in a comparable range to women in the 15–25 year age group who are in the plateau phase of long-term follow-up.

These data were current at the time of publishing *The Australian Immunisation Handbook*.

Transport, storage and handling

Transport according to *National Vaccine Storage Guidelines: Strive for 5*.[74] Store at +2°C to +8°C. Do not freeze. Protect from light.

Dosage and administration

The dose of 2vHPV vaccine is 0.5 mL administered by IM injection. The recommended schedule is 0, 1 and 6 months. The second dose of 2vHPV can be administered between 1 and 2.5 months after the first dose.

The dose of 4vHPV vaccine is 0.5 mL administered by IM injection. The recommended schedule is 0, 2 and 6 months. In clinical studies, efficacy for 4vHPV vaccine has been demonstrated in individuals who have received all 3 doses within a 1 year period. Where flexibility in the recommended dosing schedule is unavoidable, the second dose should be administered at least 1 month after the first dose and the third dose should be administered at least 3 months after the second. There is no need to repeat earlier doses. Give missing dose(s) as soon as is practicable, making efforts to complete doses within 12 months.

4vHPV vaccine has been administered concomitantly with hepatitis B vaccine in clinical trials, with no reduction in immunogenicity of either vaccine observed.

There are no clinical data regarding concomitant administration of either 2vHPV or 4vHPV vaccine with adolescent/adult formulation dTpa or varicella vaccine, but there is no reason to expect any adverse outcomes if they are given simultaneously, using different injection sites.

Recommendations

Both vaccines are recommended to provide protection against oncogenic HPV type 16 and/or 18 cervical disease. If protection against genital warts is desired, the 4vHPV vaccine provides protection against HPV types 6 and 11, which are associated with more than 90% of these lesions.[67] (See also 'Vaccines' above.)

(i) Females aged 10–13 years *(Safety-Grade B)(Efficacy-no data)(Immunogenicity-Grade B)*[67]

HPV vaccine is recommended for females 10–13 years of age. Currently only the 4vHPV vaccine is on the NIP schedule for females aged 12–13 years. Please refer to your State/Territory health authority for further information (see Appendix 1, *Contact details for Australian, State and Territory Government health authorities and communicable disease control*).

(ii) Females aged 14–18 years *(Safety-Grade B)(Efficacy-Grade B)(Immunogenicity-Grade B)*[67]

HPV vaccine is also recommended for females 14–18 years of age. While some females in this age group will already have commenced sexual activity, the majority will not yet be infected with a HPV vaccine type.

(iii) Females aged 19–26 years *(Safety-Grade A)(Efficacy-Grade A)(Immunogenicity-Grade A)*[67]

HPV vaccine is also recommended for females 19–26 years of age.

In females in this age group who have never had sexual intercourse the vaccine efficacy will be comparable to younger women, and HPV vaccination is recommended. In sexually active females 19–26 years of age, the overall benefit from HPV vaccination is likely to be less; however, past or current infection with all HPV types covered by the vaccine is unlikely.

NB. The absolute benefit of HPV vaccine to an individual sexually active woman cannot be determined clinically, as appropriate tests to detect both previous and current HPV infection with vaccine types are not available.

In all sexually active women, the most important preventive intervention against cervical disease remains regular Pap screening. Vaccination is not an alternative to Pap screening but is complementary. The National Cervical Screening Program recommends routine screening with Pap smears every 2 years for all women between the ages of 18 (or 2 years after first sexual intercourse, if later) and 69 years.

(iv) Females aged ≥27 years *(Safety 2vHPV vaccine-Grade B; 4vHPV vaccine-no data)(Efficacy-no data)(Immunogenicity 2vHPV-Grade B; 4vHPV-no data)*[67]

2vHPV vaccine is registered for use in females 27–≤45 years of age on the basis of safety and bridging immunogenicity data. The extent of benefit that can be expected to be derived from the use of HPV vaccine in this age group will depend upon past sexual history and the likelihood of new sexual partners in the future (ie. an assessment of likely past and future HPV exposure) and the sexual behaviour of her male partner(s). HPV-related cervical infection and Pap test abnormalities peak in women aged <30 years in Australia.

4vHPV vaccine is not registered for use in females over the age of 27 years as there are no safety or efficacy data to support its use in this age group.

In all sexually active women, the most important preventive intervention against cervical disease remains regular Pap screening. Vaccination is not an alternative to Pap screening but is complementary. The National Cervical Screening Program recommends routine screening with Pap smears every 2 years for all women between the ages of 18 (or 2 years after first sexual intercourse, if later) and 69 years.

For women who have recently been diagnosed with cervical dysplasia, or have been treated for this in the past, HPV vaccine will have no impact on current disease, but may prevent future dysplasia due to a different HPV vaccine type.

(v) Males [For males aged 9–15 years *(Safety 4 vHPV vaccine-Grade B; 2vHPV vaccine-no data)(Efficacy-no data)(Immunogenicity 4vHPV vaccine-Grade B; 2vHPV vaccine-no data)*][67]

4vHPV vaccine is licensed for use in males aged 9–15 years. 4vHPV vaccine produces high antibody titres in pre-adolescent and adolescent males but it is not known whether vaccination of males can either prevent transmission of HPV or provide protection against genital HPV infection, genital warts, anogenital dysplasia or anogenital cancers. 2vHPV vaccine is not registered for use in males.

There is no recommendation for vaccination of males at this time due to the lack of clinical efficacy data.

Contraindications

The only absolute contraindications to HPV vaccine are:

- anaphylaxis following a previous dose of the vaccine, or
- anaphylaxis to any vaccine component. The 4vHPV vaccine may contain minute amounts of yeast proteins.

Precautions

People with impaired immunity

There are limited clinical trial data available for this group. However, as HPV vaccines are not live vaccines, they can be administered to women who are immunosuppressed as a result of disease or medications. The immune response and vaccine efficacy might be less than in individuals who are immunocompetent (see Chapter 2.3, Subsection 2.3.3, *Vaccination of individuals with impaired immunity due to disease or treatment).*

Adverse events

Both the 2vHPV and 4vHPV vaccines are generally safe and well tolerated. A variety of comparators were used in clinical trials of 2vHPV and 4vHPV, but data comparing vaccine adverse events with an aluminium-containing placebo are available for both vaccines and are quoted below for common local adverse reactions. More detailed information about adverse events occurring in the vaccine trials is available from the product information for 2vHPV vaccine and from the US FDA for 4vHPV.[75]

In clinical trials of the 2vHPV vaccine, the most commonly reported adverse events were injection site pain 78%, swelling ~26% and erythema ~30% compared to ~53%, ~8% and 11% in the aluminium hydroxide placebo group. Incidence of injection site pain decreased across the 3 doses, whereas there was

a slight increase in the reported proportion with swelling and erythema after successive doses.

In clinical trials of the 4vHPV vaccine the most commonly reported adverse events were injection site pain ~81%, swelling ~24% and erythema ~24%, compared to ~75%, ~16% and ~18% in the aluminium-containing placebo group. The incidence of injection site pain was approximately equal across the 3 doses, whereas there was a modest increase in the reported proportion with swelling and erythema after successive doses.

HPV vaccines are well tolerated by those who have already been exposed to the HPV types included in the vaccine.

Use in pregnancy

HPV vaccine should not be given during pregnancy (see Chapter 2.3, Subsection 2.3.2, *Vaccination of women planning pregnancy, pregnant or breastfeeding women, and preterm infants*).

It should be noted that there is no evidence from animal studies, or among HPV vaccine trial participants who inadvertently became pregnant, of teratogenicity or of adverse fetal outcomes and, therefore, HPV vaccination during pregnancy is not an indication for termination.

Where vaccine has inadvertently been administered during pregnancy, further doses should be deferred until after delivery.

Use during lactation

HPV vaccine may be given while lactating (see Chapter 2.3, Subsection 2.3.2, *Vaccination of women planning pregnancy, pregnant or breastfeeding women, and preterm infants*).

In trials, 995 nursing mothers received 4vHPV vaccine or placebo, and no relation between vaccination and adverse events was observed. The effect on breastfed infants of the administration of 2vHPV vaccine to their mothers has not been evaluated in clinical studies. It is not known whether HPV vaccine antigens or HPV antibodies are excreted in human milk.

Variations from product information

None.

References

Full reference list available on the electronic *Handbook* or website http://immunise.health.gov.au.

3.8 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 2 types of immunoglobulin, normal and specific. It is important to recognise that separate immunoglobulin preparations are provided for intramuscular (IM) use and for intravenous (IV) use. These have different properties, and the preparations should be given only by the recommended route. Administration of IM immunoglobulin by the IV route will lead to severe reactions.

- ### 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

Specific immunoglobulin preparations are obtained from pooled blood donations from patients convalescing from the relevant infection, donors recently vaccinated with the relevant vaccine, or those who, on screening, have been found to have sufficiently high antibody concentrations. These blood-derived specific immunoglobulins therefore contain concentrations of antibody to an individual organism or toxin at a higher titre than would be present in normal immunoglobulin.

Donors of blood used for the production of NHIG and specific immunoglobulin products are screened and products treated to minimise the risk of the immunoglobulin preparations containing HIV, hepatitis A, hepatitis B or hepatitis C viruses, or parvovirus. Two dedicated pathogen inactivation steps are incorporated into the manufacturing process. A pasteurisation step is usually used during manufacture. The risk of prion transmission remains theoretical.

Potential interaction with vaccines

Live attenuated virus vaccines

- Immunoglobulin preparations 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 vaccines, should be deferred for at

least 3 months after the IM administration of NHIG, and for at least 9 months after the administration of NHIG (intravenous).[4] For the same reason, administration of immunoglobulin products should be deferred if possible until at least 2 weeks after a vaccine has been given, unless it is essential that immunoglobulin be 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 any time in relation to each other (see Chapter 2.3, *Groups with special vaccination requirements*, Table 2.3.5 *Recommended intervals between either immunoglobulins or blood products and MMR, MMRV or varicella vaccination*).

Inactivated vaccines

- Inactivated vaccines such as tetanus, hepatitis B or rabies may be administered concurrently with immunoglobulin preparations, or at any time after, 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 IM use. Rabies immunoglobulin can be obtained only upon application from State/Territory health authorities. Respiratory syncytial virus (RSV) monoclonal antibody (Synagis; Abbott Australia) is available commercially.

The specific immunoglobulins and the CSL Bioplasma NHIG for IV use, which are derived from Australian donated plasma, can be obtained only from the Australian Red Cross Blood Service (ARCBS) with permission from a ARCBS medical officer. The Red Cross Blood Service 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 at +2°C to +8°C. Do not freeze.

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 Immunoglobulin-VF (human) (NHIG)** – CSL Bioplasma. A sterile preservative-free solution of immunoglobulin G (IgG) 160 mg/mL prepared from Australian blood donations and made available through the Australian Red Cross Blood Service. It is supplied in 2 mL and 5 mL vials for IM injection.

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 IV 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 Chapter 3.5, *Hepatitis A*)

NHIG contains sufficiently high levels of antibody against hepatitis A to be able to prevent or ameliorate infection in susceptible individuals,[5] if administered within 2 weeks of exposure.[6]

Because the hepatitis A vaccine is readily available, there is no place for the routine use of NHIG to prevent hepatitis A in travellers. It should be given (at the same time as a dose of hepatitis A vaccine) only to those, such as non-immune aid-workers to be deployed within 2 weeks, who will be living in very inadequate circumstances.[7,8]

(ii) Prevention of hepatitis B

See Chapter 3.6, *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 Chapter 3.11, *Measles*)

NHIG contains a sufficiently high concentration of antibody against measles to be able to prevent or ameliorate infection in susceptible individuals. NHIG should be given as soon as possible and within 7 days of exposure. Passive protection against measles particularly may be required if the exposed individual has an underlying immunological disorder (HIV/AIDS, immunosuppressive

therapy), or to control an outbreak of measles among non-immunised individuals, eg. in a childcare centre. The use of NHIG should be considered in HIV-positive individuals exposed to a patient with measles.

(iv) Prevention of varicella (see also Chapter 3.24, *Varicella*)

Zoster immunoglobulin (ZIG) is able to prevent or ameliorate varicella in infants <1 month of age, in children who are being treated with immunosuppressive therapy, and in pregnant women.[9,10] ZIG should be given as soon as possible, and preferably within 96 hours, after exposure. ZIG is recommended for non-immune HIV-positive individuals up to 7 days after 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 given by the IM route.

(v) Immune deficiency

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

However, in some cases, NHIG is given by IM injection in a dose of 400–600 mg/kg (0.4–0.6 g/kg) every 2 to 4 weeks. The aim of therapy is to maintain serum IgG levels above 6 g/L. Some patients may receive the IM (160 mg/mL) preparation subcutaneously.

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.

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 absolute IgA deficiency, as the small amounts of IgA in NHIG could theoretically lead to the development of anti-IgA antibodies in these individuals. NHIG should not be administered to individuals who have severe thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injections.

Adverse events and precautions

Local tenderness, erythema and muscle stiffness at the site of injection sometimes occurs and may persist for several hours after injection. Systemic adverse events such as mild pyrexia, malaise, drowsiness, urticaria and angioedema may occur occasionally. Skin lesions, headache, dizziness, nausea, general hypersensitivity reactions and convulsions may occur rarely.

Anaphylaxis following an injection of NHIG is very rare, but has been reported. Anaphylaxis is more likely to occur if NHIG for IM use is inadvertently given intravenously.

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. Intragam P contains only trace amounts of IgA, and the final solution contains 100 mg/mL maltose. It is supplied as 3 g in 50 mL and 12 g in 200 mL bottles (for intravenous use).
- **Sandoglobulin NF liquid** – CSL Bioplasma (sterile preservative-free solution of immunoglobulin G (IgG), 120 mg/mL). It is supplied as 6 g in 50 mL and 12 g in 100 mL bottles (for intravenous use). 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 6 g vials (for intravenous use).
- **Octagam** – Octapharma. A sterile preservative-free solution of immunoglobulin G (IgG) 50 mg/mL prepared from multiple blood donors. It is supplied as 1 g in 20 mL vials, and as bottles of 2.5 g in 50 mL, 5 g in 100 mL and 10 g in 200 mL (for intravenous use).

The available NHIG (intravenous) preparations in Australia have different recommendations for dosage and administration and the product information must be consulted before the use of each individual product. The text below provides an overview of dosage and administration for NHIG (intravenous).

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 their temperature every hour. All these observations should also be made and recorded before the commencement of the infusion.

The dose for replacement therapy in individuals with immune deficiency is 0.4–0.6 g/kg every 3 to 4 weeks. In Kawasaki disease, a single dose of 2 g/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.[11-15]

(iii) Other uses

NHIG (intravenous) has been used in the management of immune thrombocytopenia,[16] Guillain-Barré syndrome,[17,18] chronic inflammatory demyelinating polyneuropathy,[18] toxic shock syndrome,[19] post-transfusion purpura, in patients with bacterial infections associated with secondary immunodeficiency, and in other inflammatory and infective disorders.[3]

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

Contraindications

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

Adverse events and precautions

Adverse events with NHIG (intravenous) consist of shivering, headache, 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 an equal volume of normal saline before 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).

Specific immunoglobulins

These products are used to protect individuals against specific microbial agents such as hepatitis B,[20] rabies and varicella-zoster viruses,[9,10] and tetanus toxin. Each of these specific immunoglobulins is described in more detail in this *Handbook* in the chapter or section relevant to these specific infections.

In addition, specific immunoglobulins are available for botulism, cytomegalovirus (CMV) and respiratory syncytial virus (RSV) as described below. Adverse events and storage requirements for these specific immunoglobulins are similar to those for NHIG (IM) and, therefore, are not repeated here.

Botulism antitoxin (formerly known as Botulism Immune Globulin, BIG)

Equine antitoxin made in horses has long been used in the treatment of adult botulism, but has not been shown to be effective in infant botulism.[21]

Equine antitoxin is manufactured by major vaccine producing companies such as Chiron. Use in Australia is governed by the Therapeutic Goods Administration's Special Access Scheme and physicians wishing to access this stock should initially contact their State/Territory health authority. Hypersensitivity, 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.

A new intravenous botulinum antitoxin, produced in the USA, reduced the duration of mechanical ventilation and hospitalisation significantly in infant botulism.[22] It is not currently registered in Australia, but is registered by the US FDA. The sponsor is Californian Department of Health Services. Access to this product should be sought through the Special Access Scheme.

CMV immunoglobulin

CMV immunoglobulin is indicated for the prevention of CMV infection in immunodeficient people at high risk of severe CMV infection, such as after bone marrow and renal transplants.[23-31] The treatment of established CMV infection is primarily with antivirals such as ganciclovir, and there is scant evidence that the addition of CMV immunoglobulin improves outcome.[25,26,28] It would seem most logical to reserve the use of CMV immunoglobulin to treat established CMV infection in those patients with hypogammaglobulinaemia.

The product contains no antibacterial agent, and so it must be used immediately after opening. Any unused portion must be discarded. If the solution has been frozen, it must not be used. If the use of CMV immunoglobulin is contemplated, detailed protocols for administration and management of adverse events should be consulted, in addition to the Product Information.

- **CMV Immunoglobulin-VF (human)** – CSL Bioplasma (sterile solution of immunoglobulin prepared from human plasma containing high levels of antibody to CMV). The plasma protein content is approximately 60 mg/mL of which at least 98% is IgG immunoglobulin with a CMV immunoglobulin activity of 1.5 million CMV units per vial. Maltose is added to achieve isotonicity.

RSV immunoglobulin

Several clinical studies of immunoglobulin against RSV have been conducted overseas using hyperimmune polyclonal RSV immunoglobulin (RSVIG) derived from blood donations.[32-34] 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), for those with prematurity without BPD, and children with haemodynamically significant congenital heart disease.[34,35] RSVIG has caused severe cyanotic episodes and poor outcome after surgery in children with congenital heart disease and is contraindicated in such children.[36] RSVIG is not registered in Australia.

A humanised mouse monoclonal antibody to RSV produced by cultured cells – palivizumab – is now registered in Australia for prevention of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease. This product is given by IM injection each month during periods of anticipated risk of RSV. Palivizumab was found to reduce the absolute risk of hospitalisation from about 10% to about 5% for babies born prematurely,[37] for babies with BPD,[37] and also for babies with haemodynamically significant congenital heart disease.[35] It has not been shown to reduce the incidence of more severe outcomes such as the need for ventilation, nor has it been shown to reduce mortality.[35,37] Palivizumab is more effective and less costly than RSVIG, but its cost is still prohibitive. Cost-effectiveness analyses have not shown palivizumab to be cost-beneficial, and even analysis of sub-groups of children at high risk has not shown a single subgroup where prophylaxis results in net savings.[38,39]

- **Synagis –** Abbott Australia (palivizumab). Supplied in single-use vials of powder, to be reconstituted with sterile water for injection; 50 mg in 4 mL vial; 100 mg in 10 mL vial.

Dosage and administration

Palivizumab is administered by IM injection preferably in the anterolateral thigh, in a dose of 15 mg/kg once a month. Where possible, the first dose should be administered before commencement of the RSV season.

Use in pregnancy

Refer to Chapter 2.3, *Groups with special vaccination requirements*, Table 2.3.1 *Vaccinations in pregnancy*.

References

Full reference list available on the electronic *Handbook* or website http://immunise.health.gov.au.

3.9 INFLUENZA

Virology

The influenza viruses are orthomyxoviruses. They are classified antigenically as types A, B or C, but only influenza A and B are clinically important in human disease.[1] Influenza viruses possess 2 surface glycoprotein antigens, the haemagglutinin (H) which is involved in cell attachment during infection, and the neuraminidase (N) which facilitates the release of newly synthesised virus from the cell. 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 infection or severe illness due to influenza.

Both influenza A and influenza B viruses undergo frequent changes in their surface antigens. Both influenza A and B undergo stepwise mutations of genes coding for H and N. This results in cumulative changes in influenza antigens, or 'antigenic drift'. This is responsible for the annual outbreaks and epidemics of influenza and is the reason that the composition of influenza vaccines requires annual review. Antigenic shift, defined as a dramatic change in H antigen with or without a similar change in N, occurs occasionally and unpredictably and can cause pandemic influenza.[1] Pandemic subtypes arise spontaneously from antigenic shift or as a result of genetic reassortment (mixing) between bird (avian) or animal viruses and human strains.

Three pandemics are recognised in the 20th century, in 1918 (H1N1), 1957 (H2N2) and 1968 (H3N2). These pandemic strains have gone on to circulate in the community, with various subtypes causing seasonal influenza and, since 1977, 2 subtypes of influenza A, A (H1N1) and A (H3N2), co-circulating in the human population together with influenza B. Recently, the avian influenza virus subtypes, A (H5N1) and A (H9N2), have been observed to cause human infections. The most notable of these is the A (H5N1) subtype which has become established in domestic poultry throughout southeast Asia and has spread to Europe and Africa in either wild birds or domestic poultry. Although growing numbers of people have contracted the virus by contact with birds and there is a high mortality rate (of ≥50%), there has been no evidence of ongoing person to person transmission.

Clinical features

Influenza is transmitted from person to person via virus-containing respiratory aerosols, droplets produced during coughing or sneezing, or by direct contact with respiratory secretions.[1,2] Influenza virus infection causes a wide spectrum of disease from minimal or no symptoms, to respiratory illness with systemic features, to multisystem complications and death from primary viral or

secondary bacterial pneumonia. Severe disease is more likely with advanced age, lack of previous exposure to antigenically related influenza virus, greater virulence of the viral strain, chronic conditions such as heart or lung disease, renal failure and diabetes, chronic neurological conditions, 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.[2]

In adults, the onset of illness due to influenza is usually abrupt, after an incubation period of 1 to 3 days, and includes systemic features such as malaise, feverishness, chills, headache, anorexia, and myalgia. These may be accompanied by a cough, nasal discharge and sneezing. Fever is a prominent sign of infection and peaks at the height of the systemic illness. Symptoms are similar for influenza A and B viruses. However, infections due to influenza A (H3N2) strains are more likely to lead to severe morbidity and increased mortality than influenza B or influenza A (H1N1) strains.[1,2]

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 result in febrile convulsions in the susceptible age group) and otitis media and gastrointestinal manifestations are more prominent. Infection in neonates may be associated with more non-specific symptoms.

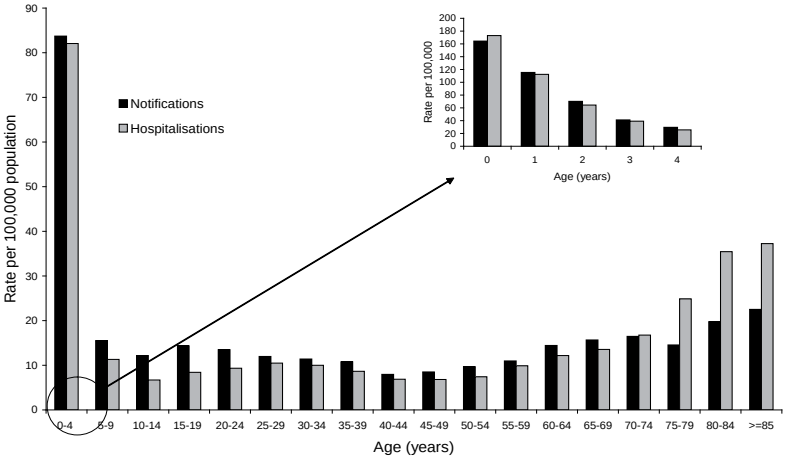
Complications of influenza include acute bronchitis, croup, acute otitis media, pneumonia (both primary viral and secondary bacterial pneumonia), cardiovascular complications including myocarditis and pericarditis, post-infectious encephalitis, Reye syndrome, and various haematological abnormalities. Primary viral pneumonia occurs rarely, but secondary bacterial pneumonia is a frequent complication in individuals whose medical condition makes them vulnerable to the disease. Such individuals 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. In Australia, 85 deaths and 4250 hospitalisations are notified, on average, per year, although this is almost certainly an underestimate due to failure to recognise the excess mortality and hospitalisation associated with the disease. Extrapolation from US estimates, based on more detailed surveillance, suggests 2000 deaths and 10 000 hospitalisations are likely to occur annually in Australia. 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]

Figure 3.9.1 shows the Australian hospitalisation and notification data for the period 2003–2005.

Figure 3.9.1: Influenza notification rates 2003–2005 and hospitalisation rates 2002/2003 to 2004/2005, Australia,* by age group[4]



* Notifications where the month of diagnosis was between January 2003 and December 2005; hospitalisations where the month of separation was between 1 July 2002 and 30 June 2005.

Pandemic influenza

It is now recognised that influenza A viruses have evolved in birds and that all 16 subtypes of influenza A persist in the avian reservoir. Occasionally, human infections may occur, with influenza subtypes not currently present in the human population, through close contact with infected poultry or poultry products. These may result, as in the case of recent A (H5N1) infections, in severe or fatal disease.

Avian influenza viruses are not naturally transmissible from person to person. However, adaptation to human to human transmission can occur either if an individual is concurrently infected with a human and an avian influenza virus, permitting genetic reassortment to occur, or if the virus acquires this ability via mutation. Genetic studies have shown that avian influenza viruses are the source of new human pandemic strains and that both these processes resulted in pandemic influenza in the 20th century.

Vaccines in routine inter-pandemic use will not protect against a pandemic strain which, by definition, is new and unpredictable. If a pandemic occurs, there will be a delay in producing a pandemic vaccine. Once the pandemic vaccine is available, 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 interval between doses may differ. The Australian Influenza Pandemic Planning Committee has

developed guidelines for vaccine use and will advise health authorities about priority groups, dosing schedules and timing of vaccination, should a pandemic occur.

See http://www.health.gov.au/internet/wcms/publishing.nsf/Content/phd-pandemic-plan.htm.

Vaccines

The administration of 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 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.

- **Fluad** – Delpharm Consultants/Novartis Vaccines (inactivated influenza vaccine). Each 0.5 mL pre-filled syringe contains 15 µg haemagglutinin of the 3 recommended strains, adjuvanted with MF59C; 0.05 mg thiomersal. May contain traces of kanamycin, neomycin, formaldehyde and egg protein.
- **Fluarix** – GlaxoSmithKline (inactivated influenza vaccine). Each 0.5 mL pre-filled syringe contains 15 µg haemagglutinin of each of the 3 recommended strains; polysorbate 80/octoxinol 9. May contain traces of thiomersal, formaldehyde, gentamicin and egg protein.
- **Fluvax** – CSL Biotherapies (inactivated influenza vaccine). Each 0.5 mL pre-filled syringe contains 15 µg haemagglutinin of each of the 3 recommended strains. May contain traces of neomycin, polymyxin and egg protein.
- **Fluvirin** – Medeva/Ebos Health & Science (inactivated influenza vaccine). Each 0.5 mL pre-filled syringe contains 15 µg haemagglutinin of the 3 recommended strains. May contain traces of neomycin, polymyxin and egg protein.
- **Influvac** – Solvay Pharmaceuticals (inactivated influenza vaccine). Each 0.5 mL pre-filled syringe contains 15 µg haemagglutinin of each of the 3 recommended strains. May contain traces of gentamicin and egg protein.
- **Vaxigrip** – Sanofi Pasteur Pty Ltd (inactivated influenza vaccine). Each 0.5 mL pre-filled syringe contains 15 µg haemagglutinin of each of the 3 recommended strains. May contain traces of formaldehyde, neomycin and egg protein.

- **Vaxigrip Junior** – Sanofi Pasteur Pty Ltd (inactivated influenza vaccine). Each 0.25 mL pre-filled syringe contains 7.5 µg haemagglutinin of each of the 3 recommended strains. May contain traces of formaldehyde, neomycin and egg protein.

Fluvax and Fluarix 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. Some influenza vaccines distributed in Australia contain thiomersal, a mercury-containing compound, as preservative, and other antibacterials or antibiotics may be used in the manufacturing process. The product information should be consulted for specific information.

Influenza vaccines normally contain the 3 recommended strains of virus, 2 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. Vaxigrip Junior contains 7.5 µg of viral haemagglutinin of each of the 3 recommended strains found in the adult formulations. 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 attenuated intranasal vaccine) have not yet been licensed in Australia.[5]

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 individuals <65 years of age, influenza vaccine is 70 to 90% effective when the antigenic match between vaccine and circulating viruses is close.[6] Among elderly people, 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.[7] 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

Transport according to *National Vaccine Storage Guidelines: Strive for 5*.[8] Store at +2°C to +8°C. Do not freeze. At the end of each year, vaccine should be appropriately discarded to avoid inadvertently using a product with incorrect formulation in the following year.

Dosage and administration

Shake the pre-filled syringe vigorously before injection. Influenza vaccine is administered by either IM or SC injection. The IM route causes fewer local reactions and is preferred.[9]

Table 3.9.1: Recommended doses of influenza vaccine

Age	Dose	Number of doses (first vaccination)	Number of doses* (subsequent years)
6 months–<3 years	0.25 mL	2†	1
3–9 years	0.5 mL	2†	1
>9 years	0.5 mL	1	1

* If a child 6 months to ≤9 years of age receiving influenza vaccine for the first time inadvertently does not receive the second dose within the same year, he/she should have 2 doses administered the following year.[7]

† Two doses at least 1 month apart are recommended for children aged ≤9 years who are receiving influenza vaccine for the first time. The same vial should not be re-used for the 2 doses.

Note:

(i) Some influenza vaccines available in Australia are packed in syringes graduated for measurement of recommended paediatric doses. Vaxigrip Junior presentation is a 0.25 mL pre-filled syringe ready for use. Fluvax and Fluarix 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 the product information sheets have some differences from Table 3.9.1. Fluvirin does not have a dose recommendation for children <4 years of age. The safety of Fluad, which is adjuvanted with MF59C, has not been established in children and it is registered for use only in people ≥65 years of age.

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 individuals at increased risk should not be missed when they present for routine care.

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

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

Recommendations

Annual influenza vaccination is recommended for any person ≥6 months of age who wishes to reduce the likelihood of becoming ill with influenza.

Influenza vaccination is strongly recommended and should be actively promoted for the following groups:

1. People at increased risk of complications from influenza infection

(i) All individuals ≥65 years of age[3,10-13]

Influenza vaccine has been shown to reduce hospitalisations from pneumonia and all-cause mortality by about half in adults ≥65 years of age.

(ii) All Aboriginal and Torres Strait Islander people ≥15 years of age

Annual influenza vaccine is recommended for Aboriginal and Torres Strait Islander people ≥15 years of age in view of the substantially increased risk of hospitalisation and death from influenza and pneumonia (see Chapter 3.15, *Pneumococcal disease*). In Aboriginal and Torres Strait Islander people ≥50 years of age, routine pneumococcal polysaccharide vaccination is also recommended (see Chapter 2.1, *Vaccination for Aboriginal and Torres Strait Islander people* and Chapter 3.15, *Pneumococcal disease*).

(iii) Individuals ≥6 months of age with conditions predisposing to severe influenza

- *Cardiac disease* including cyanotic congenital heart disease, coronary artery disease and congestive heart failure.[14,15] Influenza causes increased morbidity and mortality in children with congenital heart disease and adults with coronary artery disease and congestive heart failure.[14]
- *Chronic respiratory conditions* including:
    - Suppurative lung disease, bronchiectasis, and cystic fibrosis.[16] Patients with these diseases are at greatly increased risk from influenza, which may cause irreversible deterioration in lung function.

- Chronic obstructive pulmonary disease and chronic emphysema. There is clinical trial evidence that inactivated influenza vaccination has a clinically important protective effect on influenza-related exacerbations, and probably an effect on the total of exacerbations in COPD patients. There is no evidence that inactivated influenza vaccination causes exacerbations of COPD.[16]
- Severe asthma. In patients with severe asthma, defined as requiring frequent hospital visits, annual influenza vaccine is an important part of routine care.[17-19] There are insufficient data from randomised controlled trials of influenza vaccine to define efficacy across the whole spectrum of asthma,[20] but influenza can cause severe exacerbations of wheezing, and about 10% of episodes of virus-induced wheezing are attributable to influenza.

- *Other chronic illnesses requiring regular medical follow-up or hospitalisation* in the preceding year, including:
  - diabetes mellitus,
  - chronic metabolic diseases,
  - chronic renal failure,
  - haemoglobinopathies, and
  - impaired immunity (including drug-induced immune impairment).[7,21,22]
- *Chronic neurological conditions* (eg. multiple sclerosis, spinal cord injuries, seizure disorders or other neuromuscular disorders) that can compromise respiratory function or the expulsion of respiratory secretions or that can increase the risk for aspiration.[7] NB. Because they can experience severe, even fatal, influenza, vaccination is particularly important for children ≥6 months of age with chronic neurological conditions.[7]
- *People with impaired immunity*, including HIV infection.[23,24] Patients with impaired immunity, including HIV infection, malignancy and chronic steroid use, are at greatly increased risk from influenza, although they also have a reduced immune response to the vaccine. While patients with advanced HIV disease and low CD4 T-lymphocyte counts may not develop protective antibody titres, there is evidence that for those with minimal symptoms and high CD4 T-lymphocyte counts (see Chapter 2.3, *Groups with special vaccination requirements*, Table 2.3.4), protective antibody titres are obtained after influenza vaccination.[24] Influenza vaccine has been shown in a clinical trial to reduce the incidence of influenza in HIV-infected patients,[24] and although viral load may increase transiently, there is no impact on CD4 count.[23]
- *Long-term aspirin therapy in children* (aged 6 months to 10 years). Such children are at increased risk of Reye syndrome after influenza.

(iv) Pregnant women

It is 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.[25,26] Influenza vaccination is estimated to prevent 1 to 2 hospitalisations per 1000 women vaccinated during the second or third trimester.

(v) Residents of nursing homes and other long-term care facilities

This is due to high rates of transmission and complications during outbreaks.[3,9-13,27]

(vi) Homeless people and those providing care to them

The living conditions and prevalence of underlying medical conditions among homeless people will predispose to complications and transmission of influenza.

2. People who may potentially transmit influenza to those at high risk of complications from influenza

The following groups of people can potentially transmit influenza to high-risk patients and it has been shown that vaccinating the former protects those at high-risk:

- staff of nursing homes,
- healthcare providers[28] (particularly of patients with impaired immunity),
- staff of long-term care facilities,
- household contacts (including children ≥6 months of age) of individuals in high-risk groups.

3. People involved in the commercial poultry industry or in culling poultry during confirmed avian influenza activity[29]

Vaccination using the current influenza season vaccine composition is recommended for poultry workers and others in regular close contact with poultry during an avian influenza outbreak.[29] Although routine influenza vaccine does not protect against avian influenza, there is a possibility that a person who was infected at the same time with avian and human strains of influenza virus could allow reassortment of the 2 strains to form a virulent strain that could spread from human to human (ie. initiate a pandemic).

4. People providing essential services

Vaccination of those who provide essential community services will minimise disruption of essential activities during influenza outbreaks. Influenza viral infections can place considerable pressure upon both public and private healthcare services (see Chapter 2.3, *Groups with special vaccination requirements*, Table 2.3.6).

5. Workers in other industries

The cost-effectiveness of influenza vaccination in industry varies from year to year, depending on the amount of circulating influenza, but the overall impact over time is judged to be cost-saving in several settings.[6,7] Individual industries should consider the benefits of offering influenza vaccine in the workplace.

6. Travellers

Large tourist groups, especially those including elderly people and those travelling on cruises, who are likely to be in confined circumstances for days to weeks, are at risk of influenza, either acquired before departure or from travel to areas of the world where influenza is currently circulating. Influenza vaccination, preferably using the strain prevalent in the areas in which they will be travelling, is recommended if travelling during the influenza season, especially if it is known before travel that there are high rates or epidemics of influenza.[7]

Contraindications

Absolute contraindications to influenza vaccine are:

- anaphylaxis following a previous dose of any influenza vaccine,
- anaphylaxis following any vaccine component,
- individuals with anaphylactic sensitivity to eggs should *not* be given influenza vaccine. This includes those who, soon after ingesting eggs, develop swelling of the lips or tongue, or experience acute respiratory distress or collapse.

Precautions

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 developing the syndrome again, the chance of them coincidentally developing the syndrome following influenza vaccination may be higher than in individuals with no history of GBS.

Adverse events[27,30]

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

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

Immediate adverse events (such as hives, angioedema, or anaphylaxis) are a rare consequence of influenza vaccination. They probably represent an allergic response to a residual component of the manufacturing process, most likely egg protein. Individuals 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 to 1994 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 reported in Australia in association with influenza vaccine.[31]

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 'Recommendations' above.

Variations from 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 Fluarix states the influenza vaccine may be used in children from 3 months of age. NHMRC recommends influenza vaccine in children ≥6 months of age.

The product information for some vaccines gives a dose of 0.125 mL for children 3 or 6 months to 2 years old. NHMRC recommends that the lowest dose for any influenza vaccine is 0.25 mL. This is because influenza vaccine is relatively poorly immunogenic in infants, and 0.25 mL is the dose recommended in the USA for children aged ≥6 months where it has been shown to be safe.[32]

The product information for Fluvirin states that the product should not be given to children <4 years of age. Although the NHMRC recommends that children as young as 6 months of age can be vaccinated if they are at risk of complications of influenza, the suitability of the vaccine formulation for accurate preparation of 0.25 mL doses should be taken into account.

References

Full reference list available on the electronic *Handbook* or website http://immunise.health.gov.au.

3.10 JAPANESE ENCEPHALITIS

Virology

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

Clinical features

The disease is typically an acute neurological illness characterised by headache, fever, convulsions, focal neurological signs and depressed level of consciousness. It has a high case-fatality rate and there is a high prevalence of neurological sequelae (up to 50%) in those who survive the acute illness.[1] Less commonly, the disease may present as an acute flaccid paralysis.[1] Milder forms include febrile illness with headache, and aseptic meningitis. It is recognised, however, that most infections are asymptomatic; published estimates of the symptomatic to asymptomatic infection ratio vary in different populations from 1:25 to 1:1000.[1]

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, outbreaks occurring in the Torres Strait and north Queensland in 1995 and 1998.[2,3]

The JE virus is essentially a zoonosis of pigs and wading birds, and is transmitted between these animals by Culicine mosquitoes.[1] The virus replicates, leading to a transient high-level viraemia, within these so-called 'amplifying' hosts but not within other large vertebrates such as horses and humans.

Indeed, humans are an incidental host infected when living in close proximity to the enzootic cycle; this usually occurs in rural areas where there is prolific breeding of the vectors in flooded rice fields.[1]

There are two recognised epidemiological patterns of JE.[1] In the temperate or subtropical regions of Asia (northern Thailand, northern Vietnam, Korea, Japan, Taiwan, China, Nepal and northern India), the disease occurs in epidemics during the summer or wet season months (April to May until September to October). In the tropical regions (most of southeast Asia, Sri Lanka, southern India), the disease is endemic, occurring throughout the year, but particularly during the wet season.[1]

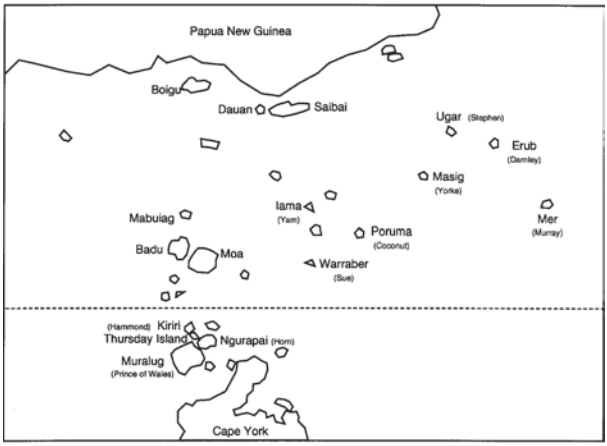
In some countries (Japan, Taiwan, South Korea, and some provinces of China), the incidence of JE has declined considerably in recent decades, and it has been eradicated from Singapore. Immunisation, changes in pig husbandry, a reduction in land utilised for rice farming, and improved socioeconomic circumstances have all contributed to these changes.[1]

In early 1995, 3 cases of JE, 2 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 (see Figure 3.10.1) at or about that time.[2] Although the 1995 outbreak was the first known incursion of JE virus into Australia, surveillance using sentinel pigs has shown incursions into the Torres Strait in virtually every wet season (December to May) since then.

In early 1998, a further case of JE occurred in an unvaccinated Badu resident and the first ever mainland case of JE occurred in a person working on the west coast of Cape York.[3] However, serological surveys revealed no evidence of JE virus infection in people in several nearby communities.[3] To date, there have been 5 cases of JE acquired in Australia.

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] A severe case of JE acquired near Port Moresby occurred in early 2004,[5] indicating that the JE virus is now probably widespread in Papua New Guinea.

Figure 3.10.1: Map of the Torres Strait. The outer islands are north of the dotted line



Vaccine

- **JE-VAX** – Sanofi Pasteur Pty Ltd (Japanese encephalitis virus vaccine inactivated). Each 1.0 mL reconstituted monodose vial contains formaldehyde inactivated Japanese encephalitis virus; 0.007% thiomersal; 470 µg gelatin; <100 µg formaldehyde; 5 mg monosodium glutamate; <50 ng mouse brain serum protein.

The JE vaccine available in Australia is an inactivated mouse brain-derived vaccine manufactured in Japan. However, the manufacturer has recently discontinued its production and, although the Australian distributor has access to a stockpile, shortages of the vaccine could occur over the next few years. New generation JE vaccines are expected in the mid to longer term.

The vaccine 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%.[6] However, immunogenicity studies have demonstrated that 3 doses of the vaccine are required to ensure adequate immunity in vaccinees from JE non-endemic areas.[7]

Transport, storage and handling

Transport according to *National Vaccine Storage Guidelines: Strive for 5*.[8] Store at +2°C to +8°C. Do not freeze. Reconstituted vaccine should be used immediately, but it can be stored at +2°C to +8°C and used within 8 hours.

Dosage and administration

JE vaccine is administered by the subcutaneous route. The volume injected is 0.5 mL in 1–3-year-old children and 1.0 mL for all individuals >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. An accelerated schedule of 0, 7 and 14 days can be used, but this is likely to result in lower antibody levels than the standard schedule.[7] If the accelerated schedule is used, a further dose should, if possible, be administered 1 to 3 months later.

NB. The volume of the reconstituted vaccine is greater than 1.0 mL. Because the dose of JE vaccine is 1.0 mL (0.5 mL in 1–3-year-old children) this means a small portion of the total reconstituted vaccine should be discarded.

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.[9] 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.

NB. A recent study has shown that the JE virus is hyperendemic in Bali, that it causes substantial human illness, and that it circulates year round.[10]

Therefore JE vaccination is recommended for:

- travellers spending 1 month or more in rural areas of Asia. However, as JE has occurred in travellers after shorter periods of travel, JE vaccination should be considered for shorter-term travellers, particularly if the travel is during the wet season, and/or there is considerable outdoor activity, and/or the accommodation is not mosquito-proof,[9]
- for all other travellers spending a year or more in Asia (except Singapore), even if much of the stay is in urban areas, and
- travellers intending to spend a month or more in Papua New Guinea, particularly if the travel is during the wet season.

(ii) Residents of Far North Queensland

JE vaccination is recommended for:

- all residents (>1 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 require vaccination.

(iii) Laboratory personnel

JE vaccination is recommended for all research laboratory personnel who potentially might be exposed to the virus.

(iv) Booster doses

Single booster doses are recommended at 3-yearly intervals.

Contraindications

- Anaphylaxis following a previous dose of JE vaccine or a significant allergic reaction, such as generalised urticaria, to a previous dose.
- Anaphylaxis following any component of the vaccine. A past history of allergic disorders (including urticaria, angioedema, anaphylaxis) following bee-stings, medications, foods etc. must be considered as possible contraindications to vaccination.
- The inactivated mouse brain-derived JE vaccine is contraindicated in those <1 year of age.

Precautions

There are few data on the safety and efficacy of JE vaccine in people with impaired immunity. 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;[11] the response to further doses was not studied.

Adverse events

- Local reactions and minor systemic reactions are common to very 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.
- Although the manufacturing process purifies the infected mouse brain suspension so that no myelin basic protein can be detected in the vaccine, serious neurological events following immunisation have been reported. In 1994, 4 cases of severe neurological illness, 2 of which were fatal, were reported from South Korea, and surveillance in Japan indicates the rate of severe neurological adverse events following JE vaccination is 1.8 cases per 1 million doses of vaccine.[7]
- Hypersensitivity (allergic) reactions are uncommon and occur in about 0.5% (ie. 1 in 200) vaccinees. These reactions include urticaria that is often widely distributed over the body, angioedema 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.[7] 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.[7] 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.[7] As a precaution, vaccinees should ideally remain within access to medical care for 10 days after vaccination.

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, pregnant women at risk of acquiring JE should be offered JE vaccine.

Variations from 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'. The NHMRC recommends that single booster doses be given at 3-yearly intervals.

References

Full reference list available on the electronic *Handbook* or website http://immunise.health.gov.au.

3.11 MEASLES

Virology

Measles is a paramyxovirus, genus *Morbillivirus*. It is an RNA virus with 6 structural proteins, 3 complexed to the RNA and 3 associated with the viral envelope. Two of the envelope proteins, the F (fusion) protein and the H (haemagglutinin) protein, are the most important in pathogenesis. The measles virus can survive up to 2 hours in air, but is rapidly inactivated by heat, light and extremes of pH.[1,2]

Clinical features

Measles is a highly infectious, acute viral illness spread by respiratory secretions, including air-borne transmission via aerosolised droplets.[2] It is infectious from the beginning of the prodromal period and up to 4 days after the appearance of the rash. The incubation period is usually 10 to 14 days. The prodrome, lasting 2 to 4 days, is characterised by fever and malaise followed by a cough, coryza and conjunctivitis. The maculopapular rash typically begins on the face and upper neck, and then becomes generalised.

Measles is often a severe disease, frequently complicated by otitis media (in ~9%), pneumonia (in ~6%) and diarrhoea (in ~8%).[1,2] Acute encephalitis occurs in 1 per 1000 cases, and has a mortality rate of 10 to 15%, with 15 to 40% of survivors suffering permanent brain damage.[3] Subacute sclerosing panencephalitis (SSPE) is a late complication of measles, occurring on average 7 years after infection in approximately 0.5 to 1 per 100 000 measles cases.[2] SSPE causes progressive brain damage and is always fatal. Complications from measles are more common and more severe in the chronically ill, in children <5 years of age, and in adults.[1] Approximately 60% of deaths from measles are attributed to pneumonia, especially in the young, while complications from encephalitis are more frequently seen in adults.[1,2] Measles infection during pregnancy can result in miscarriage and premature delivery but has not been associated with congenital malformation.[1]

Epidemiology

Evidence suggests that endemic measles has been eliminated from Australia, an indigenous measles strain being absent for several years.[4] Although measles outbreaks of limited duration continue to occur, they have usually been linked to imported cases.[5-7] In a recent measles outbreak, linked to an imported case, 25% of notified cases were in children aged 1–4 years, most of whom were not vaccinated.[8] Measles notifications and hospitalisations for the 5 years 2001–2005 have been the lowest recorded in Australia.[9,10] In the 30 years (1976–2005) since measles vaccination was recommended in Australia, there have been 95 deaths

recorded from measles, 1 death in 2004 being the only one recorded since 1995.[9-11] High-level vaccination coverage is imperative to maintain measles elimination, requiring rates for each new birth cohort of >95% for a single dose and >90% for 2 doses.[12] In 2004, the Australian Childhood Immunisation Register (ACIR) recorded that 93.6% of children aged 2 years (born in 2002) had received at least 1 dose of measles-containing vaccine and 84.8% of children aged 6 years (born in 1998) had received both doses.[13] It is likely that, when corrected for under-reporting, the target of 95% coverage for 1 dose of measles vaccine is reached at 2 years, but, if the second dose is not given until 4 years of age, 95% 2-dose coverage is not achieved.[14] Scheduling of the second dose of measles-containing vaccine at 18 months of age (see 'Recommendations' below) will provide 2-dose protection at an earlier age and may also improve second dose coverage.

Following the National 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 2–5 years, 94% of those aged 6–11 years, and 91% of those aged 12–18 years, were immune to measles.[15,16] The serosurvey evaluating the young adult MMR campaign in 2000 showed that those most at risk of measles infection in Australia were infants <12 months of age, 1–<2-year-olds due to delayed vaccine uptake, and individuals born in the late 1960s to mid 1980s (especially the 1978–1982 birth cohort).[17] Young adults are recognised to be at a greater risk of measles infection. Many missed being vaccinated as infants (when coverage was low), while during their childhood a second dose was not yet recommended and disease exposure was decreasing.[18]

Worldwide, measles is thought to be the fifth leading cause of childhood morbidity and mortality with 770 000 deaths estimated to have occurred in 2000. More than half these deaths occurred in Africa.[1,19] Following extensive vaccination campaigns, measles accounted for approximately 454 000 deaths worldwide in 2004.[20] The WHO is overseeing efforts to eliminate measles worldwide through immunisation and surveillance strategies that aim to interrupt the circulation of the virus.[21]

Vaccines

One measles-mumps-rubella (MMR) vaccine is currently available in Australia. It is anticipated that measles-mumps-rubella-varicella (MMRV) vaccines will become available in the near future. A monovalent vaccine is available for rubella where this is specifically required (see Chapter 3.19, *Rubella*). Separate administration of measles, mumps or rubella vaccine is not recommended as an alternative to MMR vaccine and no monovalent vaccines for mumps or measles are licensed in Australia.

Measles immunity induced by single-dose vaccination provides long-term immunity in most recipients.[1,22] However, approximately 5% of recipients fail to develop immunity to measles after 1 dose.[23] Following a second vaccine dose,

approximately 99% of subjects overall will be immune to measles. Combination MMRV vaccines have been shown, in clinical trials, to produce similar rates of seroconversion to all 4 vaccine components compared with MMR and monovalent varicella vaccines administered at separate injection sites.[24,25] Data on the use of MMRV vaccines are not available for people >12 years of age.

- **Priorix (MMR)** – 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 monodose of the reconstituted, lyophilised 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; lactose; neomycin; amino acids; sorbitol and mannitol as stabilisers.

Transport, storage and handling

Transport according to *National Vaccine Storage Guidelines: Strive for 5*.[26] Store at +2°C to +8°C. Protect from light. Do not freeze. Reconstituted vaccine should be used immediately, but can be stored at +2°C to +8°C for up to 8 hours before use.

Dosage and administration

For both children and adults, the dose of MMR is 0.5 mL, administered by either SC or IM injection.

MMR can be given at the same time as other vaccines (including DTPa, hepatitis B, MenCCV and varicella), using separate syringes and injection sites. If MMR is not given simultaneously with other live viral parenteral vaccines (eg. varicella vaccine), they should be given at least 4 weeks apart (see 'Precautions' below).[27,28]

Recommendations

(i) Routine vaccination of children

Two doses of MMR are recommended for all children. The first dose should be given at 12 months of age and the second dose at 18 months of age. The minimum interval between doses is 4 weeks.

When MMRV vaccines are available, the 12 month and 18 month doses may be given as MMRV.

The scheduled age at administration of the second dose of measles-containing vaccine has been moved from 4 years of age to 18 months of age to provide earlier 2-dose protection against measles and to improve vaccine uptake (see 'Epidemiology' above). The second dose of measles-containing vaccine at 18 months of age can be given as either MMR or, when available, MMRV. Receipt of 2 doses of varicella vaccine (VV) provides increased protection against

varicella, and MMRV, when available, should be preferred over MMR for the second dose of measles-containing vaccine at 18 months of age. (For further information, see also Chapter 3.24, *Varicella*.)

(ii) Vaccination of adults and adolescents

Those born before 1966:

No vaccination is required (unless serological evidence indicates otherwise) as circulating virus and disease were prevalent before this time suggesting most people would have acquired immunity from natural infection. However, recent confirmed cases of measles have occurred in individuals born before 1966 and, if doubt exists, it may be more expedient to offer vaccination than serological testing.[8]

Those born during or since 1966:

Infants ≥12 months up to 18 months of age should have documented evidence of 1 dose of MMR (or MMRV when available), or serological evidence of protection for measles.

Those ≥18 months of age should have documented evidence of 2 doses of MMR (administered at least 4 weeks apart with both doses administered at 12 months of age or over), or serological evidence of protection for measles, mumps and rubella.

Catch-up vaccination of children who have not received MMR or MMRV at 18 months of age should occur at the 4-year-old schedule point, until all the relevant children have reached 4 years of age. It is also acceptable to use MMRV in place of MMR at the 4-year-old schedule point. This would have the added benefit of providing a 2-dose VV schedule to an additional 2.5 birth cohorts of infants who had received single-dose monovalent VV at 18 months.

There are no increased adverse events from vaccinating those with pre-existing immunity to 1 or more of the vaccine components.

(iii) Healthcare workers and those who work with children

All workers in these categories who were born during or since 1966 and are non-immune or who have only received 1 dose of MMR, should be vaccinated with MMR, and have documented evidence of 2 doses or serological evidence of protection for measles, mumps and rubella (see 'Vaccination of adults and adolescents' above). (See also Section 2.3, Table 2.3.6 *Recommended vaccinations for those at risk of occupationally acquired vaccine-preventable diseases*.)

(iv) Travellers

Those born during or since 1966 should be encouraged to complete the MMR vaccination schedule (using MMR or MMRV, when appropriate) before embarking on international travel if they do not have evidence of receipt of 2 doses of MMR (see 'Vaccination of adults and adolescents' above).

Infants travelling to endemic countries may be vaccinated with MMR between 9 and 12 months of age. In these cases, another dose of MMR (or MMRV) should be given at 12 months of age or 4 weeks after the first dose, whichever is later. This should be followed by the routine administration of the next dose of MMR or MMRV at 18 months of age. This is because maternal antibodies to measles are known to persist in many infants until 11 months of age and may interfere with active immunisation before 12 months of age[1] (see 'Vaccination during an outbreak' below).

Contraindications

If using MMRV vaccine, additional contraindications relating to the varicella vaccine component are outlined in Chapter 3.24, *Varicella*.

(i) Allergy to vaccine components

Vaccination is contraindicated where there has been:

- anaphylaxis following a previous dose of MMR or MMRV, or
- anaphylaxis following any component of the vaccine.

Providers should consult the product information regarding vaccine components when MMRV vaccines are available.

(ii) People with impaired immunity

Measles-, mumps-, rubella- and varicella-containing vaccines are contraindicated in individuals with impaired immunity. In addition, there are no clinical trials or post-licensure data to address the safety and immunogenicity of MMRV in children or adults with impaired immunity. However, based on recommendations for the component live attenuated vaccine viruses, both MMR and MMRV are contraindicated in the following groups:

- those with primary or acquired cellular immunodeficiency states, including impaired immunity due to HIV/AIDS or conditions in which normal immunological mechanisms may be impaired. MMR (but not MMRV) vaccine can be given to HIV-positive children who do not have impaired immunity (see 'Precautions' below),
- those taking high-dose oral corticosteroids (in children equivalent to either >2 mg/kg per day prednisolone (≥20 mg per day total) for >1 week or >1 mg/kg per day for >4 weeks) (see Section 2.3.3, *Vaccination of individuals with impaired immunity due to disease or treatment*),
- those receiving high-dose systemic immunosuppressive treatment, general radiation or x-ray therapy,
- those suffering from malignant conditions of the reticuloendothelial system (such as lymphoma, leukaemia, Hodgkin's disease).

(iii) Recent administration of antibody-containing blood product

- The expected immune response to measles, mumps, rubella and varicella vaccination may be impaired after receipt of antibody-containing blood products.[23,27,29] The duration of interference with the response to measles vaccination depends on the amount of immunoglobulin contained in each product, and ranges from 3 to 11 months.[27] Vaccination with MMR or MMRV should be delayed after administration of antibody-containing products as indicated in Table 2.3.5 (see Section 2.3.5, *Vaccination of patients following receipt of other blood products including blood transfusions*).
- After vaccination with MMR or MMRV, immunoglobulin-containing products should not be administered for 3 weeks unless the benefits exceed those of vaccination. If immunoglobulin-containing products are administered within this interval, the vaccinee should either be revaccinated later at the appropriate time following the product as indicated in Table 2.3.5, or tested for immunity 6 months later and then revaccinated if seronegative.
- Blood transfusion with washed red blood cells is *not* a contraindication to MMR or MMRV vaccinations.
- Rh (D) immunoglobulin (anti-D) does not interfere with the antibody response to MMR vaccine and may be given at the same time in different sites with separate syringes or at any time in relation to each other.

(iv) Pregnant women

- If MMR vaccines are given to women of child-bearing age, pregnancy should be avoided for 28 days[30] (see Chapter 3.19, *Rubella*). Data on the use of MMRV vaccines in individuals >12 years of age are not available.

Precautions

- MMR can be administered on the same day as other live viral parenteral vaccines, such as monovalent varicella vaccine. However, if this is not possible, MMR should be deferred for at least 4 weeks after vaccination with other live viral parenteral vaccines.
- MMR can be given to asymptomatic or mildly symptomatic HIV-positive individuals providing they do not have severely impaired immunity.[23] (see Section 2.3.3, Table 2.3.4, *Immunological categories based on age-specific CD4 counts and percentage of total lymphocytes*). This is because the risk posed by measles infection is considered to be greater than the likelihood of adverse events from vaccination.[31] As there are no data available on the safety, immunogenicity or efficacy of MMRV vaccine in HIV-infected children, MMRV vaccine should not be administered as a substitute for MMR when vaccinating these children.[23,29]

- Children on daily doses of ≤2 mg/kg per day of systemic corticosteroids for <1 week, and those on lower doses of 1 mg/kg per day or alternate-day regimens for longer periods, may be given live viral vaccines.
- Children receiving >2 mg/kg per day or ≥20 mg per day in total of prednisolone (or equivalent) for >14 days can receive live viral vaccines after corticosteroid therapy has been discontinued for at least 1 month.[31] Some experts suggest withholding lower doses of steroids 2 to 3 weeks before vaccination with live viral vaccines if this is possible[29,31] (see Section 2.3.3, *Vaccination of individuals with impaired immunity due to disease or treatment)*.
- Use of salicylates (aspirin) is not recommended for 6 weeks following MMRV vaccination. This is because of the association between use of salicylates during natural varicella infection and Reye syndrome (see Chapter 3.24, *Varicella*). There is no need to avoid salicylates (aspirin) after MMR vaccination.
- Thrombocytopenia is a rare adverse event following vaccination with MMR.[2,32,33] Authorities differ in their opinion about whether the risk of vaccine-associated thrombocytopenia is increased in those who have previously had immune thrombocytopenia.[23,33] Post-marketing experience of live MMR vaccine in the USA indicates that individuals with current thrombocytopenia may develop more severe thrombocytopenia after vaccination. Recent studies found that children with immune thrombocytopenia before MMR had no vaccine-associated recurrences.[32,33] There are no systematic studies of the outcome of a second dose of MMR in children who developed thrombocytopenia after a first dose.[33]
- Children with a personal or close family history of seizures or convulsions should be given MMR or MMRV vaccine, provided the parents understand that there may be a febrile response 5 to 12 days after vaccination.[23] Advice for reducing fever with paracetamol and other measures should be given. Specialist advice should be sought rather than refusing to provide MMR or MMRV vaccination.
- Measles virus inhibits the response to tuberculin, so tuberculin-positive individuals may become tuberculin-negative for up to a month after measles infection or administration of measles-containing vaccines.[23] Mantoux testing is therefore unreliable for at least 4 weeks after the administration of MMR or MMRV. As measles infection may cause exacerbation of tuberculosis, there is a theoretical concern that measles-containing vaccine may exacerbate tuberculosis. Patients with tuberculosis should be under treatment when vaccinated.
- Children with egg allergy, even anaphylactic egg allergy, can be safely given MMR or MMRV vaccine.[2,34] Skin testing has been shown to be of no value in the management of these cases.[2] Although measles and mumps (but not rubella or varicella) vaccine viruses are grown in chick embryo tissue cultures,

it is now recognised that MMR (and MMRV) vaccine contains negligible amounts of egg protein (see 'Variations from product information' below).

- MMR and MMRV vaccines can be administered to susceptible children who have mild illnesses (eg. diarrhoea or upper respiratory infection), with or without low-grade fever (<38.5°C).

Adverse events

(If using MMRV vaccine, additional adverse events relating to the varicella vaccine component are outlined in Chapter 3.24, *Varicella*.)

- Malaise, fever and/or a rash may occur after MMR vaccination, most commonly 7 to 10 days (range 5–12 days) after vaccination and lasting about 2 to 3 days. High fever (>39.4°C) occurs in approximately 5 to 15% (common to very common), and rash occurs in approximately 5% (common) of MMR vaccinees.[1,23] The risk for febrile seizures is approximately 1 case per 3000 doses of MMR vaccine administered.[23] Slightly higher rates of fever were observed in clinical trials of MMRV vaccines, as compared with giving MMR and monovalent varicella vaccine at the same time but at separate sites.[24,25]
- A varicelliform rash may occur after vaccination with MMRV (see Chapter 3.24, *Varicella* 'Adverse events'). The appearance of a rash after monovalent varicella vaccine occurs in <5% (common) of vaccinees, and similar rates are observed with the use of MMRV.[35]
- Adverse events are much less common after the second dose of MMR and MMRV than after the first dose.
- Anaphylaxis following the administration of MMR is very rare (less than 1 in 1 million doses distributed).[23] Although no cases of anaphylaxis were reported in MMRV clinical trials, the incidence is likely to be similar to that occurring with use of MMR. Anaphylaxis after vaccination is likely due to gelatin or neomycin anaphylactic sensitivity, not egg allergies (see 'Precautions' above).
- It is uncertain whether encephalopathy occurs after measles vaccination. If it does, it is at least 1000 times less frequent than as a complication from natural infection.[1,23]
- Other rare adverse events attributed to MMR vaccine include transient lymphadenopathy and arthralgia (see Chapter 3.19, *Rubella*). Parotitis has been reported rarely.[23]
- Thrombocytopenia (usually self-limiting) has been very rarely associated with the rubella or measles component of MMR occurring in 3 to 5 per 100 000 doses of MMR vaccine administered.[2,23,32,33] This is considerably less than after natural measles, mumps and rubella infections[33] (see also Chapter 3.19, *Rubella*). Any association with MMRV vaccine is expected to be similar.

- It is recommended that parents/vaccine recipients be advised about possible symptoms, and given advice for reducing fever, including the use of paracetamol for fever in the period 5 to 12 days after vaccination. The use of aspirin after MMRV vaccination is not recommended for 6 weeks (see Chapter 3.24, *Varicella*).
- It had been hypothesised that the measles component of the MMR vaccine may be causally linked with autism, autistic spectrum disorder and inflammatory bowel disease.[36] There has been no credible scientific evidence to support this claim. Most proponents of the hypothesis have retracted this claim[37] and there is now good evidence to refute it[38] (see Appendix 5, *Commonly asked questions about vaccination*).

Transmissibility of MMR vaccine viruses

Measles, mumps and rubella vaccine viruses are not transmissible to contacts.[23] It is, therefore, safe to vaccinate the healthy siblings of children with impaired immunity and safe for children with impaired immunity to go to school with children recently vaccinated with the MMR vaccine. If using MMRV, see Chapter 3.24, *Varicella* for information about varicella vaccine virus transmission.

The public health management of measles

(i) Definition of a person who is considered ***not*** susceptible to measles

A person is considered not susceptible to measles if he/she meets 1 of the following criteria:

- born during or since 1966 with documented evidence of receiving 2 doses of a measles-containing vaccine, with both doses of vaccine having been given at ≥12 months of age and at least 4 weeks apart. This applies unless serological evidence indicates otherwise,
- born before 1966 (unless serological evidence indicates otherwise),
- documented evidence of immunity,
- documented evidence of laboratory confirmed measles infection.

NB. These criteria have been revised since publication of the *Guidelines for the control of measles outbreaks in Australia* in 2000.[39]

(ii) Vaccination of measles contacts

As vaccine-induced measles antibody develops more rapidly than that after natural infection, MMR vaccine can be used to protect susceptible contacts.[23] 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). 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 are too slow for effective use of vaccine as prophylaxis after exposure to these infections. Alternatively, MMRV vaccine, when available, could also be used in this setting if varicella vaccination is indicated. However, there are no data on the use of MMRV vaccines in individuals >12 years of age.

Immunoglobulin is available for contacts for whom measles-containing vaccine is contraindicated (see 'Use of immunoglobulin to prevent measles' below), for infants aged 6–9 months, and for susceptible individuals who did not receive a measles-containing vaccine within 72 hours of contact (see Table 3.11.1 below).

Isolation of susceptible close contacts by exclusion from school or the workplace should occur until 14 days after their last exposure[39] *unless* they receive either the MMR vaccine within 72 hours or immunoglobulin within 7 days of their first exposure. If they do not receive MMR vaccine or immunoglobulin within these specified timeframes, they should be excluded.

(iii) Vaccination during an outbreak

During a confirmed measles outbreak, MMR vaccine may be given (on the direction of public health authorities) to infants between 9 and 12 months of age, and even to those between 6 and 9 months of age.[39] In these cases, another dose of MMR (or MMRV when available) should be given at 12 months of age or 4 weeks after the first dose, whichever is later. This should be followed by the routine administration of the next dose of measles-containing vaccine at 18 months of age. This is because maternal antibodies to measles are known to persist in many infants until 11 months of age and may interfere with active immunisation before 12 months of age.[1]

Children between 12 and 18 months of age who have received 1 dose of measles-containing vaccine can be offered their second dose early (ie. at least 4 weeks after the first dose) if they are considered at risk of coming in contact with measles[39] (see 'Recommendations (i)' above). If a child receives the second dose early, he/she is considered to have completed the vaccination schedule and, therefore, does not require another dose at 18 months of age or beyond, provided 2 doses were given at ≥12 months of age and at least 4 weeks apart.

Any older children, adolescents or adults who are considered susceptible to measles (see (i) above) during an outbreak should receive MMR (or MMRV if appropriate).

(iv) Use of immunoglobulin to prevent measles

Normal human immunoglobulin (NHIG) should be considered for contacts of patients with confirmed or suspected measles[39] (see Table 3.11.1). If NHIG is administered by IM injection within 7 days of exposure, it can prevent or modify measles in non-immune individuals.

The dose of NHIG is 0.2 mL/kg by deep IM injection for healthy children, adolescents and adults (including pregnant women), and 0.5 mL/kg by deep IM injection for people with impaired immunity. The maximum dose is 15 mL.

NHIG should be given to exposed individuals if contact was within the previous 7 days in the following instances:

- infants <6 months of age where the infant's mother is the measles case, or the infant was born before 28 weeks' gestation,
- infants 6–9 months of age (see 'Vaccination during an outbreak' above),
- all those ≥9 months of age in whom administration of MMR vaccine would be contraindicated,
- non-immune pregnant women,
- those exposed to measles who have impaired immunity,
- those who have never received a measles-containing vaccine, and who did not receive a MMR or MMRV vaccine within 72 hours of contact.

Children with impaired immunity, where MMR 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 individuals with significantly impaired immunity.[23,39] 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 6–9 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.[39] MMR vaccine should then be given as close as possible to 12 months of age, after an interval of at least 5 months following the administration of immunoglobulin (see Chapter 2.3, *Groups with special vaccination requirements*, Table 2.3.5 *Recommended intervals between either immunoglobulins or blood products and MMR, MMRV or varicella vaccination*). NHIG is not usually given to babies <6 months of age, who are protected by passive maternal antibodies. However, if the mother of an infant <6 months of age does not have documented evidence of having received 2 doses of MMR, or is the measles case, the infant should be given NHIG. Similarly, premature infants (<28 weeks' gestation) have little or no acquisition of transplacental maternal antibody, irrespective of the number of doses of MMR the mother has received, and should also be offered NHIG (see Table 3.11.1).

Table 3.11.1: Management of significant measles exposure using vaccination or normal human immunoglobulin (NHIG)

Age	Action
<6 months	NHIG 0.2 mL/kg* IM injection *if* mother has not received 2 documented doses of MMR, or the mother is the measles case, or the infant was premature (<28 weeks' gestation)
≥6–≤9 months	NHIG 0.2 mL/kg IM injection*
≥10 months	MMR or MMRV vaccine within 72 hours of exposure OR NHIG 0.2 mL/kg IM injection* if 3–7 days after exposure†

* The dose of NHIG is 0.2 mL/kg in immunocompetent individuals and 0.5 mL/kg in those with impaired immunity.

† Immunoglobulin is not required if the person has received at least 1 measles-containing vaccine at ≥12 months of age or is assessed as being not susceptible (see (i) 'Definition of a person who is considered *not* susceptible to measles' above), unless the person has impaired immunity.

Use in pregnancy

MMR vaccine is not recommended in pregnancy due to the theoretical risk of transmission of the rubella component of the vaccine to a susceptible fetus. Pregnancy should be avoided for 28 days after vaccination[30] (see Chapter 3.19, *Rubella* and Chapter 2.3, *Groups with special vaccination requirements*, Table 2.3.1 *Vaccinations in pregnancy)*.

Variations from 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 MMR or MMRV vaccines, whereas the NHMRC recommends 28 days.[30]

The product information for Priorix states that people with a history of anaphylactic or anaphylactoid reactions should not be vaccinated with Priorix, but it is established that MMR vaccine can be given in this situation.[23]

References

Full reference list available on the electronic *Handbook* or website http://immunise.health.gov.au.

3.12 MENINGOCOCCAL DISEASE

Bacteriology

Meningococcal disease is caused by the bacterium *Neisseria meningitidis* (*N. meningitidis* or the meningococcus), a Gram-negative diplococcus. There are 13 known serogroups distinguished by differences in surface polysaccharides of the outer membrane capsule. Meningococcal serogroups are designated by letters of the alphabet. Globally, serogroups A, B, C, W_{135} and Y most commonly cause disease. Meningococci can be further differentiated by differences in their outer membrane proteins, which are referred to as serotypes and serosubtypes.[1] More recently, molecular typing has been used to further differentiate meningococci. 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.

N. meningitidis is carried and transmitted only by humans. There are no known animal reservoirs. Asymptomatic respiratory tract carriage of meningococci is present in about 10% of the population, and the prevalence may be higher when groups of people occupy small areas of living space.[2-8] Recent studies indicate that there may be a number of factors which contribute to the increased risk of contracting meningococcal disease, including exposure to smokers, recent illness, living in crowded conditions and multiple intimate kissing partners.[4-8] People 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]

The disease is transmitted via respiratory droplets, and has an incubation period of between 1 and 10 days, but commonly 3 to 4 days.[4] The capacity of meningococcal disease to have a fulminant and rapidly fatal course in previously healthy (and usually young) 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.[9]

Epidemiology

Meningococci cause 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 increased in incidence in the 1990s in some developed countries such as Australia and the United Kingdom.[4] Serogroup C meningococci have also been occasionally associated with small clusters of meningococcal disease cases in schools, universities and nightclubs in Australia over the past 10 years.[10-15]

As in other temperate climates, meningococcal disease cases occurring in Australia tend to follow a seasonal trend, the majority of cases being reported during late winter and early spring. The overall notification rate of meningococcal disease to the National Notifiable Diseases Surveillance System increased gradually from 1.8 per 100 000 in 1991, to a peak of 3.5 per 100 000 in 2001, but declined to 1.8 per 100 000 in 2005.[16] There are considerable differences noted in the incidence of meningococcal disease between States and Territories, with 5.4 cases per 100 000 notified from the Northern Territory to 1.9 per 100 000 reported for Queensland during 2005.[16] These figures include meningococcal disease cases which were diagnosed on clinical grounds alone, and those cases that were confirmed by laboratory methods such as culture, serology or nucleic acid testing of clinical material. In 2005, 369 cases were reported nationally, of which 345 were laboratory confirmed.[16,17] The majority of laboratory-confirmed meningococcal cases were serogroup B (73%) and serogroup C (14.5%).[17] There has been a steady decline in serogroup C meningococcal disease among the 0–18 years age group since the 2003 introduction of routine meningococcal C vaccination and catch-up programs in this age group.[18]

Meningococcal disease can occur in any age group, but the majority of cases occur in those <5 years of age, with a secondary peak seen in the 15–24 years age group. In Australia, meningococcal disease in the <5 years age group is due predominantly to infection with serogroup B meningococci; very few cases of serogroup C meningococcal disease are now seen in this age group.[17] In the 15–19 years age group, both serogroup B and C disease were seen before the introduction of the meningococcal C conjugate vaccine in 2003.

In contrast to Australia, New Zealand has, over the past 14 years, experienced an epidemic of meningococcal disease which has been almost exclusively associated with a particular strain of serogroup B (B:4:P1.7b,4).[19,20] Meningococcal disease rates in NZ rose from 1.5 cases per 100 000 during 1989–1990 to 14.5 cases per 100 000 in 2003.[19] A meningococcal B outer membrane vesicle vaccine (MeNZB™), currently being used in New Zealand, is only effective against the serotype and serosubtype of the New Zealand serogroup B strain and is not available in Australia.[20]

Vaccines

There are 2 different types of meningococcal vaccine: the meningococcal C conjugate vaccines (MenCCV) and the tetravalent meningococcal polysaccharide vaccines (4vMenPV). The differences between these 2 types of vaccines lie in the different way that each vaccine stimulates an immune response.

Other than the New Zealand specific vaccine, there is currently no vaccine effective against serogroup B meningococcal disease although extensive research is being undertaken in this area.

CONJUGATE VACCINES

Meningococcal C conjugate vaccines (MenCCV)

- **Meningitec** – Wyeth Australia Pty Ltd (meningococcal serogroup C–CRM_{197} conjugate vaccine). Each 0.5 mL monodose vial contains 10 µg *N. meningitidis* serogroup C oligosaccharide conjugated to approximately 15 µg of a non-toxic *Corynebacterium diphtheriae* CRM_{197} protein; aluminium phosphate.
- **Menjugate Syringe** – CSL Biotherapies/Novartis Vaccines (meningococcal serogroup C–CRM_{197} conjugate vaccine). Lyophilised powder in a monodose vial with a pre-filled diluent syringe. Each 0.5 mL dose of reconstituted vaccine contains 10 µg *N. meningitidis* serogroup C polysaccharide conjugated to 12.5–25 µg of a non-toxic *Corynebacterium diphtheriae* CRM_{197} protein; 1.0 mg aluminium hydroxide. 5 or 10 monodose packs also available.
- **NeisVac-C** – Baxter Healthcare (meningococcal serogroup C–tetanus toxoid protein conjugate vaccine). Each 0.5 mL pre-filled syringe contains 10 µg *N. meningitidis* serogroup C polysaccharide conjugated to 10–20 µg of tetanus toxoid protein; 0.5 mg aluminium hydroxide. 10 or 20 monodose packs available.

In January 2003, the Australian Government commenced the National Meningococcal C Vaccination Program which provided free MenCCV to all children who turned 1 to 19 years of age during 2003. MenCCV was also added to the National Immunisation Program (NIP) schedule at 12 months of age at that time.

MenCCVs confer protection *only* against serogroup C disease. In these vaccines, an 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 the United Kingdom, 98 to 100% of infants given 3 doses of MenCCV in a 2, 3 and 4 month schedule developed protective antibody titres after the third dose,[21,22] but evidence of waning immunity and vaccine failures led to a booster dose being recommended for children vaccinated according to the 2, 3 and 4 month schedule of MenCCV,[23] which has now been altered to a 3-dose schedule at 3, 4 and 12 months of age.[24] In Australia, although some children have received MenCCV before 12 months of age, this was according to a 2, 4, 6 month schedule and there is no evidence of vaccine failure. NHMRC, therefore, does not recommend recall for a booster dose in children *previously* vaccinated before 12 months of age (unless they have inherited defects of properdin or complement, or functional or anatomical asplenia – see 'Recommendations' below).

In children >12 months of age, a single dose of MenCCV appears sufficient to induce protective antibody responses. In children 12–18 months of age receiving a single dose of MenCCV, 91 to 100% achieved serum bactericidal antibodies (SBA) titres ≥1:8.[25] In older children, seroconversion rates increase with age: 96% of 3-year-olds, 98% of 4–5-year-olds, and 98% of 14–17-year-olds achieved SBA titres ≥1:8 after a single dose.[25] In those children aged ≥1 year who have received only a single dose of the meningococcal C conjugate vaccine, the duration of immunity and the need for booster doses is not yet known. The Netherlands routinely vaccinates with MenCCV at 14 months of age, and data from 2002 onwards currently indicates that vaccination after the 1st birthday results in longer protection than multiple doses in infancy.[26]

POLYSACCHARIDE VACCINES

Meningococcal polysaccharide vaccines (4vMenPV)

- **Mencevax ACWY** – GlaxoSmithKline (serogroup A, C, W_{135} and Y meningococcal polysaccharide vaccine). Each 0.5 mL monodose of the reconstituted lyophilised vaccine contains 50 µg of each polysaccharide; lactose. 10-dose vials in packs of 50 contain 0.25% phenol as a preservative. Saline diluent for each vial.
- **Menomune** – Sanofi Pasteur Pty Ltd (serogroup A, C, W_{135} and Y meningococcal polysaccharide vaccine). Each 0.5 mL monodose of the reconstituted lyophilised vaccine contains 50 µg of each polysaccharide; lactose.

4vMenPVs provide protection against serogroups A, C, W_{135} and Y. The vaccine induces antibodies in 10 to 14 days in 90% of recipients >2 years of age. Immunity decreases markedly during the first 3 years following a single dose of vaccine, particularly in infants and young children. However, clinical protection persists for at least 3 years in school children and adults.

The duration of immunity is further complicated by the induction of immunological hyporesponsiveness to the serogroup C component following repeated vaccination with 4vMenPV, as revaccination results in a reduced antibody response compared with the primary immunisation.[27] This phenomenon has been noted in both children and adults.[28-31] The demonstration of subsequent hyporesponsiveness has led to the concern that vaccinating low-risk individuals may reduce the effectiveness of revaccination in a subsequent high-risk situation, although this has not been clinically demonstrated. This hyporesponsiveness can be overcome with MenCCV, although additional doses of the conjugate vaccine may be required in young children.[32,33] 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.[34,35]

Transport, storage and handling

Meningococcal C conjugate vaccines

Transport according to *National Vaccine Storage Guidelines: Strive for 5*.[36] Storage of all MenCCVs should be at +2°C to +8°C. Do not freeze. Protect from light.

The product information for NeisVac-C states that this vaccine can be stored at +25°C for a period of up to 9 months *but must not be returned to the refrigerator.*

Meningococcal polysaccharide vaccines

Transport according to *National Vaccine Storage Guidelines: Strive for 5*.[36] Store at +2°C to +8°C. Do not freeze. Protect from light. Reconstituted vaccine should be used immediately but may be stored in the refrigerator at +2°C to +8°C, and must be discarded if not used within 8 hours.

Dosage and administration

Meningococcal C conjugate vaccines

The MenCCV dose is 0.5 mL 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. MenCCVs may be administered simultaneously with other vaccines in the NIP (see 'Variations from product information' below). MenCCVs are registered for use in Australia from 6 weeks of age.

Meningococcal polysaccharide vaccines

The 4vMenPV dose is 0.5 mL, administered by SC injection. 4vMenPVs are approved for use in Australia in children ≥2 years of age, adolescents and adults.

Administration of MenCCV after administration of 4vMenPV

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 before the conjugate vaccine is given.[21,37]

Administration of 4vMenPV after administration of MenCCV

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.

Recommendations

Meningococcal C conjugate vaccines

(i) Routine vaccination

It is recommended that a single dose be given to all children at the age of 12 months.

Vaccination before 12 months of age is not recommended, except in infants with inherited defects of properdin or complement, or functional or anatomical asplenia (see (ii) below). Infants, other than those described in the circumstances below, who receive dose(s) of vaccine at <12 months of age, should be given a further dose at 12 months of age or 4 weeks after the last dose, whichever is later. However, it is not necessary to recall older children who received 3 doses of MenCCV before 12 months of age, as there has been no evidence to date of vaccine failure in infants vaccinated according to a 2, 4, 6 month schedule (see 'Vaccines' above).

(ii) Vaccination of people at high risk for meningococcal disease

The vaccine is also recommended for:

- close (household or household-like) contacts of meningococcal disease cases due to serogroup C, >2 months of age, who have not previously been vaccinated (refer to 'The early clinical and public health management of meningococcal disease' below),
- control of outbreaks caused by serogroup C (refer to 'The early clinical and public health management of meningococcal disease' below),
- laboratory personnel who frequently handle *N. meningitidis,* who should also receive 4vMenPV,
- those >6 weeks of age with inherited defects of properdin or complement, or functional or anatomical asplenia. When MenCCV is given to these individuals at <12 months of age, in addition to a booster dose of MenCCV at 12 months of age, a dose of 4vMenPV is recommended at ≥2 years of age.

Under the circumstances as described above, a child under the recommended age of 12 months requiring vaccination should receive doses as follows:

- Infants <6 months of age require 2 doses of 0.5 mL, given at least 8 weeks apart, followed by a booster dose at 12 months of age.
- Children 6–11 months of age require 1 dose of 0.5 mL, followed by a booster dose at 12 months of age or 8 weeks after the first dose, whichever is later.

Meningococcal polysaccharide vaccines

Routine vaccination with 4vMenPV is not recommended. However, it is recommended in the following situations:

- people who intend travelling to parts of the world where epidemics of group A, W_{135} or Y disease are frequent (a current list of those countries is available from the World Health Organization at either http://www.who.int/ith or http://www.who.int/disease-outbreak-news/),
- close (household or household-like) contacts, ≥2 years of age, of cases of serogroup A, W_{135} or Y meningococcal disease,
- control of outbreaks caused by serogroup A, W_{135} or Y. A Cochrane review examined the use of polysaccharide vaccine for the prevention of serogroup A meningococcal meningitis. The review assessed 8 randomised controlled trials and the protective effect from the vaccine was consistent across all the trials with a vaccine efficacy of around 95%,[38]
- laboratory personnel who frequently handle *N. meningitidis*, who should also receive MenCCV,
- those ≥2 years of age 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).

A single revaccination with 4vMenPV is indicated for people at continued high risk of infection (such as those living in epidemic areas, and those with impaired immunity as defined above), particularly 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. Data regarding the benefit of subsequent revaccinations with 4vMenPV are unavailable at this time.

Contraindications

Meningococcal C conjugate vaccines

The only absolute contraindications to MenCCV are:

- anaphylaxis following a previous dose, or
- anaphylaxis following any component of the vaccine

Previous serogroup C disease is not a contraindication to administration of MenCCV.

Meningococcal polysaccharide vaccines

The only absolute contraindications to 4vMenPV are:

- anaphylaxis following a previous dose, or
- anaphylaxis following any vaccine component.

Adverse events

Meningococcal C conjugate vaccines

Very 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.[37]

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% (common) of young children, and may persist for 48 hours or longer, but significant general adverse events are rare.

The 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 parenteral (usually IM) penicillin and transferred to hospital. The relevant Public Health Unit must be contacted as soon as possible.[4]

Table 3.12.1: Early clinical management of suspected meningococcal disease

The patient should receive immediate benzylpenicillin (usually IM).	Age <1 year	300 mg benzylpenicillin
	Age 1–9 years	600 mg benzylpenicillin
	Age ≥10 years	1200 mg benzylpenicillin
The patient should be transferred to hospital urgently.		
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. Rather, it is carrier(s) passing on the bacteria to other susceptible individuals who 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. The public health management of close contacts includes

information, clearance antibiotics and vaccination. Clearance antibiotics should be offered to all identified close contacts regardless of previous vaccination history. Clearance antibiotics are not recommended for healthcare workers unless they were engaged in either mouth-to-mouth resuscitation or were not wearing a mask while intubating a case.

Non-vaccinated close contacts of a proven vaccine-preventable strain of invasive meningococcal disease should be advised in writing by their local Public Health Unit to visit their usual healthcare provider at the next available opportunity to receive the appropriate vaccine.[4]

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 <12 years of age, 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 <1 month of age is 5 mg/kg twice daily for 2 days. Pharyngeal carriage will be eliminated in 75 to 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.

Use in pregnancy

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 before vaccination is not justified.

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.[1,39,40] The number of pregnant vaccinees who received 4vMenPV as reported in the literature is small. A North American study of 109 women who received the 4vMenPV vaccine between 30 and 38 weeks' gestation reported no birth defects.[39] A further study of 34 pregnant women in the US who received 4vMenPV during their second and third trimester revealed no teratogenicity and the infants were assessed for 2 years after birth. No developmental abnormalities were detected.[40]

Variations from product information

Meningococcal C conjugate vaccines

The product information for meningococcal C conjugate vaccines state that, under the age of 12 months, either 2 (NeisVac-C) or 3 (Meningitec and Menjugate) doses of vaccine are required. The NHMRC recommends that meningococcal C vaccination is not required before 12 months of age (unless specifically indicated).

The NeisVac-C product information states that the vaccine should not be administered with pneumococcal conjugate vaccine, hepatitis B vaccine and PRP-OMP *Haemophilus influenzae* type b vaccine unless 'medically important'. However, the NHMRC states that the vaccine may be administered simultaneously with other vaccines in the NIP. There have been recent publications citing the coadministration of MenCCV with other combination vaccines and it was found to be immunogenic and safe.[41,42]

The product information for all 3 conjugate vaccines states 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 vaccinating.

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

Meningococcal polysaccharide vaccines

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

References

Full reference list available on the electronic *Handbook* or website http://immunise.health.gov.au.

3.13 MUMPS

Virology

Mumps is a paramyxovirus, genus *Rubulavirus*, with a single-stranded RNA genome. It is rapidly inactivated by heat, formalin, ether, chloroform and ultraviolet light.[1]

Clinical features

Mumps is an acute viral illness with an incubation period of 14 to 25 days.[2] Asymptomatic infection occurs in one-third of cases.[3] Symptomatic disease ranges from mild upper respiratory symptoms to widespread systemic involvement.[3] A high proportion of mumps infections involve non-specific symptoms including fever, headache, malaise, myalgia and anorexia.[4] The characteristic bilateral, or occasionally unilateral, parotid swelling occurs in 60 to 70% of clinical cases.[4] 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, mastitis).[1,4] Patients may be infectious from 6 days before parotid swelling to 9 days after.[2] Mumps encephalitis has been reported to range as high as 1 in 200 cases, with a case-fatality rate of around 1.0%.

Mumps infection during the first trimester of pregnancy may result in spontaneous abortion.[3,4] Maternal infection is not associated with an increased risk of congenital malformation.[3,4]

Epidemiology

Mumps is reported worldwide, and is a human disease. Transmission is by the respiratory route in the form of air-borne droplets or by direct contact with saliva or possibly urine.[2] Before universal vaccination, mumps was primarily a disease of childhood, the peak incidence being in the 5–9 year age group. However, since 2000, peak rates have been reported in older adolescents and young adults, especially the 20–24 year age group.[5-7] Between 2001 and 2005, the average notification rate for mumps in Australia was 0.6 per 100 000.[8] There have been recent outbreaks of mumps in the USA, and also in the United Kingdom, where the peak rates of disease have been in the 18–24 year age group.[9,10] Approximately 2000 cases were reported in the USA in a 2006 outbreak, parotitis being reported in 66% of clinical cases.[11] Mumps attack rates in outbreaks are lowest in individuals who have received 2 doses of mumps-containing vaccines, as this provides optimal long-term protection.[10,11] In Australia, over the 10-year

period from 1996 to 2005, mumps has been reported as the underlying cause of death in 4 subjects, all adults aged over 80 years.[5-7]

Vaccines

Monovalent mumps vaccine is no longer available in Australia. Mumps vaccination is provided using either MMR vaccine or MMRV vaccine when available.

Clinical trials of mumps vaccine indicate 95% seroconversion after a single dose of MMR.[4] However, outbreak investigations and post-marketing studies have reported 1-dose vaccine effectiveness to be between 60 and 90%.[10] Protection is greater in 2-dose vaccine recipients, who have seroconversion rates of up to 100%.[4,10,12]

- **Priorix (MMR)** – 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 monodose of the reconstituted, lyophilised 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; lactose; neomycin; amino acids; sorbitol and mannitol as stabilisers.

Transport, storage and handling

Transport according to *National Vaccine Storage Guidelines: Strive for 5*.[13] Store at +2°C to +8°C. Protect from light. Do not freeze. Reconstituted vaccine should be used immediately, but can be stored at +2°C to +8°C for up to 8 hours before use.

Dosage and administration

For both children and adults, the dose of MMR is 0.5 mL, administered by either SC or IM injection.

MMR can be given at the same time as other vaccines (including DTPa, hepatitis B, MenCCV and varicella), using separate syringes and injection sites. If MMR is not given simultaneously with other live viral parenteral vaccines (eg. varicella vaccine), they should be given at least 4 weeks apart (see 'Precautions' below).

Recommendations

All children should receive 2 doses of MMR vaccine (or MMRV vaccine, when available, if ≤12 years of age). Routine administration of MMR (or MMRV) is now recommended at 12 months and 18 months of age in order to maximise protection at an early age. The minimum interval between doses is 4 weeks.

In older individuals, who have received only 1 dose of mumps-containing vaccine, a second dose can be given, as MMR, at any age.

For further information on the recommendations for MMR (and MMRV when available) see Chapter 3.11, *Measles* and Chapter 3.24, *Varicella*.

Contraindications

See information on MMR and MMRV vaccines in Chapter 3.11, *Measles* and Chapter 3.24, *Varicella*.

Precautions

If MMR is not given simultaneously with other live viral parenteral vaccines (eg. varicella vaccine), they should be given at least 4 weeks apart.

See further information on MMR and MMRV vaccines in Chapter 3.11, *Measles* and Chapter 3.24, *Varicella*.

Adverse events

In Australia, vaccine-associated aseptic meningitis is not considered a problem. Post-licensure surveillance of mumps vaccine recipients in Germany, over a 2-year period, found no increase in cases of aseptic meningitis. However, other estimates in countries using mumps vaccines with different vaccine virus strains suggest 1 case occurs per 800 000–1 million doses.[4,14] Vaccine-associated meningoencephalitis is invariably mild or asymptomatic and resolves spontaneously. When mumps virus is isolated from the cerebrospinal fluid in such cases, laboratory tests can be undertaken to distinguish between wild and vaccine strains. The assistance of State virology laboratories should be sought in such cases.

Re-vaccination with mumps-containing vaccines is not associated with an increased incidence of adverse events.

For further information on the adverse events associated with MMR and MMRV, see Chapter 3.11, *Measles* and Chapter 3.24, *Varicella*.

Use of immunoglobulin to prevent mumps

Normal human immunoglobulin (NHIG) has not been shown to be of value in post-exposure prophylaxis for mumps.[1,15] Live mumps-containing vaccine does not provide protection if given after an individual has been exposed to mumps.[1,15] However, if the exposure did not result in infection, the vaccine would induce protection against subsequent infection.

Use in pregnancy

MMR vaccine is not recommended in pregnancy due to the theoretical risk of transmission of the rubella component of the vaccine to a susceptible fetus (see Chapter 3.19, *Rubella*). Pregnancy should be avoided for 28 days after vaccination.[16] Data on the use of MMRV vaccines in individuals >12 years of age are not available.

Variations from product information

See information on MMR vaccines in Chapter 3.11, *Measles*.

References

Full reference list available on the electronic *Handbook* or website http://immunise.health.gov.au.

3.14 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] Identification of pertussis is limited by patient and physician awareness and the limited sensitivity of diagnostic tests; it is generally believed to be significantly under-diagnosed.

Clinical features

Pertussis is an epidemic respiratory infection with an incubation period of 7 to 20 days. In unvaccinated individuals, *B. pertussis* is highly infectious, spreading by respiratory droplets to 80% of susceptible household contacts.[2] The characteristic paroxysmal cough with inspiratory whoop seen in unvaccinated children is less common in older children and adults who have varying degrees of immunity acquired from vaccination or infection. It has been estimated that *B. pertussis* accounts for up to 7% of cough illness per year in adults and, each year, more than 25% of adults experience a coughing illness of at least 5 days' duration.[2,3] Even in adults, pertussis can be associated with significant morbidity, with cough persisting for up to 3 months, and other significant symptoms, such as sleep disturbance or, rarely, rib fracture.[4]

Death due to pertussis is rare in people >10 years of age. However, the case fatality rate in unvaccinated infants <6 months of age is estimated to be 0.8%.[5,6] The most common cause of death in pertussis infection is pertussis pneumonia, sometimes complicated by seizures and hypoxic encephalopathy.[2] Both hospitalisations and deaths are likely to be under-estimated.[7] In Australia between 1993 and 2005, there were 18 deaths attributed to pertussis, all but 2 in infants <12 months of age.[8-11]

Epidemiology

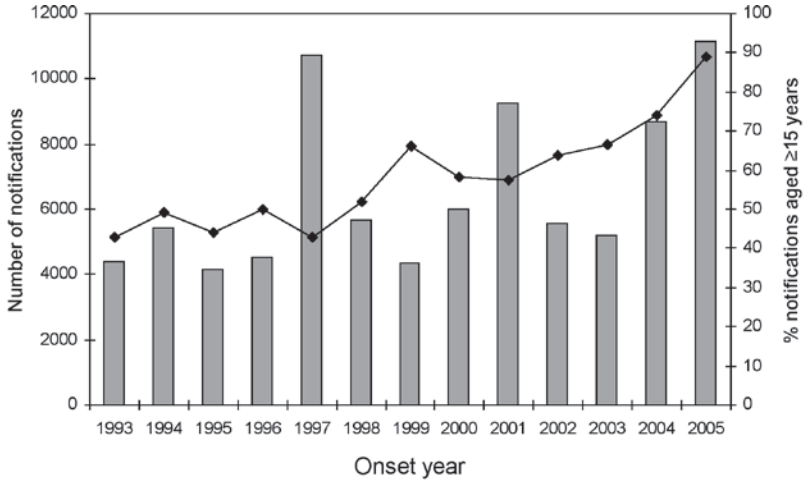
Epidemics occur every 3 to 4 years. In unvaccinated populations, these outbreaks can be very large. In vaccinated populations, outbreaks are smaller, with greatly reduced mortality and morbidity, and may continue to occur every 3 to 4 years or be more widely spaced. Maternal antibody does not provide reliable protection against pertussis, and the maximal risk of infection and severe morbidity is before infants are old enough to have received at least 2 vaccine doses.[7] In recent years, among highly immunised communities, many cases of pertussis in adults and adolescents, due to waning immunity, have been recognised due to the increased availability of serological testing.[6,12] These individuals are a significant reservoir of infection. From 1993 to 2005, 4 epidemics of pertussis

occurred in Australia. A total of more than 84 000 cases was reported in this time, an annual incidence of 22.8 to 57.4 cases per 100 000 population.[13]

Introduction of a fifth dose of diphtheria, tetanus and pertussis vaccine (DTP) for 4–5-year-old children in August 1994 was followed by a pattern of decrease in notifications consistent with a vaccine effect, occurring first among children aged 5 and 6 years, followed by those in the 7–9-year age group.[14,15] Subsequently, the average age of those notified with pertussis has continued to increase.

In 2004–2005, more than 70% of pertussis notifications were in individuals >15 years of age[13,16] compared with 40 to 50% in the early 1990s. This supports the need for booster doses in those >10 years of age, both to reduce individual morbidity, and to reduce transmission to those most at risk (infants <6 months of age).[17] Vaccination of adolescents, who have a high risk of pertussis infection, and adults in contact with very young infants, is expected to result in the greatest health benefits. A single booster dose using an adolescent/adult formulation acellular pertussis-containing vaccine (dTpa) has been included in the National Immunisation Program (NIP) for 15–17-year-olds since January 2004.

Figure 3.14.1: Pertussis notifications by year of onset, Australia 1993–2005. The percentage of notifications in those aged ≥15 years is shown (-◆-)



Vaccines

Acellular pertussis-containing vaccines have been used for both primary and booster vaccination of children in Australia since 1999. There are a number of acellular pertussis vaccines, which contain 3 or more purified components of *B. pertussis*. In the 3 component vaccines, these are pertussis toxin (PT), filamentous haemagglutinin (FHA) and pertactin (PRN). In the 5 component vaccines, fimbrial antigens or agglutinogens are also included. Acellular pertussis vaccines with 3 or more antigens have similar efficacy to good quality whole-cell vaccines[18] and are immunogenic and safe. Although serious adverse events such as hypotonic-hyporesponsive episodes can still occur, they are much less common than with whole-cell vaccines.[18] Vaccines containing DTPa are also available in various combinations with inactivated polio, hepatitis B and *Haemophilus influenzae* type b vaccines.

The acronym DTPa, using capital letters, signifies child formulations of diphtheria, tetanus and acellular pertussis-containing vaccines. The acronym dTpa is used for adolescent/adult formulations which contain substantially lesser amounts of diphtheria toxoid and pertussis antigens (see formulations).

The adolescent/adult formulation dTpa vaccines are immunogenic, safe and well tolerated in adults.[19-21]

Formulations for children aged <8 years

- **Infanrix hexa** – GlaxoSmithKline (DTPa-hepB-IPV-Hib; diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliomyelitis vaccine-*Haemophilus influenzae* type b (Hib)). The vaccine consists of *both* a 0.5 mL pre-filled syringe containing 30 IU diphtheria toxoid, 40 IU tetanus toxoid, 25 µg pertussis toxoid (PT), 25 µg filamentous haemagglutinin (FHA), 8 µg pertactin (PRN), 10 µg recombinant HBsAg, 40 D-antigen units inactivated polioviruses type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett) adsorbed onto aluminium hydroxide/phosphate; phenoxyethanol as preservative; traces of formaldehyde, polymyxin and neomycin *and* a vial containing a lyophilised pellet of 10 µg purified Hib capsular polysaccharide (PRP) conjugated to 20–40 µg tetanus toxoid. The vaccine *must be reconstituted* by adding the entire contents of the syringe to the vial and shaking until the pellet is completely dissolved. May also contain yeast proteins.
- **Infanrix-IPV** – GlaxoSmithKline (DTPa-IPV; diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis vaccine). Each 0.5 mL pre-filled syringe contains 30 IU diphtheria toxoid, 40 IU tetanus toxoid, 25 µg PT, 25 µg FHA, 8 µg PRN, 40 D-antigen units inactivated polioviruses type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett) adsorbed onto aluminium hydroxide; phenoxyethanol as preservative; traces of formaldehyde, polymyxin and neomycin.

- **Infanrix Penta** – GlaxoSmithKline (DTPa-hepB-IPV; diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliomyelitis vaccine). Each 0.5 mL pre-filled syringe contains 30 IU diphtheria toxoid, 40 IU tetanus toxoid, 25 µg PT, 25 µg FHA, 8 µg PRN, 10 µg recombinant HBsAg, 40 D-antigen units inactivated polioviruses type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett) adsorbed onto aluminium hydroxide/phosphate; phenoxyethanol as preservative; traces of formaldehyde, polymyxin and neomycin. May also contain yeast proteins.

Formulations for people aged ≥8 years

Combination vaccines

- **Adacel** – Sanofi Pasteur Pty Ltd (dTpa; diphtheria-tetanus-acellular pertussis). Each 0.5 mL monodose vial contains ≥2 IU diphtheria toxoid, ≥20 IU tetanus toxoid, 2.5 µg PT, 5 µg FHA, 3 µg PRN, 5 µg pertussis fimbriae (FIM) 2+3; 1.5 mg aluminium phosphate; phenoxyethanol as preservative; traces of formaldehyde.
- **Adacel Polio** – Sanofi Pasteur Pty Ltd (dTpa; diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis vaccine). Each 0.5 mL monodose vial contains ≥2 IU diphtheria toxoid, ≥20 IU tetanus toxoid, 2.5 µg PT, 5 µg FHA, 3 µg PRN, 5 µg FIM 2+3, 40 D-antigen units inactivated polioviruses type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett); 1.5 mg aluminium phosphate; phenoxyethanol as preservative; traces of formaldehyde, polymyxin, neomycin and streptomycin.
- **Boostrix** – GlaxoSmithKline (dTpa; diphtheria-tetanus-acellular pertussis). Each 0.5 mL monodose vial or pre-filled syringe contains ≥2 IU diphtheria toxoid, ≥20 IU tetanus toxoid, 8 µg PT, 8 µg FHA, 2.5 µg PRN, adsorbed onto 0.5 mg aluminium hydroxide/phosphate; 2.5 mg phenoxyethanol as preservative. May contain traces of formaldehyde.
- **Boostrix-IPV** – GlaxoSmithKline (dTpa-IPV; diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis vaccine). Each 0.5 mL pre-filled syringe contains ≥2 IU diphtheria toxoid, ≥20 IU tetanus toxoid, 8 µg PT, 8 µg FHA, 2.5 µg PRN, 40 D-antigen units inactivated polioviruses type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett) adsorbed onto aluminium hydroxide/phosphate; traces of formaldehyde, polymyxin and neomycin.

Transport, storage and handling

Transport according to *National Vaccine Storage Guidelines: Strive for 5*.[22] Store at +2°C to +8°C. Do not freeze. Protect from light.

Dosage and administration

The dose of DTPa-combinations, dTpa and dTpa-IPV is 0.5 mL by IM injection.

Do not mix DTPa-containing vaccines with any other vaccine in the same syringe, unless specifically registered for use in this way.

Recommendations

(i) Vaccination of children and adolescents

Acellular pertussis antigens are given in combination with diphtheria and tetanus toxoids (DTPa) in a primary course of vaccination at 2, 4 and 6 months of age. In view of the high morbidity and occasional 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; catch-up doses may be given as little as 4 weeks apart. The same formulation of vaccine should be used for each of the 3 doses. If it is not known which brand was used, vaccination should be provided using any available brand.

For the booster dose of DTPa given at 4 years of age, all brands of DTPa-containing vaccines are considered interchangeable. In view of the prolonged immunity now known to result from a primary course of DTPa at 2, 4 and 6 months of age,[23] the 18-month dose was omitted in 2003. It is expected 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 occurred in 2% of children following a fourth dose at 18 months of age.[24,25]

A second booster, between 12 and 17 years of age, using the adolescent/adult formulation dTpa, is essential for maintaining immunity to pertussis through the adolescent period and into early adulthood. By the age of 17 years, young adults should have received 5 doses of a pertussis-containing vaccine. Most adolescents would have either had at least 3 previous 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 12–17 years is indeed a booster dose.

For details on the management of children who have missed doses in the NIP schedule, see Section 1.3.5, *Catch-up*.

(ii) Vaccination of adults

dTpa vaccines are recommended in Australia for booster vaccination of individuals ≥8 years of age who have previously had a primary course of

diphtheria-tetanus-pertussis vaccine. dTpa vaccines have a lower content of diphtheria and pertussis antigens than DTPa formulations for young children.

Primary vaccination

If a 3-dose primary course of diphtheria/tetanus toxoids is given to an adolescent/adult without a previous history of having received pertussis-containing vaccine, the preferred option is that dTpa replace the first dose of dT, to provide pertussis immunity as early as possible,[26] with subsequent doses as dT. In the event that dT is *not* available, dTpa can be used for all primary doses, but this is not routinely recommended as there are no data on the safety, immunogenicity or efficacy of dTpa for primary vaccination. For detailed recommendations regarding a primary dT course in adults, see Chapter 3.21, *Tetanus.*

Duration of protection and spacing of booster doses

A single booster dose of dTpa is recommended for the following groups provided that no documented dTpa booster dose has been previously received:

- Adults planning a pregnancy, or for both parents as soon as possible after delivery of an infant (preferably before hospital discharge), unless contraindicated.[17] Other adult household members, grandparents and carers of young children should also be vaccinated. This recommendation is based on evidence from several studies of infant pertussis cases, which indicated that family members, particularly parents, were identified as the source of infection in more than 50% of cases and were the presumed source in a higher proportion.[27-29]
- Adults working with young children. Vaccination is especially recommended for childcare workers (see Chapter 2.3, *Groups with special vaccination requirements*, Table 2.3.6 *Recommended vaccinations for those at risk of occupationally acquired vaccine-preventable diseases*).[30,31]
- All healthcare workers (see also Chapter 2.3, *Groups with special vaccination requirements*, Table 2.3.6 *Recommended vaccinations for those at risk of occupationally acquired vaccine-preventable diseases*). Several case reports have documented nosocomial infection in young infants acquired from healthcare workers.[30,31]
- Any adult expressing an interest in receiving a booster dose of dT vaccine should be encouraged to do so with dTpa vaccine. At the age routinely recommended for tetanus and diphtheria booster (50 years), dTpa produces immune responses to tetanus and diphtheria antigens equivalent to dT vaccine, and would also provide protection against pertussis.[32]

Data on the duration of immunity to pertussis following a single booster dose of dTpa are limited in adults and adolescents.[20,33] Although subsequent doses of dTpa may prove beneficial, especially in high-risk groups such as healthcare workers, such boosters are unlikely to be required before 10 years and recommendations must await further data.

Minimum interval between dTpa and other tetanus/ diphtheria-containing vaccines

A single dose of dTpa can be administered at any time after a dose of a vaccine containing tetanus and diphtheria toxoids.

Recent studies from Canada have shown that a single dose of dTpa can be safely administered as soon as 18 months after a previous dose of a vaccine containing tetanus or diphtheria toxoids.[34-36] Where a tetanus- or diphtheria-containing vaccine has been given even less than 18 months previously, the benefits of protection against pertussis are likely to outweigh the risk of an adverse event,[37] and justify vaccination with dTpa or dTpa-IPV.

Special considerations

Previous pertussis infection

Vaccination with pertussis vaccine in children, adolescents or adults who have had laboratory-confirmed pertussis infection is safe but will not confer any additional protection. If there is any uncertainty about a previous diagnosis of pertussis, then vaccinate. In particular, incompletely vaccinated infants <6 months of age who develop pertussis may not mount an adequate immune response following infection and should receive all routinely scheduled vaccines, including pertussis.

Pre-existing neurological disease and pertussis vaccination

Infants and children known to have active or progressive neurological disease can be safely vaccinated with DTPa-containing vaccines. A large Canadian study found no evidence of encephalopathy following acellular pertussis vaccines.[38] For infants and children with stable neurological disease (including cerebral palsy), or a family history of idiopathic epilepsy or other familial neurological disorder, the risk of adverse events following DTPa-containing vaccines are essentially the same as for other infants of the same age.

Contraindications

The only true contraindications to acellular pertussis vaccines are:

- anaphylaxis following a previous dose of an acellular pertussis vaccine, or
- anaphylaxis following any vaccine component.

Precautions

Children who have a hypotonic-hyporesponsive episode (defined in 'Adverse events' below) following DTPa-containing vaccines should receive further doses as scheduled in the National Immunisation Program. Supervision may be required under some circumstances and specialist advice can be obtained from a clinic specialising in the assessment and management of putative adverse events

following vaccination (see Appendix 1, *Contact details for Australian, State and Territory Government health authorities and communicable disease control*).

A history of extensive limb swelling after a booster dose of DTPa is not a contraindication to adolescent/adult formulation dTpa at 12–17 years of age (or older).[24] Parents of children about to receive the booster dose of a DTPa-containing vaccine (at 4 years of age) should be informed of the small but well-defined risk of this adverse event which, even when extensive, is usually not associated with significant pain or limitation of movement.

Adverse events

Significant adverse events following pertussis vaccination should be reported as set out in Section 1.5.2, *Adverse events following immunisation*.

- Acellular pertussis vaccines are associated with a much lower incidence of fever (approximately 20%, very common) and local adverse events (approximately 10%, common) than whole-cell pertussis vaccines (approximately 45% and 40%, respectively) which are no longer used in Australia).[18,39]
- Following the introduction of DTPa in Australia, there was an increase in the incidence of extensive local adverse events in children receiving booster doses at 18 months and 4 years of age.[40]

  Extensive limb swelling, defined by swelling and/or redness involving at least half the circumference of the limb, and the joints both above and below the injection site, was common (occurring in 2% of vaccinees) following a booster dose of DTPa given at 18 months of age; this was 1 reason for ceasing this booster dose in 2003. Although it is still too early to assess the effect that removing the 18-month booster dose has had on the incidence of local adverse events following the booster dose at 4 years of age, recent anecdotal reports of much less extensive swelling are encouraging.[41]

  Such reactions commence within 48 hours of vaccination, last for 1 to 7 days and resolve completely without sequelae.[25] The pathogenesis of extensive limb swelling is poorly understood. In an analysis of fourth and fifth dose follow-up studies that examined 12 different DTPa vaccines, 2% (common) of 1015 children who received consecutive doses of the same DTPa vaccine reported entire thigh swelling, which resolved completely.[25]
- Children who experience a febrile convulsion after a dose of DTPa-containing vaccines are at increased risk (albeit low) of further febrile convulsion following a subsequent dose of DTPa-containing vaccines. These risks can be minimised by appropriate measures to prevent fever, so vaccination is still recommended.

  Febrile convulsions are very infrequently reported following DTPa-containing vaccines. The risk is even lower in infants who complete their primary course at 6 months of age, as febrile convulsions are uncommon under 6 months of age.

- Hypotonic-hyporesponsive episodes (HHE), defined by an episode of pallor, limpness and unresponsiveness 1 to 48 hours after vaccination, often preceded by irritability and fever, occur rarely following DTPa. Shallow respiration and cyanosis may also occur in an HHE. The whole episode lasts from a few minutes to 36 hours. In Australia during 2005, 1.33 cases of HHE were reported per 100 000 doses of DTPa or DTPa-hepB vaccines given.[41] Follow-up of children with HHE shows no long-term neurological or other sequelae and they can receive further doses of DTPa-containing vaccines.[42]
- Pertussis vaccine does not cause infantile spasms or epilepsy.
- Sudden infant death syndrome (SIDS) is not associated with either DTPa or any pertussis-containing vaccine.[43] Some studies suggest a decreased risk of SIDS in children who have been vaccinated (see Appendix 5, *Commonly asked questions about vaccination*).

The public health management of pertussis

(i) 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 a person epidemiologically linked to a laboratory-confirmed case. The diagnosis can be definitively confirmed by either culture or PCR of a per-nasal swab or nasopharyngeal aspirate. The serological tests available in most areas of Australia are based on detection of IgA antibodies to *B. pertussis* antigens and are insensitive, so that false negative results are a problem, especially if performed on only one occasion.[44] In those who have not received a pertussis-containing vaccine within the previous 5 years, detection of IgA to pertussis antigens is highly specific in the presence of appropriate symptoms. If pertussis is suspected in someone who has received a pertussis-containing vaccine within 5 years, PCR is the diagnostic method of choice, but has progressively decreasing sensitivity with increased duration of symptoms. In a research setting, an IgG PT level of at least 125 EU/mL has been shown to be indicative of a recent or active pertussis infection; however, this assay is not available in routine pathology laboratories.[45,46]

A detailed history is required when a case of pertussis is suspected, including date of onset, vaccination status and details of household contacts. To reduce the risk of transmission, cases should be commenced on antibiotic therapy on clinical suspicion, but only if commenced within 21 days of the onset of coryza. There is no evidence of any reduction in pertussis transmission following antibiotic treatment if the case has had symptoms for more than 21 days. Appropriate macrolide antibiotics for treatment of pertussis are azithromycin, clarithromycin and erythromycin. An alternative for those unable to take macrolides is trimethoprim-sulfmethoxazole. Table 3.14.1 shows the dose regimens for each of these antibiotics. (See also 'Variations from product information' below.)

Table 3.14.1: Recommended antimicrobial therapy and chemoprophylaxis regimens for pertussis in infants, children and adults[47-54]

Age group	Azithromycin	Clarithromycin	Erythromycin	TMP-SMX*
<1 month	10 mg/kg single dose for 5 days†	Not recommended	If azithromycin is unavailable; ≤7 days old: 10 mg/kg/dose 12-hourly for 7 days;‡ 8–28 days old: 10 mg/kg/dose 8-hourly for 7 days	Not recommended in infants <2 months of age unless macrolides cannot be used
1–5 months	10 mg/kg single dose for 5 days	7.5 mg/kg/dose twice daily for 7 days	10 mg/kg/dose 6-hourly for 7 days	≥2 months of age; TMP: 4 mg/kg twice daily, SMX: 20 mg/kg twice daily for 7 days
Infants (≥6 months) and children	10 mg/kg single dose on day 1, then 5 mg/kg single dose for days 2–5 (maximum 250 mg/day)	7.5 mg/kg/dose (up to a maximum dose of 500 mg) twice daily for 7 days (maximum 1 g/day)	10 mg/kg/dose (up to a maximum dose of 250 mg) 6-hourly for 7 days (maximum 1 g/day)	TMP: 4 mg/kg, SMX: 20 mg/kg twice daily for 7 days (maximum 160 mg TMP and 800 mg SMX 12-hourly)
Adults	500 mg single dose on day 1, then 250 mg single dose for days 2–5	500 mg twice daily for 7 days	Erythromycin: 250 mg 6-hourly for 7 days; Erythromycin ethyl succinate (EES): 400 mg 6-hourly for 7 days	TMP: 160 mg twice daily, SMX: 800 mg twice daily for 7 days

* Trimethoprim-sulfmethoxazole

† Preferred for this age; refer to '(c) Pertussis in pregnancy' and '(d) Use in infants and infantile hypertrophic pyloric stenosis' below.

‡ Please refer to '(d) Use in infants and infantile hypertrophic pyloric stenosis' below.

Cases should be excluded from, for example, childcare facilities and school, until they have taken 5 days of antibiotic treatment. All cases, both suspect and confirmed, should be notified to the State/Territory public health authorities (see Appendix 1, *Contact details for Australian, State and Territory Government health authorities and communicable disease control*).

(ii) 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 8th birthday should be offered DTPa-containing vaccines and older individuals a single dose of dTpa (see Section 1.3.5, *Catch-up*).

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

(b) Chemoprophylaxis

In the usual clinical setting of delayed presentation and imperfect compliance, the benefit of chemoprophylaxis in preventing the secondary transmission of pertussis is likely to be limited.[49,55] In view of this, the well established (mainly gastrointestinal) side effects of erythromycin and the cost of the newer macrolides, the use of chemoprophylaxis 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 high 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 work in or attend the same institutional setting (eg. maternity hospital ward, newborn nursery, childcare centre) as a case.

Based on these principles, prophylaxis is recommended for the following 'high-risk' contacts of pertussis cases:

- All household members when the household includes any child <24 months of age who has received fewer than 3 effective doses of pertussis vaccine (ie. commenced after 6 weeks of age with at least a 4-week interval between doses, and the last dose given at least 14 days previously).
- Any woman in the last month of pregnancy, regardless of vaccination status (see 'Pertussis in pregnancy' below).
- All other children and adults in the same care group if the case, regardless of his/her vaccination status, attended childcare for more than 1 hour while infectious and that care group includes 1 or more children <24 months of age who have received fewer than 3 effective doses of pertussis vaccine.
- Healthcare staff, regardless of vaccination status, working in a maternity hospital or newborn nursery. Chemoprophylaxis is not recommended routinely for healthcare staff caring for older infected children or adults.
- Where a case worked in a maternity ward or newborn nursery for more than an hour while infectious, then all babies in that ward should receive antibiotics.

Antibiotic regimens for chemoprophylaxis are the same as for cases (Table 3.14.1 above). Antibiotics should be given only 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. Childcare contacts in the same room as the case, who are not age-appropriately vaccinated, should be excluded from childcare until the expiry of 14 days from their last exposure to the infectious case, unless they have already completed 5 days of a recommended antibiotic treatment, in which case they may return.

(c) Pertussis in pregnancy

Treatment of pregnant women with pertussis onset within a month of delivery is important for the prevention of neonatal pertussis and, if the onset is within 3 weeks of delivery, their newborn babies should also be given antibiotic therapy (Table 3.14.1). Erythyromycin use earlier in pregnancy has well documented safety (Category A). There are only limited data on the use of azithromycin in pregnancy (Category B1).

(d) Use in infants and infantile hypertrophic pyloric stenosis

Several studies have shown an increased risk of infantile hypertrophic pyloric stenosis (IHPS) when erythromycin is given for prophylaxis following exposure to pertussis, especially in the first 2 weeks of life.[56,57] While there are, as yet, no data available on the effectiveness of azithromycin use in infants <1 month of age, published case series report fewer adverse events following azithromycin use when compared with erythromycin and, to date, there have been no reports of IHPS in infants following use of azithromycin, although the size and number of these studies is limited.[58,59] Therefore, on currently available evidence, and because of the risks of severe pertussis in this age group, azithromycin is preferred to erythromycin for treatment and prophylaxis in infants aged <1 month by US authorities. Azithromycin is available as a suspension and approved for use in Australia, but treatment and prophylaxis of pertussis are not currently referred to in the product information. Parents of newborns prescribed either erythromycin or azithromycin should be informed about the possible risks for IHPS and counselled about signs of developing IHPS.

Use in pregnancy

Refer to Chapter 2.3, *Groups with special vaccination requirements*, Table 2.3.1 *Vaccinations in pregnancy*.

Variations from product information

The product information for both Infanrix hexa and Infanrix Penta states that these vaccines may be given as a booster dose at 18 months of age. NHMRC recommends that a booster dose of DTPa (or DTPa-containing vaccines) is not necessary at 18 months of age. However, DTPa-containing vaccine may be used for catch-up of the primary schedule in children <8 years of age.

The product information for Infanrix-IPV states that this vaccine may be used as a booster dose for children ≤6 years of age who have previously been vaccinated against diphtheria, tetanus, pertussis and poliomyelitis. NHMRC recommends that booster doses of DTPa and IPV be given at 4 years of age; however, this product may be used for catch-up of the primary schedule or as a booster in children <8 years of age.

The product information for adolescent/adult formulations of dTpa-containing vaccines states that these vaccines are indicated for booster doses only. NHMRC recommends that, when a 3-dose primary course of diphtheria/tetanus toxoids is given to an adolescent/adult, that dTpa replace the first dose of dT, with 2 subsequent doses of dT. If dT is *not* available, dTpa can be used for all 3 primary doses, but this is *not* routinely recommended.

The product information for Adacel and Boostrix (adolescent/adult formulations of dTpa) states that these vaccines are recommended for use in those aged >10 years. However, NHMRC recommends that they may be used in people aged ≥8 years. The product information also states that dTpa should not be given within 5 years of a tetanus toxoid-containing vaccine. However, NHMRC recommends that a single dose of dTpa vaccine can be administered at any time following receipt of a diphtheria and tetanus toxoid-containing vaccine.

The product information for both clarithromycin and azithromycin do not list the treatment or prophylaxis of pertussis as an approved indication for either antibiotic. NHMRC recommends that these antibiotics may be used for the treatment or prophylaxis of pertussis as per Table 3.14.1 above.

References

Full reference list available on the electronic *Handbook* or website http://immunise.health.gov.au.

3.15 PNEUMOCOCCAL DISEASE

Bacteriology

Streptococcus pneumoniae are lancet shaped Gram-positive streptococci. 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 with 2004 Australian data indicating that up to 18% of invasive 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 IPD, while, in children, bacteraemia accounts for more than two-thirds of cases.[2-4]

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

Epidemiology

The highest rates of IPD are seen in children <2 years of age and adults >85 years of age. In 2004, 2375 cases of IPD were notified to the National Notifiable Diseases Surveillance System, a notification rate of 11.8 per 100 000 population.[1] The overall rate of IPD in Indigenous Australians was 3.2 times that in non-Indigenous Australians.[1] In 2004, after implementation of the pneumococcal conjugate vaccine program for high-risk children in 2001, the rate of IPD in children <2 years of age had decreased in Indigenous children (91.5 cases per 100 000) to become similar to their non-Indigenous peers (93.6 cases per 100 000).[1]

In the less-developed world and in some groups of Aboriginal and Torres Strait Islander people, 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. Most non-Indigenous adults who develop IPD have at least 1 risk factor, while most cases occurring in Indigenous adults are associated with multiple risk factors. In adults, most IPD isolates belong to serotypes contained in the 23-valent pneumococcal polysaccharide vaccine.[7-9]

Among Indigenous children in northern Australia, before the introduction of the 7-valent pneumococcal conjugate vaccine, only about one-half to two-thirds of IPD was caused by serotypes in the 7-valent pneumococcal conjugate vaccine compared with 85% or more among non-Indigenous children.[7,8,10] Nevertheless, in north Queensland, a decrease in the annual incidence of IPD in the <5 years age group from 170 to 78 cases per 100 000 was documented in the 3 years after introduction of the 7-valent pneumococcal conjugate vaccine.[11] Similarly, the annual incidence of vaccine-preventable IPD in Indigenous adults has declined by 86% since the 23-valent pneumococcal polysaccharide vaccine was introduced to north Queensland in 1986.[11]

Vaccines

There are currently 2 different types of pneumococcal vaccine available in Australia. A 7-valent pneumococcal conjugate vaccine (7vPCV) became available in 2001 for immunisation of infants and children aged from 6 weeks to 9 years. 7vPCV was added to the NIP for high-risk children in 2001 and for all children up to 2 years of age from January 2005. The 23-valent pneumococcal polysaccharide vaccine (23vPPV) has been available since 1983. A funded program with 23vPPV for Indigenous Australians aged ≥50 years began in 1999. Non-Indigenous Australians aged 65 years became eligible to receive the vaccine under the NIP from January 2005. In addition, people aged <65 years with underlying chronic conditions predisposing them to IPD can access 23vPPV through the PBS.

Pneumococcal conjugate vaccine, 7-valent (7vPCV)

- **Prevenar** – Wyeth (7-valent pneumococcal conjugate vaccine; 7vPCV). Each 0.5 mL monodose pre-filled syringe contains 2 µg of pneumococcal serotypes 4, 9V, 14, 18C, 19F, 23F and 4 µg of serotype 6B, conjugated to a mutant non-toxic diphtheria toxin (CRM_{197}) carrier protein, adsorbed onto 0.5 mg aluminium phosphate. Available in packs of 10 monodose pre-filled syringes.

7vPCV is approved for use in infants and children aged 6 weeks to 9 years. Efficacy data from a pivotal trial in California found greater than 95% protective efficacy against IPD due to the serotypes contained in the vaccine.[12] A Cochrane review of 4 trials assessing the efficacy of 7vPCV in children <2 years of age found 7vPCV to be effective in reducing the incidence of IPD due to all serotypes, the greater effect being seen in the reduction of IPD due to vaccine-related serotypes.[13]

Other pneumococcal infections in children (pneumonia and otitis media), not associated with a positive sterile site culture, are also reduced by 7vPCV, but the estimated reduction varies with case definition and severity. For clinically defined otitis media or pneumonia, the reduction is similar at approximately 5%.[14,15]

A post-licensure study of 157 471 children in California showed evidence of disease reduction in unimmunised people, confirmed by a larger US study showing a decline in the incidence of IPD of 52% in those 20–39 years of age and 26% in those ≥60 years of age.[16-18]

Pneumococcal polysaccharide vaccine, 23-valent (23vPPV)

- **Pneumovax 23** – CSL Biotherapies/Merck & Co Inc (23-valent pneumococcal polysaccharide vaccine; 23vPPV). Each 0.5 mL monodose vial contains 25 µg of each of pneumococcal serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F and 33F; 0.25% phenol.

23vPPV contains polysaccharides derived from the 23 most frequent or most virulent capsular types of *S. pneumoniae* 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 patients with impaired immunity and, in children <2 years of age, is limited to a small number of serotypes unless there has been previous 7vPCV vaccination.[19]

In developing countries with high attack rates, controlled trials have shown that pneumococcal polysaccharide vaccine reduces mortality from pneumonia in younger adults which, in this setting, is very likely to be pneumococcal. Among at-risk individuals in developed countries with much lower attack rates, a Cochrane review examining vaccines for preventing pneumococcal disease reported that 23vPPV was effective in reducing the incidence of IPD, but not non-bacteraemic pneumonia, among adults and the immunocompetent elderly.[20] Similarly, a recent retrospective study in a managed care setting in the USA studied 47 365 adults >65 years of age over 3 years, of whom 1428 were hospitalised with community-acquired pneumonia and 61 developed documented pneumococcal bacteraemia. Receipt of 23vPPV vaccine was associated with a significant reduction in pneumococcal bacteraemia but not in hospitalisation for non-bacteraemic pneumonia.[21] In Australia, Victoria introduced a publicly funded 23vPPV program for the >65 years age group in 1998, resulting in an estimated 36% reduction in the incidence of IPD and vaccine effectiveness of 71% (95% CI: 54–82%).[22]

Transport, storage and handling

7-valent pneumococcal conjugate vaccine

Transport according to *National Vaccine Storage Guidelines: Strive for 5*.[23] Store at +2°C to +8°C. Do not freeze. Protect from light.

23-valent pneumococcal polysaccharide vaccine

Transport according to *National Vaccine Storage Guidelines: Strive for 5*.[23] Store at +2°C to +8°C. Do not freeze. Protect from light.

Dosage and administration

7-valent pneumococcal conjugate vaccine

The dose is 0.5 mL by IM injection in the opposite limb to other injectable vaccines if possible.

23-valent pneumococcal polysaccharide vaccine

The dose is 0.5 mL as a single dose, by either SC or IM injection, in the opposite limb to other injectable vaccines if possible.

Recommendations

7-valent pneumococcal conjugate vaccine

Vaccination of children

7vPCV is recommended in the NIP for all infants from 2 months of age with a catch-up for children up to 2 years of age.

7vPCV may be safely given at the same time as other vaccines listed on the NIP but must be administered using a separate injection site and limb.

(i) Healthy children

7vPCV should be administered in a primary series of 3 doses at 2, 4 and 6 months of age. Unless there is an increased risk of IPD (see below), the additional benefits are not considered sufficient to justify a routine (fourth) booster dose. This recommendation is based on data from the pivotal randomised controlled trial suggesting similar efficacy against type-specific IPD with either 3 or 4 doses.[12] Subsequent studies from the UK examining immunogenicity data[24] and the US examining vaccine effectiveness[25] were consistent with significant protection after 2 or more doses. The US study found higher vaccine effectiveness among those who had received a fourth dose at 12 months of age, but this was not statistically significant.[25] The current Australian dosing regimen will be regularly reviewed in the light of trends in Australian IPD data and emerging international experience.

(ii) Aboriginal and Torres Strait Islander children living in the Northern Territory, Queensland, South Australia and Western Australia

7vPCV should be administered at 2, 4 and 6 months of age, followed at 18–24 months of age by a dose of 23vPPV. This recommendation is based on: (i) data from several Australian studies which showed lower serotype coverage from the 7vPCV in similar populations;[7,8,10] (ii) 2 large studies which demonstrated adequate boosting responses to serotypes contained in the 7vPCV following 23vPPV;[26,27] and (iii) 2 large studies which demonstrated adequate primary responses to some serotypes in 23vPPV, but not in 7vPCV, from 18–24 months of age.[28,29]

(iii) Children with underlying medical conditions (listed in Table 3.15.2) associated with greater risk or severity of IPD

7vPCV should be administered at 2, 4 and 6 months of age, followed by a fourth dose of 7vPCV at 12 months of age and a booster dose of 23vPPV at 4–5 years of age. This is based on data showing lower immune responses in these children to certain serotypes in 7vPCV which can be enhanced by an additional dose, and their continuing susceptibility to IPD at older ages, with a higher prevalence of serotypes not contained in the 7vPCV.[30]

(iv) Children with asplenia (functional or anatomical) ≤9 years of age (ie. before their 10th birthday)

- ***with no previous history of pneumococcal vaccination*** **with 7vPCV or 23vPPV**
  - 2 doses of 7vPCV given 2 months apart, followed by 23vPPV at least 2 months after the last dose of 7vPCV. This is based on an inadequate response to 1 dose of 7vPCV among some asplenic individuals which is enhanced by a second dose.[27]
- ***with previous history of pneumococcal vaccination*** **with 7vPCV or 23vPPV**
  - where a dose of 23vPPV was given more than 6 months ago but no doses of 7vPCV have been administered, give 2 doses of 7vPCV at least 2 months apart. This is based on inadequate response to 1 dose of 7vPCV in some asplenic individuals which seems unlikely to be influenced by previous receipt of 23vPPV, although no specific data are available.
  - where previous doses of 7vPCV have been administered but no 23vPPV, give 23vPPV at least 2 months after the last 7vPCV dose. This is based on similar considerations to those above.

NB. Children with asplenia should also be considered for other interventions (see Chapter 2.3, Subsection 2.3.3.5, *Individuals with functional or anatomical asplenia*).

(v) Children ≤9 years of age (ie. before their 10th birthday) who have been diagnosed with an underlying medical condition (listed in Table 3.15.2 below) after they received the infant schedule of 7vPCV at 2, 4 and 6 months of age

Where a previously healthy child, currently aged >12 months, was vaccinated according to the NIP schedule and received 7vPCV at 2, 4 and 6 months of age but has since developed or been diagnosed with a condition listed in Table 3.15.2 below, he/she should receive a further dose of 7vPCV followed 2 months later by a dose of 23vPPV.

Table 3.15.1: Summary table – pneumococcal vaccination schedule for children ≤9 years of age (see also Section 1.3.5, *Catch-up*)

For childhood immunisation schedule (children ≤5 years of age)			
	7vPCV	**23vPPV**	**Comments**
All healthy children (including Indigenous children residing in ACT, NSW, TAS and VIC)	2, 4 and 6 months of age (up to 2 years of age)*	No	If delays in start of schedule after 2 months, refer Section 1.3.5, *Catch-up*, Table 1.3.9.
Indigenous children residing in NT, QLD, SA and WA only	2, 4 and 6 months of age (up to 2 years of age)	18–24 months	If delays in start of schedule after 2 months, refer Section 1.3.5, *Catch-up*, Table 1.3.10.
Children with underlying medical conditions (refer Table 3.15.2)	2, 4, 6 and 12 months of age	4–5 years	If delays in start of schedule after 2 months, refer Section 1.3.5, *Catch-up*, Table 1.3.11.
For children 6–≤9 years of age with underlying medical conditions as listed in Table 3.15.2			
	7vPCV	**23vPPV**	**Comments**
No history of any pneumococcal vaccination	2 doses, at least 2 months apart	Give 1 dose at least 2 months after last dose of 7vPCV	For revaccination schedules for children ≥10 years, refer to Table 3.15.3 below.
Has received 7vPCV primary course at 2, 4 and 6 months of age	1 dose	Give 1 dose at least 2 months after last dose of 7vPCV	For revaccination schedules for children ≥10 years, refer to Table 3.15.3 below.
History of at least 2 7vPCV doses, and no 23vPPV	1 dose	Give 1 dose at least 2 months after last dose of 7vPCV	For revaccination schedules for children ≥10 years, refer to Table 3.15.3 below.
History of 23vPPV, but no 7vPCV	Give 2 doses at least 2 months apart, starting at least 6 months after dose of 23vPPV	Refer revaccination schedule Table 3.15.3 for further schedules	For revaccination schedules for children ≥10 years, refer to Table 3.15.3 below.

* Immunisation of healthy children (including Indigenous children residing in ACT, NSW, VIC, and TAS) only up to 2 years of age.

Booster doses of 7vPCV

With the exception of children with underlying medical conditions (see above), booster doses of 7vPCV are not required.

For details of catch-up schedules, please refer to Section 1.3.5, *Catch up*.

Table 3.15.2: Underlying medical conditions predisposing children ≤9 years of age to IPD

Diseases compromising immune response to pneumococcal infection:
• congenital immune deficiency including symptomatic IgG subclass or isolated IgA deficiency (but children who require monthly immunoglobulin infusion are unlikely to benefit from vaccination),
• immunosuppressive therapy (including corticosteroid therapy ≥2 mg/kg per day of prednisolone or equivalent for more than 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,
• haematological malignancies,
• HIV infection, before and after development of AIDS,
• renal failure, or relapsing or persistent nephrotic syndrome,
• Down 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 (CSF) leak,
• intracranial shunts and cochlear implants.

23-valent pneumococcal polysaccharide vaccine

23vPPV may be safely given at the same time as other vaccines listed on the NIP but must be administered using a separate injection site and limb.

(i) 23vPPV is recommended for:

- All people aged ≥65 years.
- Aboriginal and Torres Strait Islander people ≥50 years of age and those 15–49 years of age who have underlying conditions placing them at risk of IPD.
- People aged ≥10 years who have underlying chronic illnesses predisposing them to IPD including:

- asplenia either functional (including sickle-cell disease) or anatomical; where possible, the vaccine should be given at least 14 days before splenectomy,
- conditions associated with increased risk of IPD due to impaired immunity, eg. HIV infection before the development of AIDS, acute nephrotic syndrome, multiple myeloma, lymphoma, Hodgkin's disease and organ transplantation,
- chronic illness associated with increased risk of IPD including chronic cardiac, renal or pulmonary disease, diabetes, alcohol-related problems,
- CSF leak.

- Tobacco smokers.

(ii) 23vPPV 'booster' dose is recommended following previous 7vPCV

- At 18–24 months of age, after a primary series of 7vPCV, in Aboriginal and Torres Strait Islander children in the Northern Territory, Queensland, South Australia and Western Australia (see Section 1.3.5, *Catch up*, Table 1.3.10).
- At 4–5 years of age in children at risk of either high incidence or severity of IPD because of underlying medical conditions (see Table 3.15.2), following a primary series of 7vPCV (see Section 1.3.5, *Catch up*, Table 1.3.11).

iii) Revaccination with 23vPPV

A maximum of 3 doses (ie. 2 revaccinations) of 23vPPV are recommended, based on data concerning adverse events and effectiveness.

Although an early study raised concerns about extensive local adverse events following revaccination with 23vPPV,[31] several recent studies have shown that 3 doses (ie. 2 revaccinations) of 23vPPV are not associated with more local adverse events compared to 1 or 2 doses.[32,33]

Less clear, however, is the adequacy of the immune response after revaccination with 23vPPV. Although an earlier study reported that there was an immune hyporesponsiveness after a first revaccination, more recent studies suggest that the immune responses to revaccination may be adequate.[31,34]

Table 3.15.3: Revaccination with 23vPPV for people ≥10 years of age

Primary dose 23vPPV given to	First 23vPPV revaccination	Second 23vPPV revaccination
Non-Indigenous adults ≥65 years	5 years after first dose	No
Non-Indigenous adults <65 years with underlying chronic medical condition or smoker	5 years after first dose	Either 5 years after first revaccination or at 65 years of age (whichever is later)
Indigenous adults aged ≥50 years	5 years after first dose	No
Indigenous adults aged <50 years with underlying chronic medical condition or smoker	5 years after first dose	Either 5 years after first revaccination or at 50 years of age (whichever is later)
Asplenic individuals	5 years after first dose	Either 5 years after first revaccination or at 50 years of age (for Indigenous adults) or 65 years of age (for non-Indigenous adults), whichever is later

NB. Indigenous children in the Northern Territory, Queensland, South Australia and Western Australia receive 23vPPV at 18–24 months of age (see 'Recommendations', point (ii) above). This childhood dose is not relevant to the recommendations concerning revaccination given in Table 3.15.3.

Contraindications

7-valent pneumococcal conjugate vaccine

The only absolute contraindications to 7vPCV are:

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

23-valent pneumococcal polysaccharide vaccine

The only absolute contraindications to 23vPPV are:

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

Relative contraindications include the following:

- Age <2 years – the immune response in young children is restricted to a few serotypes (so benefits of immunisation are limited) unless previously given 1 or more doses of 7vPCV.
- Recent use of immunosuppressive therapy or radiation of lymph nodes. However, once it is considered that these patients are immunologically 'stabilised', they should be promptly vaccinated.

Adverse events

7-valent pneumococcal conjugate vaccine

Among the most commonly reported are injection site adverse events and fever. 7vPCV is more commonly associated with local adverse events, with rates of erythema ranging from 10.0 to 11.6% (very common) for 7vPCV, compared with 6.7 to 11.4% (common to very common) for DTPa. There is no pattern of increasing local reactogenicity with subsequent doses.[12] A higher rate of local adverse events has been observed in older children after a single dose. Prophylactic antipyretic medication is recommended in children who have seizure disorders or a previous history of febrile seizures.

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% (common) of recipients.[31] Low-grade fever occurs occasionally, but fever above 39°C occurs in less than 0.5% (uncommon) of recipients.[31]

Previously, there were concerns about extensive local adverse events following revaccination with 23vPPV[31] but recent studies indicate that revaccination is not associated with more local adverse events compared to 1 or 2 doses.[32,33] Revaccination is not associated with an increase in systemic adverse events such as fever or headache.[32-34]

Use in pregnancy

7-valent pneumococcal conjugate vaccine

Vaccination during pregnancy has not been evaluated for potential harmful effects in animals or humans. Although unlikely to result in adverse effects to mother or fetus, it is neither indicated nor recommended.

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 there is an increased risk of IPD.[35,36] Women of reproductive age with known risk factors for IPD should be vaccinated before planned pregnancy.

Variations from product information

7-valent pneumococcal conjugate vaccine

The product information recommends a 4-dose 7vPCV schedule for vaccination commencing at 2 months of age with doses at 2, 4, 6 and 12 months of age, 3 doses for vaccination commencing between 7 and 12 months of age, and 2 doses for vaccination commencing between 13 and 23 months of age. However, NHMRC recommends 1 dose less than that stated in the product information for healthy children who are not at increased risk of IPD.

23-valent pneumococcal polysaccharide vaccine

23vPPV is licensed for use only in children >24 months of age, but NHMRC considers that it can be used from 18 months of age in children who have previously received 7vPCV.

References

Full reference list available on the electronic *Handbook* or website http://immunise.health.gov.au.

3.16 POLIOMYELITIS

Virology

Polioviruses are classified as enteroviruses in the family Picornaviridae.[1] They have an RNA genome, and are transient inhabitants of the gastrointestinal tract (GIT). There are 3 poliovirus serotypes, PV1, PV2 and PV3. The virus enters through the mouth, multiplies in the pharynx and GIT and is 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 and, occasionally, oral-oral spread.[3] The infection may be clinically inapparent. If symptoms occur, they may include headache, gastrointestinal disturbance, malaise and stiffness of the neck and back, with or without paralysis. Paralysis is classically asymmetrical. Paralytic polio is a complication of poliovirus aseptic meningitis, and may be spinal (79%), bulbar (2%) or bulbospinal (19%). The case-fatality rate in paralytic polio is 2 to 5% in children, 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. Infected individuals are most infectious from 7 to 10 days before to 7 to 10 days after the onset of symptoms. The oral vaccine virus may be shed in the faeces for 6 weeks or more,[2] and for up to several years in people with impaired immunity. Oral vaccine strains shed for many years may mutate into potentially neurovirulent strains.[4-9]

Epidemiology

The incidence of poliomyelitis has been dramatically reduced worldwide, but cases still occur in developing countries in the Indian subcontinent, the eastern Mediterranean and Africa.[10,11] The World Health Organization (WHO) aimed to eradicate poliomyelitis by the year 2005 and, although not successful, is still hopeful this will be achieved by 2010 or soon after.[12] In 1994, the continents of North and South America were certified to be free of polio,[13] followed by the Western Pacific region (including Australia) in 2000 and the European region in 2002.[14,15] In countries where the disease incidence is low but transmission is still occurring, poliomyelitis cases are seen sporadically or as outbreaks among non-vaccinated individuals. In 2005, 12 countries previously declared polio-

free, including Indonesia, experienced outbreaks due to importations of wild poliovirus from one of the remaining endemic countries: Afghanistan, India, Nigeria and Pakistan.[11]

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 1977 due to an importation from Turkey, but 2 vaccine-associated cases were notified in 1986 and 1995.[16,17] Because of the rapid progress in global polio eradication and diminished risk of wild virus associated disease, inactivated poliomyelitis vaccine (IPV) is now used for all doses of polio vaccine in Australia.[3,18] This change was implemented because of concern about the risk of causing vaccine-associated paralytic poliomyelitis (VAPP), which is about 1 case for every 2.4 million doses of oral poliomyelitis vaccine (OPV) distributed.[19] The advantage of using IPV is that it cannot cause VAPP.

Global eradication of polio

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.[20] However, most countries which can afford IPV now use IPV in preference to OPV, in order to eliminate the risk of VAPP and also to reduce the risk of prolonged shedding of potentially neurovirulent strains of poliovirus by individuals with impaired immunity.[3] A vaccine-derived poliovirus (VDPV) is derived from OPV but has a number of significant mutations due to long-term replication in an individual with impaired immunity (iVDPV) or through person-to-person transmission in areas of low polio vaccine coverage (circulating VDPV or cVDPV). Outbreaks of poliomyelitis due to cVDPV have been reported worldwide.[6] People travelling to countries still using OPV are at risk of VAPP, as was reported for an unimmunised adult from the USA who travelled to Costa Rica in 2005.[21] The WHO is planning for global OPV cessation, once the interruption of wild poliovirus transmission has been certified, to remove the incidence of VAPP and VDPVs.[22] Further information is available from the WHO Polio Eradication website http://www.polioeradication.org.

Vaccines

- **IPOL –** Sanofi Pasteur Pty Ltd (IPV; inactivated poliomyelitis vaccine). Each 0.5 mL pre-filled syringe contains poliovirus 40D antigen units of type 1, 8D antigen units of type 2 and 32D antigen units of type 3 grown on monkey kidney cells, inactivated with formaldehyde; traces of phenoxyethanol as preservative, neomycin, streptomycin and polymyxin B.

Combination vaccines that include IPV

Formulations for children aged <8 years

- **Infanrix hexa** – GlaxoSmithKline (DTPa-hepB-IPV-Hib; diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliomyelitis vaccine-*Haemophilus influenzae* type b (Hib)). The vaccine consists of *both* a 0.5 mL pre-filled syringe containing 30 IU diphtheria toxoid, 40 IU tetanus toxoid, 25 µg pertussis toxoid (PT), 25 µg filamentous haemagglutinin (FHA), 8 µg pertactin (PRN), 10 µg recombinant HBsAg, 40 D-antigen units inactivated polioviruses type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett) adsorbed onto aluminium hydroxide/phosphate; phenoxyethanol as preservative; traces of formaldehyde, polymyxin and neomycin *and* a vial containing a lyophilised pellet of 10 µg purified Hib capsular polysaccharide (PRP) conjugated to 20–40 µg tetanus toxoid. The vaccine *must be reconstituted* by adding the entire contents of the syringe to the vial and shaking until the pellet is completely dissolved. May also contain yeast proteins.
- **Infanrix-IPV** – GlaxoSmithKline (DTPa-IPV; diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis vaccine). Each 0.5 mL pre-filled syringe contains 30 IU diphtheria toxoid, 40 IU tetanus toxoid, 25 µg PT, 25 µg FHA, 8 µg PRN, 40 D-antigen units inactivated polioviruses type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett) adsorbed onto aluminium hydroxide; phenoxyethanol as preservative; traces of formaldehyde, polymyxin and neomycin.
- **Infanrix Penta** – GlaxoSmithKline (DTPa-hepB-IPV; diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliomyelitis vaccine). Each 0.5 mL pre-filled syringe contains 30 IU diphtheria toxoid, 40 IU tetanus toxoid, 25 µg PT, 25 µg FHA, 8 µg PRN, 10 µg recombinant HBsAg, 40 D-antigen units inactivated polioviruses type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett) adsorbed onto aluminium hydroxide/phosphate; phenoxyethanol as preservative; traces of formaldehyde, polymyxin and neomycin. May also contain yeast proteins.

Formulations for people aged ≥8 years

- **Adacel Polio** – Sanofi Pasteur Pty Ltd (dTpa; diphtheria-tetanus-acellular pertussis- inactivated poliomyelitis vaccine). Each 0.5 mL monodose vial contains ≥2 IU diphtheria toxoid, ≥20 IU tetanus toxoid, 2.5 µg PT, 5 µg FHA, 3 µg PRN, 5 µg pertussis fimbriae (FIM) 2+3; 40 D-antigen units inactivated polioviruses type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett); 1.5 mg aluminium phosphate; phenoxyethanol as preservative; traces of formaldehyde, polymyxin, neomycin and streptomycin.
- **Boostrix-IPV** – GlaxoSmithKline (dTpa-IPV; diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis vaccine). Each 0.5 mL pre-filled syringe contains ≥2 IU diphtheria toxoid, ≥20 IU tetanus toxoid, 8 µg PT, 8 µg FHA, 2.5 µg PRN, 40 D-antigen units inactivated polioviruses type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett) adsorbed onto aluminium hydroxide/phosphate; traces of formaldehyde, polymyxin and neomycin.

IPV (IPOL) and IPV-containing combination vaccines contain polioviruses of types 1, 2 and 3 inactivated by formaldehyde. A course of 3 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.

Transport, storage and handling

Transport according to *National Vaccine Storage Guidelines: Strive for 5*.[23] Store at +2°C to +8°C. Do not freeze. Protect from light.

Dosage and administration

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. If IPV (IPOL) is inadvertently given intramuscularly, there is no need to repeat the dose.

Recommendations

Primary vaccination of infants and children

(i) IPV (IPOL) or IPV-containing vaccines are recommended for infants from 2 months of age. An open, randomised, multi-centre trial comparing the hexavalent and pentavalent IPV-containing vaccines found that infants receiving either vaccine at 2, 4 and 6 months of age had seroprotective levels of antibody to polio virus types 1, 2 and 3.[24]

Extra doses of IPV (IPOL) or IPV-containing vaccines are not needed for babies born prematurely.

(ii) The primary course consists of 3 separate doses of vaccine. An interval of 2 months between each dose is recommended, but the minimum interval can be as short as 1 month for catch-up.

(iii) Interchangeability of OPV and IPV: Oral poliomyelitis vaccine (OPV) is no longer in use in Australia. OPV and IPV are interchangeable. Children commenced on OPV should complete their polio vaccination schedule using IPV (IPOL) or IPV-containing vaccines.

Primary vaccination of adults

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

Booster doses

Children

A booster dose of IPV (IPOL) or IPV-containing vaccine should be given at 4 years of age. A fifth dose of IPV is no longer recommended as Australia has been declared polio free since 2000[14] and, as in the US, a completed poliomyelitis vaccination schedule for children is 3 primary doses and 1 booster dose of IPV (IPOL) or an IPV-containing vaccine.[25]

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 (see http://www.polioeradication.org for more information on affected countries), or
- healthcare workers, including laboratory workers, in possible contact with poliomyelitis cases.

For those exposed to a continuing risk of infection, booster doses are desirable every 10 years. dTpa-IPV combination vaccines can be used where otherwise indicated.

Contraindications

The only absolute contraindications to IPV (IPOL) or IPV-containing vaccines are:

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

Adverse events

IPV-containing vaccines cause erythema (33%, very common), pain (13%, very common), and induration (1%, uncommon) at the injection site. Other symptoms reported in young babies are: fever, crying and decreased appetite (5–10%, common).

Use in pregnancy

Refer to Chapter 2.3, *Groups with special vaccination requirements*, Table 2.3.1 *Vaccinations in pregnancy*.

Variations from 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 4 years of age. NHMRC recommends the fourth dose for children at 4 years of age 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 a history of anaphylaxis to a previous dose or to any of the vaccine components.

The product information for both Infanrix hexa and Infanrix Penta states that these vaccines may be given as a booster dose at 18 months of age. NHMRC recommends that a booster dose of DTPa (or DTPa-containing vaccines) is not necessary at 18 months of age. However, DTPa-containing vaccine may be used for catch-up of the primary schedule in children <8 years of age.

The product information for Infanrix-IPV states that this vaccine may be used as a booster dose for children ≤6 years of age who have previously been vaccinated against diphtheria, tetanus, pertussis and poliomyelitis. NHMRC recommends that booster doses of DTPa and IPV be given at 4 years of age; however, this product may be used for catch-up of the primary schedule or as a booster in children <8 years of age.

References

Full reference list available on the electronic *Handbook* or website http://immunise.health.gov.au.

3.17 Q FEVER

Bacteriology

Q fever is caused by *Coxiella burnetii*, an obligate intracellular bacterium, classified in a separate genus, *Coxiella*. A near relative is *Legionella pneumophilia*.[1] The organism is slightly more resistant to heat than other vegetative bacteria, but nevertheless is inactivated at pasteurisation temperatures. It survives well in air, soil, water and dust and may also be disseminated on fomites such as wool, hides, clothing, straw and packing materials.[2,3]

Clinical features

Q fever can be acute or chronic, and there is increasing recognition of long-term sequelae. However, in many instances, infection can be asymptomatic.[4,5]

Acute Q fever usually has an incubation period of 2 to 3½ weeks, depending on the inoculum size and other variables[6] (range from 4 days up to 6 weeks). Clinical symptoms vary by country but in Australia it commonly presents with rapid onset of high fever, rigors, profuse sweats, extreme fatigue, muscle and joint pain, severe headache and photophobia.[4,5] As the attack progresses there is usually evidence of hepatitis, occasionally with frank jaundice; a proportion of patients may have pneumonia which is usually mild but can require mechanical ventilation. If untreated, the acute illness lasts 1 to 3 weeks and may be accompanied by substantial weight loss in the more severe cases.[4,5]

C. burnetii may cause chronic manifestations, the most commonly reported being subacute endocarditis. Less common presentations include granulomatous lesions in bone, joints, liver, lung, testis and soft tissues. Infection in early pregnancy, or even before conception, may recrudesce at term and cause fetal damage.[7-9]

Recent studies have also identified a late sequel to infection, post Q fever fatigue syndrome (QFS), which occurs in about 10 to 15% of patients with acute Q fever.[10-13] Laboratory research suggests that *C. burnetii* persists in most instances of acute Q fever, regardless of clinical status, and that immunogenic variation in the response to persistent infection leads to cytokine dysregulation and determines whether QFS occurs.[11,14,15]

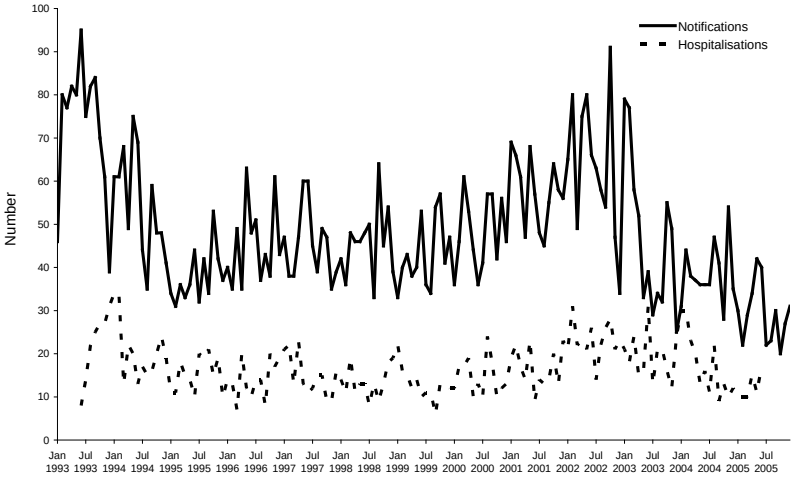
Epidemiology

C. burnetii infects both wild and domestic animals and their ticks, with cattle, sheep and goats being the main source of human infection. Companion animals such as cats and dogs may also be infected. The animals shed *C. burnetii* into the environment through their products of conception (especially high numbers of coxiellas) but also in their milk, urine, and faeces. *C. burnetii* is highly infectious[16] and can survive in the environment. The organism is transmitted to humans via

the inhalation of infected aerosols or dust. Those most at risk include workers from the meat and livestock industries and shearers, with non-immune new employees or visitors being at highest risk of infection. Nevertheless, Q fever is not confined to occupationally exposed groups; there are numerous reports of sporadic cases or outbreaks in the general population in proximity to infected animals in stockyards, feedlots, processing plants or farms.

Use of Q fever vaccine in Australia can be considered in 3 periods. First, from 1991 to 1993 when vaccine was used in a limited number of abattoirs, then from 1994 to 2000 when vaccination steadily increased to cover large abattoirs in most states,[17] and finally from 2001 to 2006 during the period of the Australian Government sponsored Q fever Management Program.[18] This program extended vaccination to farmers, their families and employees in the livestock-rearing industry. With respect to abattoir workers, there has been a clear reduction in Q fever cases and associated insurance claims since 1994.[17,19] More widely, the numbers of Q fever cases reported to the National Notifiable Diseases Surveillance System (NNDSS) have declined over the period 1994 to 2005, during which there has been an increasing use of vaccine (see Figure 3.17.1). This decline is suggestive of an impact from vaccination among people not working in abbatoirs but, as there are substantial variations in total numbers of cases from year to year, requires confirmation over a longer period.[20]

Figure 3.17.1: Q fever notifications and hospitalisations, Australia, 1993 to 2005,* by month of diagnosis or admission[20]



* Notifications where the month of diagnosis was between January 1993 and December 2005; hospitalisations where the month of admission was between 1 July 1993 and 30 June 2005.

Vaccine[4,21]

- **Q-VAX** – CSL Biotherapies (Q fever vaccine). Each 0.5 mL pre-filled syringe contains 25 µg purified killed suspension of *Coxiella burnetii*; thiomersal 0.01% w/v. May contain egg proteins.
- **Q-VAX Skin Test** – CSL Biotherapies (Q fever skin test). Each 0.5 mL liquid vial when diluted in 15 mL of sodium chloride contains 16.6 ng of purified killed suspension of *Coxiella burnetii* in each diluted 0.1 mL dose; thiomersal 0.01% w/v before dilution. May contain egg proteins.

Q fever vaccine and skin test consist of a purified killed suspension of *C. burnetii.* It is prepared from the Phase I Henzerling strain of *C. burnetii* grown in the yolk sacs of embryonated eggs. The organisms are extracted, inactivated with formalin, and freed from excess egg proteins by fractionation and ultracentrifugation. Thiomersal 0.01% w/v is added as a preservative.

Phase I whole-cell vaccines have been shown to be highly antigenic and protective against challenge both in laboratory animals and in volunteer trials.[22] 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.[23] Although the seroconversion rate may be low, long-term cell-mediated immunity develops[24] 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%.[25-28] Lack of seroconversion is not a reliable marker of lack of vaccination.[22]

During recent years, with much larger numbers vaccinated, a few instances of laboratory proven Q fever have been observed in vaccinated subjects.[21] It is important that these apparent vaccine failures are fully investigated and that vaccination status is reported for all notified cases.

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.[22]

A useful website for Q fever vaccine providers is http://www.qfever.org/vaclist.php.

Transport, storage and handling

Transport the vaccine according to *National Vaccine Storage Guidelines: Strive for 5*.[29] Store at +2°C to +8°C, and do not freeze or store in direct contact with ice packs. If vaccine has been exposed to temperatures less than 0°C, do not use. 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 tests are negative (see 'Pre-vaccination testing' below).

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, camels, sheep, goats and kangaroos or their products (including products of conception). It also includes veterinarians, veterinary nurses, veterinary students, agricultural college staff and students (working with high-risk animals) and laboratory personnel handling veterinary specimens or working with the organism (see also Chapter 2.3, *Groups with special vaccination requirements*, Table 2.3.6 *Recommended vaccinations for those at risk of occupationally acquired vaccine-preventable diseases*).

Workers at pig abattoirs do *not* require Q fever vaccination.

Pre-vaccination testing

(i) Before vaccination, people 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 serological results or skin testing, they should be repeated 2 to 3 weeks later (see (vi) below for interpretation).

(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 use 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 1 in 10 or more, or with a definite positive absorbance value in the EIA, should *not* be vaccinated (see Table 3.17.1).

(v) Skin testing and interpretation should only be carried out by experienced personnel. For further information on training and accredited Q fever immunisation service providers, contact your State or Territory Health Department (see Appendix 1, *Contact details for Australian, State and Territory Government health authorities and communicable disease control*). Skin testing is performed by diluting 0.5 mL of the Q-VAX Skin Test in 15 mL of sodium chloride (injection grade). Diluted Q-VAX Skin Test should be freshly prepared, stored at +2°C to +8°C and used within 6 hours. 0.1 mL of the diluted Q-VAX Skin Test is injected intradermally into the volar surface of the forearm. Commercial isopropyl alcohol skin wipes should not be used. If the skin is not visibly clean, then methylated spirits may be used. 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 3.17.1: Interpretation and action for serological and skin test results (with modifications from *Q fever. Your questions answered* (CSL, 1999)[4])

Serology	Skin test	Interpretation/Action
Positive antibody test*	Positive†	Sensitised: do not vaccinate
	Borderline‡	Sensitised: do not vaccinate
	Negative§	Sensitised: do not vaccinate
Equivocal antibody test^	Positive	Sensitised: do not vaccinate
	Borderline	Indeterminate (see (vi) below)
	Negative	Indeterminate (see (vi) below)
Negative antibody test#	Positive	Sensitised: do not vaccinate
	Borderline	Indeterminate (see (vi) below)
	Negative	Non-immune: vaccinate

* Positive antibody test: CF antibody or IFA positive (according to criteria used by diagnosing laboratory); or definite positive EIA absorbance value (according to manufacturer's instructions).

† Positive skin test: induration present.

‡ Borderline skin test: induration just palpable.

§ Negative skin test: no induration.

^ Equivocal antibody test: CF antibody or IFA equivocal (according to criteria used by diagnosing laboratory); or equivocal EIA absorbance value (according to manufacturer's instructions).

Negative antibody test: CF antibody or IFA negative (according to criteria used by diagnosing laboratory); or definite negative EIA absorbance value (according to manufacturer's instructions).

(vi) Test results are indeterminate when skin test induration is just palpable *and/or* there is an equivocal 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 past infection with Q fever. It may also merely indicate the presence in the subject of antibodies to antigens shared between *C. burnetii* and other bacteria. Australian Q fever vaccine users have dealt with this finding in one of two ways:

(a) Repeat the skin test and interpret as per the guidelines for initial testing. Collect serum 2 to 3 weeks later to look for a rise in titre of *C. burnetii* antibodies in the IFA test, using Phase I and Phase II antigens, and immunoglobulin class analysis. A significant increase (defined as a 4-fold rise in titre of paired sera) indicates previous Q fever infection and vaccination is then contraindicated.

(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. 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 2 to 3 weeks, 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.

Contraindications

Q fever vaccine is contraindicated in the following:

- individuals with a history of an illness suggestive of or proved to be Q fever,
- those shown to be immune by either serological testing or sensitivity to the organism by skin testing,
- those who have been previously vaccinated against Q fever,
- those with known hypersensitivity to egg proteins or any component of the vaccine (Q-VAX may contain traces of egg protein, formalin, and sucrose).[21]

There is no information available on the accuracy of skin testing or the efficacy and safety of Q fever vaccine use in individuals with impaired immunity. In general, skin testing and Q fever vaccine should be avoided in such people.

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

Precautions

Vaccination of subjects already immune to *C. burnetii*, as a result of either previous infection or subjects being rendered hyperimmune by repeated vaccination, may result in severe local or systemic adverse events.

Adverse events

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 commonly in about 10% of vaccinees and may include mild influenza-like symptoms such as headache (9%), fever (up to 2%), chills and minor sweating.[4,21]

There are also 2 patterns of more significant adverse events among the estimated more than 130 000 individuals vaccinated from 1989–2004.[5,17]

The first and familiar pattern is the intensified local reaction at the injection site which may occur shortly after inoculation in individuals sensitised immunologically by previous infection or repeated vaccination. Rarely, an immune abscess develops and requires excision and drainage. The acute reactions may be accompanied by short-term systemic symptoms resembling the post Q fever fatigue syndrome. Note, however, that not all those with positive pre-vaccination skin and/or serological tests develop severe reactions. The introduction of the pre-vaccination skin test at NIH/NIAID Rocky Mountain Laboratory,[30] later combined with antibody testing in Australia, has largely eliminated reactions due to previous immune sensitisation. Despite this, the adverse experience from the earlier American trials[22] in which subjects were not pre-tested, were vaccinated repeatedly or were inoculated with vaccines of a different composition and larger bacterial mass, are still quoted in the general Q fever literature as representative of a whole cell vaccine.

The second, much less frequent, pattern has been reported in people who were skin and antibody test negative at the time of vaccination who did not have any immediate reaction. Some 1 to 8 months after vaccination, some vaccinees, predominately women, developed an indurated lesion at the inoculation site. At the time when the indurated lesion developed, the original skin test site often became positive, presumably indicating a late developing cellular immune response. These lesions were not fluctuant and did not progress to an abscess. Most gradually declined in size and resolved over some months without treatment. A few lesions were biopsied or excised and showed accumulations of macrophages and lymphocytes.[31,32]

Use in pregnancy

Not recommended. Q fever vaccine contains inactivated products and inactivated bacterial vaccines are not considered to be harmful in pregnancy. However, safety of the vaccine in pregnancy has not been established. No information is available on the use of Q fever vaccine during breastfeeding.

Variations from product information

The product information for Q-VAX does not include the use of the reduced dose of vaccine in individuals who have indeterminate results on either serological or skin testing. However, this option has been used successfully by experienced Q fever vaccinators.

References

Full reference list available on the electronic *Handbook* or website http://immunise.health.gov.au.

3.18 ROTAVIRUS

Virology

Rotaviruses are non-enveloped RNA viruses in the family Reoviridae. Rotaviruses are classified according to the 2 surface proteins they contain: VP7, the glycoprotein (G protein), and VP4, the protease-cleaved protein (P protein). The G and P proteins are targets for neutralising antibodies thought to be necessary for protection.[1,2] Because the 2 gene segments that encode these proteins can segregate independently, a typing system consisting of both P and G types has been developed. Rotavirus strains are most commonly referred to by their G serotype, with G1, G2, G3, G4 and G9 accounting for around 90% of serotypes both globally and in Australia.[3,4] The most common P types found in combination with these G types are P1a[8] (found with all common G-types except G2) or P1b[4], usually found in combination with G2.[5]

Rotaviruses are shed in high concentrations in the stools of infected children and are transmitted by the faecal-oral route, both through close person-to-person contact and via fomites.[6] Rotaviruses are probably also transmitted by other modes, such as faecally contaminated food, water and respiratory droplets.[7,8]

Clinical features

Rotavirus is the predominant agent of severe dehydrating gastroenteritis in infants and young children in both developed and developing countries.[1,2] The spectrum of rotavirus illness ranges from asymptomatic infection, to mild, watery diarrhoea of limited duration, to severe dehydrating diarrhoea with vomiting, fever, electrolyte imbalance, shock and death. Rotavirus infections are often more severe than other common causes of diarrhoea, and are more likely to be associated with dehydration and hospitalisation.[1,7] The incubation period is 1 to 3 days, after which illness can begin abruptly with vomiting often preceding the onset of diarrhoea.[7] Up to one-third of patients have a temperature of >39°C in the first few days of illness. Symptoms generally resolve in 3 to 7 days.

Epidemiology

Although individuals can be infected with rotavirus several times during their lives, the first infection, typically between 3 and 36 months of age, is most likely to cause severe diarrhoea and dehydration.[9,10] After a single natural infection, 40% of children are protected against any subsequent infection with rotavirus, 75% are protected against diarrhoea from a subsequent rotavirus infection, and 88% are protected against severe diarrhoea.[10] Repeat infections provide even greater protection. Disease is also less likely when reinfection occurs with a serotype (G type) to which an individual has already been exposed.

In Australia, the best available estimates are that approximately 10 000 hospitalisations due to rotavirus in children <5 years of age occur each year.[11] As such, rotavirus accounts for around half the hospitalisations for acute gastroenteritis of any cause in this age group.[11,12] This translates to 3.8% of children (1 in 27) being hospitalised with rotavirus gastroenteritis by the age of 5 years. In addition to hospitalised children, an estimated 115 000 children <5 years of age visit a GP, and 22 000 children require an Emergency Department visit.[11,13] On average, there is 1 death attributed to rotavirus each year in Australia, but this is likely to be a minimum estimate.[13]

In temperate Australia, rotavirus infections follow a seasonal pattern, the peak incidence being in mid to late winter. In the northern tropical and arid regions, there is no consistent seasonal pattern and disease peaks are unpredictable.[14] Epidemics of rotavirus gastroenteritis have occurred in Central Australia, causing severe strain on healthcare services.[15,16] Overall, Indigenous Australian infants and children are hospitalised with rotavirus gastroenteritis about 3 to 5 times more commonly than their non-Indigenous peers, have a younger age at hospitalisation, and longer duration of hospital stay (an average of 5 days compared with 2 days for non-Indigenous infants).[12,14,15,17]

Children and adults with impaired immunity, such as those with congenital immunodeficiency, or post haematopoietic or solid organ transplantation, are at increased risk of severe, prolonged, and even fatal rotavirus gastroenteritis.[1,18,19] Rotavirus is an important cause of nosocomial gastroenteritis,[20-24] and can also cause disease in adults, especially those caring for children, and outbreaks of gastroenteritis in aged care facilities.[1,25,26]

Vaccines

Two oral rotavirus vaccines are available in Australia, and data on their immunogenicity, safety and efficacy has been systematically reviewed.[27] Both vaccines are live attenuated vaccines administered orally to infants, but the component vaccine viruses differ. Rotarix (GlaxoSmithKline) is a live attenuated vaccine containing 1 strain of attenuated human rotavirus (G1P1[8] strain). The human live attenuated strain protects against non G1 serotypes on the basis of their common P[8] antigen and other epitopes involved in heterotypic immunity. RotaTeq (CSL Biotherapies/Merck & Co Inc) is a pentavalent vaccine containing 5 human-bovine rotavirus reassortants with the human serotypes G1, G2, G3, G4, and P1[8] and the bovine serotypes G6 and P7. The vaccine viruses replicate in the intestinal mucosa and can be shed in the stool of vaccine recipients, particularly after the first dose. Vaccine virus shedding is more common with Rotarix and is detected in the stool a week after vaccination in up to 80% of first dose recipients, and in up to 30% of second dose recipients.[27-29] RotaTeq is only shed after the first dose (in up to 13% of recipients).[30] There have been no studies to assess the implications of shedding for horizontal spread to contacts.

Current oral rotavirus vaccines are underpinned by decades of developmental work.[31] Randomised placebo-controlled studies of both vaccines have documented their efficacy and safety in the prevention of gastroenteritis caused by rotavirus.[27,30,32] A vaccination course prevents rotavirus gastroenteritis of any severity in approximately 70% of recipients over the following 1 to 2 years. The efficacy against severe rotavirus gastroenteritis and against hospitalisation for rotavirus gastroenteritis is higher, ranging from 85 to 100% in clinical trials in many different countries.[27,30,32,33] Efficacy in the prevention of hospitalisation from rotavirus gastroenteritis ranged from 85 to 100%.[27,30,32,33] Vaccination was also highly effective in preventing Emergency Department and clinic/GP visits.[30,33] Overall, rotavirus vaccination prevented around half (42–58%) of hospital admissions for acute gastroenteritis of any cause in young children, suggesting that rotavirus is responsible for more gastroenteritis than detected using routine testing and admission practices.[30,32,33] In randomised control trials, a degree of protection against rotavirus gastroenteritis was also observed in infants who received fewer than the recommended number of doses of rotavirus vaccines. In the available clinical trials, no statistically significant differences were found between the 2 vaccines with regard to protective efficacy by serotype.[27,30,32] The efficacy and safety of both rotavirus vaccines have been evaluated only in clinical trials in which infants received vaccine within specified age limits. There are no data on the use of rotavirus vaccines outside these age ranges (see 'Recommendations' and 'Adverse events' below).

- **Rotarix** – GlaxoSmithKline (live attenuated RIX4414 human rotavirus strain expressing G1P1[8] outer capsid proteins). Each 1.0 mL monodose of the reconstituted vaccine contains not less than $10^{6.0}$ $CCID_{50}$ (cell culture infectious dose 50%) of the RIX4414 strain; sucrose; dextran 40; sorbitol; amino acids; Dulbecco's Modified Eagle Medium; calcium carbonate; xanthan gum. Calcium carbonate buffer solvent (diluent) supplied for reconstitution.
- **RotaTeq** – CSL Biotherapies/Merck & Co Inc (live, oral pentavalent vaccine). Each 2.0 mL monodose pre-filled dosing tube contains rotavirus reassortants G1, G2, G3, G4 and P1[8] each with a minimum dose level of at least 2.0 x 10^6 infectious units; sucrose; sodium citrate; sodium phosphate monobasic monohydrate; sodium hydroxide; polysorbate 80; cell culture media; trace amounts of fetal bovine serum. Also available in packs of 10 monodose pre-filled dosing tubes.

Transport, storage and handling

Transport both vaccines according to *National Vaccine Storage Guidelines: Strive for 5*.[34] Store at +2°C to +8°C. Do not freeze. Protect from light.

Dosage and administration

Rotavirus vaccines are for oral administration only. Under *no* circumstances should rotavirus vaccines be injected.

There are no restrictions on the infant's consumption of food or liquid, including breast milk, either before or after vaccination with either rotavirus vaccine.[7,35]

Rotarix is recommended for use in a 2-dose course (at 2 and 4 months of age). It is presented as a white powder for reconstitution with a separately supplied diluent, and a transfer adapter. The syringe/oral plunger containing the diluent is attached to the vial of lyophilised powder via the transfer adapter, and following reconstitution the 1 mL dose of vaccine should be administered *orally* via the syringe/oral plunger onto the inside of the infant's cheek.

RotaTeq is recommended for use in a 3-dose course (at 2, 4, and 6 months of age). It is supplied in a container consisting of a squeezable plastic, latex-free dosing tube with a twist-off cap, allowing for direct *oral* administration of the 2 mL dose onto the inside of the infant's cheek. RotaTeq does not require reconstitution or dilution. RotaTeq is a pale yellow, clear liquid that may have a pink tint.

Rotavirus vaccines can be co-administered with other vaccines included on the NIP schedule at 2 and 4 months of age (Rotarix) or 2, 4 and 6 months of age (RotaTeq). The available evidence from clinical trials suggests co-administration of oral rotavirus vaccines is safe and effective and does not interfere with the immune response to the other vaccine antigens (DTPa, Hib, IPV, hepB, and 7vPCV).[28,29,35]

Recommendations

(i) Routine infant vaccination (*Safety-Grade B)(Efficacy-Grade B)(Immunogenicity-not assessed*)[27]

Administration of a course of oral rotavirus vaccination is recommended for all infants in the first half of the first year of life. Vaccination of older infants and children is not recommended as there are theoretical concerns regarding use in older age groups (see 'Adverse events' below). Vaccination should occur at either 2 and 4 months of age (Rotarix), or 2, 4 and 6 months of age (RotaTeq), according to the following schedules (see also Table 3.18.1):

- **Rotarix** (human monovalent rotavirus vaccine)

The vaccination course of Rotarix consists of 2 doses at approximately 2 and 4 months of age. The first dose should be given between 6 and 14 weeks of age, and the second dose should be given by the end of the 24th week of age (6 months). The interval between the 2 doses should not be less than 4 weeks.

- **RotaTeq** (pentavalent human-bovine reassortant rotavirus vaccine)

The vaccination course of RotaTeq consists of 3 doses at approximately 2, 4, and 6 months of age. The first dose should be given between 6 and 12 weeks of age,

and all doses should be given by the end of the 32nd week of age (~7.5 months). The interval between doses should be 4 to 10 weeks.

Table 3.18.1: Age limits for dosing of oral rotavirus vaccines

	Doses	Age of routine oral administration	Age limits for dosing			Minimum interval between doses
			1st dose	2nd dose	3rd dose	
Rotarix (GlaxoSmithKline)	2 oral doses (1 mL/ dose)	2 and 4 months	6–14* weeks	10–24* weeks	None	4 weeks
RotaTeq (CSL Biotherapies/ Merck & Co Inc)	3 oral doses (2 mL/ dose)	2, 4 and 6 months	6–12† weeks	10–32† weeks	14–32† weeks	4 weeks

* The upper age limit for receipt of the first dose of Rotarix is 14.9 weeks, that is up to the anniversary of the 15th week of age and the upper age limit for receipt of the second dose of Rotarix is 24.9 weeks, that is up to the anniversary of the 25th week of age.

† The upper age limit for receipt of the first dose of RotaTeq is 12.9 weeks, that is up to the anniversary of the 13th week of age. The second dose of vaccine should preferably be given by 28 weeks of age to allow for a minimum interval of 4 weeks before receipt of the third dose, and the upper age limit for either the second or third doses is 32.9 weeks, that is by the anniversary of the 33rd week of age.

For infants in whom the first dose of rotavirus vaccine is inadvertently administered at an age greater than the suggested cut-off (14 weeks for Rotarix or 12 weeks for RotaTeq), the remaining vaccine doses should be administered as per the schedule, providing the minimum interval between doses can be maintained, and the course completed within the recommended age limits. The timing of the first dose should not affect the safety and efficacy of the second and third dose.[7] Infants who develop rotavirus gastroenteritis before receiving the full course of rotavirus vaccinations should still complete the full 2- or 3-dose schedule (dependent on the brand of vaccine) because one rotavirus infection only provides partial immunity.[7]

(ii) Catch-up *(no studies)*

Routine 'catch-up' or primary vaccination of older children is *not* recommended. Infants should commence the course of rotavirus vaccination within the recommended age limits for the first dose. It is also necessary to ensure that doses are not given beyond the upper age limits for the final dose of the vaccine course (see (i) above). This is based on theoretical concerns regarding possible adverse events in older age groups (see 'Adverse events' below), and because the safety of rotavirus vaccination in older infants and children has not been established.

(iii) Premature infants (*Safety-Grade C) (Efficacy-Grade C)(Immunogenicity-not assessed)*[27]

Vaccination of preterm infants using either available rotavirus vaccine is indicated at a chronologic age of at least 6 weeks if clinically stable. Premature infants (<37 weeks' gestation) appear to be at increased risk of hospitalisation from viral gastroenteritis.[36] In clinical trials, RotaTeq or placebo was administered to 2070 preterm infants (25–36 weeks' gestational age; median 34 weeks) who experienced rates of adverse events after vaccination similar to matched placebo recipients.[7,27] Efficacy against rotavirus gastroenteritis of any severity was evaluated in only a small subset of premature infants and appeared comparable to efficacy in term infants (70%; 95% CI: -15%–95%). These conclusions would also be expected to apply to Rotarix vaccine. If standard infection control precautions are maintained, administration of rotavirus vaccine to hospitalised infants, including hospitalised premature infants, would be expected to carry a low risk for transmission of vaccine viruses (see 'Precautions' below).

Contraindications

The only absolute contraindications to rotavirus vaccines are:

- anaphylaxis following a previous dose of either rotavirus vaccine, or
- anaphylaxis following any vaccine component.

Precautions

(i) Acute gastroenteritis

Infants with moderate to severe acute gastroenteritis should not be vaccinated until after recovery from their acute illness. Infants with mild gastroenteritis (including mild diarrhoea) can be vaccinated. The use of rotavirus vaccines has not been studied in infants with acute gastroenteritis.

(ii) Moderate to severe illness

As with other vaccines, infants with a moderate to severe illness should be vaccinated after recovery. In addition to the factors mentioned above in (i), this avoids superimposing potential adverse events related to vaccination with the concurrent illness.

(iii) Underlying conditions predisposing to severe rotavirus gastroenteritis

Conditions predisposing to severe or complicated rotavirus gastroenteritis include metabolic disorders or chronic gastrointestinal disease, such as Hirschsprung's disease, malabsorption syndromes or short gut syndrome.[1] Although the safety and efficacy of rotavirus vaccines have not been studied in such infants, because they are at greater risk of serious rotavirus disease over an extended age range, the potential benefits of vaccination at an age older than the upper limits recommended in Table 3.18.1 are likely to be substantial. Vaccination of such children at an older age may be judged by clinicians to warrant

discussion with parents on a case by case basis (see 'Variations from product information' below).

(iv) Infants with impaired immunity

There are no studies of the safety or efficacy of the currently available rotavirus vaccines in infants with impaired immunity. As with other live viral vaccines, there are theoretical concerns that vaccine virus-associated gastrointestinal disease could occur in infants with severely impaired immunity who receive rotavirus vaccines. However, the theoretical risk for vaccine virus-associated disease in immune-impaired vaccinated infants is likely to be less than their risk from being exposed to disease from natural infection. Risks and benefits of vaccination should be considered in the context of the infant's specific immune impairment with appropriate specialist advice[7] (see (v) below, and Section 2.3.3, *Vaccination of individuals with impaired immunity due to disease or treatment*).

(v) Infants living in households with people with impaired immunity

Infants living in households with people who have impaired immunity should be vaccinated. In general, household members with impaired immunity are afforded protection by vaccination of young children in the household. This outweighs the small risk for transmitting vaccine virus shed in stool to the household member with impaired immunity. The theoretical risk for vaccine virus-associated disease in contacts with impaired immunity is considered less than their risk of being exposed to disease from natural infection. However, there have been no studies to specifically address this question.[7] (See also Section 2.3.3, *Vaccination of individuals with impaired immunity due to disease or treatment*.)

(vi) Recent administration of antibody-containing blood products

Infants who have recently received antibody-containing blood products and are at an eligible age should be vaccinated. The interval between vaccination and receipt of the blood product should be as long as possible, but without delaying administration of vaccine beyond the suggested age limits for dosing (as per Table 3.18.1 above). This recommendation for maximising the interval is based on theoretical concern that passively acquired antibody to rotavirus may interfere with vaccine immunogenicity.[7]

(vii) Hospitalised infants

If a recently vaccinated child is hospitalised for any reason, no precautions other than routine standard precautions need be taken to prevent the spread of vaccine virus in the hospital setting. Administration of rotavirus vaccine to hospitalised infants, including hospitalised premature infants, is likely to carry a low risk for transmission of vaccine viruses if standard infection control precautions are maintained (see 'Vaccines' above).

(viii) Exposure of pregnant women to vaccinated infants

Infants living in households of pregnant women can receive rotavirus vaccines. Most pregnant women will have pre-existing immunity to rotavirus but avoidance of wild-type infection through the vaccination of infant contacts may benefit adults, including pregnant women, and outweighs any theoretical concern regarding exposure to vaccine viruses.

(ix) Regurgitation of vaccine dose

Readministration of the vaccine is not necessary after regurgitation, spitting out, or vomiting of a rotavirus vaccine. This is because there are limited data available on the safety of administering higher than the recommended dose of rotavirus vaccines. There are no studies of the efficacy of a partially administered dose(s).

Adverse events

(i) Intussusception (IS)

Current evidence indicates that intussusception (IS, a form of bowel obstruction) is not associated with either Rotarix or RotaTeq vaccines, especially when given to infants within the age limits studied in clinical trials.[27,30,32] Post-licensure data in larger numbers of children will monitor if there is an increased risk of IS following rotavirus vaccination, particularly among those inadvertently receiving doses outside the recommended age limits. Concern about association between IS and rotavirus vaccines arose because a tetravalent rhesus-reassortant vaccine, called RotaShield, licensed in the United States (but not elsewhere) in 1998–99, was associated with IS in approximately 1 in 10 000 vaccine recipients.[37] The greatest risk of IS occurred within 3 to 14 days after the first dose, with a smaller risk after the second dose.[37,38]

There is evidence that when the first dose of RotaShield was given at >3 months of age, the risk of intussusception was increased.[38] The pathogenesis of RotaShield-associated intussusception has not been determined. However, the current rotavirus vaccines (RotaTeq and Rotarix) differ in composition to RotaShield, which was also more reactogenic.[39-41] The large-scale safety studies of the 2 current rotavirus vaccines included approximately 140 000 infants, and found the risk of IS in vaccine recipients to be similar to that of placebo recipients, and less than that estimated for RotaShield.[27,30,32] To minimise background rates of IS, the clinical trials of Rotarix and RotaTeq limited administration of the first dose of vaccine to infants under 14 and 12 weeks of age, respectively, and did not give subsequent doses to infants beyond a certain age (24 weeks for Rotarix and 32 weeks for RotaTeq).[27,30,32] As such, data on safety of these vaccines in older infants is not currently available (see 'Recommendations' above).

(ii) Other adverse events

Vaccine recipients developed gastrointestinal symptoms such as diarrhoea or vomiting in the week after rotavirus vaccination more commonly than placebo recipients (increased risk of up to 3%).[27,30,32] Fever was not significantly more common in rotavirus vaccine recipients compared with placebo recipients in clinical trials of both available vaccines.[27,30,32]

Interchangeability of rotavirus vaccines

Completion of a course of rotavirus vaccine should be with vaccine from the same manufacturer whenever possible. There are no studies that address the interchangeability of the 2 available rotavirus vaccines. However, if either dose 1 or 2 of vaccine is given as RotaTeq, a third dose of either rotavirus vaccine should be given, provided that the upper age limit and inter-vaccine interval, as defined above in 'Recommendations', Table 3.18.1, are met.

Variations from product information

The product information for Rotarix states that the vaccine should not be administered to subjects with chronic gastrointestinal disease. NHMRC recommends that pre-existing chronic gastrointestinal disease is not considered to be a contraindication to rotavirus vaccination (see 'Precautions' above).

References

Full reference list available on the electronic *Handbook* or website http://immunise.health.gov.au.

3.19 RUBELLA

Virology

Rubella is an enveloped togavirus, genus *Rubivirus.* The virus has an RNA genome and is closely related to group A arboviruses, but does not require a vector for transmission. It is relatively unstable, and is inactivated by lipid solvents, trypsin, formalin, extremes of heat and pH, amantadine and UV light.[1]

Clinical features

Rubella is generally a mild and self-limiting infectious disease.[2] It causes a transient, generalised, erythematous, maculopapular rash, lymphadenopathy involving the post-auricular and sub-occipital glands, and, occasionally, arthritis and arthralgia. Other complications, such as neurological disorders and thrombocytopenia, may occur but are rare. Clinical diagnosis is unreliable since the symptoms are often fleeting and can be caused by other viruses; in particular, the rash is not unique to rubella and may be absent.[1,2] Up to 50% of rubella virus infections are subclinical or asymptomatic.[1] A history of rubella should, therefore, not be accepted without serological evidence of previous infection.[1] The incubation period is 14 to 21 days, and the period of infectivity is from 1 week before until 4 days after the onset of the rash.[2] Rubella infection in pregnancy can result in fetal infection resulting in congenital rubella syndrome (CRS) in a high proportion of cases (see 'Rubella infection in pregnancy' below).

Epidemiology

Rubella occurs worldwide and is spread from person to person by droplet contact and possibly air-borne transmission of infectious respiratory secretions.[1] In temperate climates, the incidence is highest in late winter and early spring.[3] The incidence of rubella has fallen rapidly since vaccine licensure, and there has been a shift in the age distribution of cases, with comparatively more cases being seen in older age groups, particularly the 20–24 year age group.[4] In the early 1990s, rubella epidemics were reported in those States where rubella was notifiable.[5] Over 3000 cases per year were reported between 1992 and 1995.[5] In 2004–2005, rubella notifications were the lowest yet recorded with 31 confirmed cases being reported in each year (0.15 per 100 000 per year).[4] This low notification rate most likely reflects the high vaccine coverage achieved and sustained with the National Measles Control Campaign in late 1998.[3,6,7]

The number of cases of congenital rubella syndrome has also fallen rapidly since rubella vaccine licensure in Australia. Successful vaccination campaigns and high vaccination coverage resulted in no cases of congenital rubella syndrome occurring in infants of Australian-born mothers between 1998 and 2002. However, 5 cases resulting from infection acquired outside of Australia

were reported during this time.[8,9] Between 2003 and 2005, an additional 5 cases were reported from infection that occurred in Australia[9-11] which reinforces the need for high vaccination coverage of women of child-bearing age (see 'Rubella infection in pregnancy' below).

The rubella virus was isolated in cell culture in 1962, and vaccines prepared from strains of attenuated virus have been approved for use in Australia since 1970. Mass vaccination of schoolgirls commenced in 1971.[1,12] Non-pregnant, seronegative adult women were also vaccinated. These programs were successful and there was a significant reduction in the incidence of congenital rubella syndrome from 1977.[13-15] There has also been a significant increase in the percentage of pregnant women immune to rubella (in NSW from 82% in 1971 to 96% in 1983). Based on a recent study in Melbourne, it was estimated that, in 2000, only 2.5% of all women in Australia of child-bearing age were seronegative. However, susceptibility was higher among overseas-born women, and has been reported as higher among some Indigenous women.[16,17]

Many adolescent and young adult males are not immune to rubella because they did not receive an MMR vaccine.[18] The MMR vaccination program for all adolescents replaced the rubella program for girls in 1993/94.[12] A serosurvey conducted in 1999 showed that only 84% of males aged 14–18 years (compared to 95% of females) and 89% of males aged 19–49 years (compared to 98% of females) were immune to rubella.[18] For this reason, adolescent and young adult males, as well as females, who do not have a documented history of receipt of 2 doses of MMR, should receive MMR vaccine (see 'Recommendations' below). This is both for their own protection and to prevent transmission of the infection in the community (see 'The public health management of rubella' below).

Rubella infection in pregnancy

Maternal rubella infection in the first 8 to 10 weeks of pregnancy results in fetal damage in up to 90% of affected pregnancies, and multiple defects are common.[19-21] The risk of damage declines to 10 to 20% by 16 weeks' gestation. After this stage of pregnancy, fetal damage is rare but has been reported up to 20 weeks' gestation.[19] The characteristics of congenital rubella syndrome include intellectual disabilities, cataracts, deafness, cardiac abnormalities, intrauterine growth retardation and inflammatory lesions of the brain, liver, lungs and bone marrow.[19] Any combination of these defects may occur, but defects which commonly occur alone following infection after the first 8 weeks of pregnancy are perceptive deafness and pigmentary retinopathy. Some infected infants may appear normal at birth, but defects, especially sensorineural deafness, may be detected later.[22]

Rubella reinfection can occur in individuals who have both natural and vaccine-induced antibody.[19] 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.[20,23-25]

All pregnant women with suspected rubella or exposure to rubella should be serologically tested, irrespective of a history of previous vaccination, clinical rubella or a previous positive rubella antibody result (see 'Serological testing for rubella' below). This is because the rash of rubella is not diagnostic, asymptomatic infection can occur, and acute rubella can be confirmed only by laboratory tests.[19,23,24] Pregnant women should be counselled to restrict contact with individuals with confirmed, probable or suspected rubella for 6 weeks (2 incubation periods).[26] Counselling of pregnant women with confirmed rubella regarding the risk to the fetus should be given in conjunction with the woman's obstetric service.

Serological testing for rubella

A number of commercial assays for testing immunity to rubella are available. These vary according to the method used to determine the positive cut-off value (the WHO cut-off is 10 IU/mL but, at present, there is no recommended Australian minimal level). Available data support the presumption that an antibody level found by use of a licensed assay to be above the standard positive cut-off for that assay can be considered evidence of past exposure to rubella virus.[23] Antibody levels below the cut-off are likely not to be protective, particularly if the antibodies have been generated by vaccination rather than by natural infection, and MMR vaccine (or MMRV if protection against varicella is required in children 12 months to 12 years of age) should be administered according to the 'Recommendations' below. Expert consultation and referral of sera to a reference laboratory are recommended if there is a difficulty interpreting results.

Acute rubella infection is indicated by presence of rubella IgM or 4-fold or greater increase in rubella IgG. Rubella IgM may not appear until a week after clinical symptoms. Sera for IgG testing should be taken 7 to 10 days after onset of illness and repeated 2 to 3 weeks later. The most recent date of potential exposure should be obtained, if possible, to calculate the potential incubation period. As some patients may have more than 1 exposure to a person with a rubella-like illness, and because exposure may occur over a prolonged period, it is important to ascertain the dates of the first and last exposures.[26]

Seronegative women of child-bearing age should be vaccinated (see 'Recommendations' below) and tested for seroconversion 8 weeks 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.[15,19] 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 pregnant women exposed to rubella should always be performed (see 'Rubella infection in pregnancy' above). 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).[26] If the woman has an antibody titre below the protective level, or a low level of antibodies and remains asymptomatic, a second blood specimen should be collected 28 days after the exposure (or onset of symptoms) 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.[24]

Vaccines

Rubella vaccine is available as either MMR vaccine or as a monovalent rubella vaccine. It is anticipated that combination measles-mumps-rubella-varicella (MMRV) vaccines will become available in the near future. A single dose of rubella vaccine produces an antibody response in more than 95% of vaccinees, but antibody levels are lower than after natural infection.[19,23,24] Vaccine-induced antibodies have been shown to persist for at least 16 years in the absence of endemic disease.[23,24,27,28] Protection against clinical rubella appears to be long-term in those who seroconvert.[19]

Monovalent rubella vaccine

- **Meruvax II** – CSL Biotherapies/Merck & Co Inc (rubella virus vaccine). Each 0.5 mL monodose of the reconstituted, lyophilised vaccine contains not less than 1000 $TCID_{50}$ (tissue culture infectious dose 50%) of attenuated rubella virus (Wistar RA 27/3 strain); 25 µg neomycin; 3 mg human serum albumin; sorbitol and gelatin as stabilisers.

Combination measles-mumps-rubella vaccine

- **Priorix (MMR)** – 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 monodose of the reconstituted, lyophilised 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; lactose; neomycin; amino acids; sorbitol and mannitol as stabilisers.

Transport, storage and handling

Transport both vaccines according to *National Vaccine Storage Guidelines: Strive for 5*.[29] Store at +2°C to +8°C. Protect from light. Do not freeze. Reconstituted vaccine should be used immediately, but can be stored at +2°C to +8°C for up to 8 hours before use.

Dosage and administration

For both children and adults, the dose of MMR and monovalent rubella vaccine is 0.5 mL, administered by either SC or IM injection.

MMR and monovalent rubella vaccine can be given at the same time as other vaccines (including DTPa, hepatitis B, MenCCV and varicella), using separate syringes and injection sites. If MMR or monovalent rubella vaccine is not given simultaneously with other live viral parenteral vaccines (eg. varicella vaccine), they should be given at least 4 weeks apart (see 'Precautions' below).

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 rubella-containing vaccine in children and adults of both sexes.

(i) Routine vaccination of children

Two doses of rubella-containing vaccine are recommended for all children. The first dose should be given at 12 months of age and the second dose at 18 months of age (MMR or MMRV when available). The minimum interval between the first and second doses of MMR or MMRV is 4 weeks. A history of rubella is not a contraindication to vaccination. Individuals who are already immune to rubella have no increased risk of side effects from vaccination.[19,23]

(ii) Vaccination of women of child-bearing age

Every effort should be made to identify non-pregnant seronegative women of child-bearing age. The following women are more likely to be seronegative to rubella: women born overseas (especially in Asia, Pacific islands, sub-Saharan Africa and South America) who have entered Australia after the age of routine vaccination; non-English speaking women; women over the age of 35; and Muslim women.[5,13,14,16,30] Seronegative women should be given MMR vaccine and advised not to become pregnant for 28 days after vaccination. Monovalent rubella vaccine can be used where there is a contraindication to the measles or mumps components of MMR. Vaccinated women should be tested for seroconversion 6 to 8 weeks after vaccination (see 'Serological testing for rubella' above). 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.[19] Although 2 doses of MMR vaccine are routinely recommended, if rubella immunity is demonstrated after receipt of 1 dose of a rubella-containing vaccine, no further dose is required, unless indicated by subsequent serological testing (see 'Serological testing for rubella' above).

(iii) Vaccination of adolescent and adult males

All males born during or after 1966 require 2 doses of MMR at least 4 weeks apart if they have no record of receiving the vaccine, as they are especially likely to be non-immune to rubella (see 'Epidemiology' above).

(iv) Vaccination post-partum

Women found to be seronegative on antenatal rubella immunity testing should be vaccinated after delivery and before discharge from the maternity unit. MMR vaccine is recommended, although monovalent rubella vaccine can also be used for this purpose. These women should be tested for rubella immunity 6 to 8 weeks after vaccination (see 'Vaccination of women of child-bearing age' above). Anti-D immunoglobulin does not interfere with the antibody response to vaccine.[1,19] If anti-D immunoglobulin is also 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[24] (see 'Contraindications' below).

(v) Vaccination of healthcare workers and people working with children

All healthcare staff and people working with children, born during or since 1966, including medical, nursing, and other health professional students, either without vaccination records or seronegative upon screening, should receive 2 doses of MMR vaccine, both for their own protection and to avoid the risk of transmitting rubella to pregnant patients and/or colleagues[31] (see Table 2.3.6 *Recommended vaccinations for those at risk of occupationally acquired vaccine-preventable diseases*). Preferably, MMR should be used. Where necessary, those vaccinated can be tested for seroconversion 8 weeks after vaccination and revaccinated if seronegative (see 'Vaccination of women of child-bearing age' above).

For further recommendations related to MMR vaccination, see Chapter 3.11, *Measles*.

Contraindications

Vaccination is contraindicated in the following circumstances:

(i) Allergy to vaccine components

- anaphylaxis following a previous dose of rubella, MMR or MMRV, or
- anaphylaxis following any vaccine component.

(ii) People with impaired immunity

Rubella-containing vaccine should not be administered to patients with congenital or acquired impaired immunity (see Section 2.3.3, *Vaccination of individuals with impaired immunity due to disease or treatment*). This includes those receiving high-dose corticosteroid or immunosuppressive treatment, general radiation, 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.[1,23] Rubella vaccine or MMR may be given to HIV-positive individuals unless they have severely impaired immunity.[23] (For further information on MMR and MMRV vaccines, see Chapter 3.11, *Measles* and Chapter 3.24, *Varicella*).

(iii) Recent administration of antibody-containing blood product

Rubella-containing vaccine should not be given within at least 3 months after an injection of immunoglobulin, other antibody-containing blood product, or whole-blood transfusion, because the expected immune response may be impaired.[19,24] The recommended intervals for receipt of rubella-containing vaccines after receipt of blood products are given in Table 2.3.5 *Recommended intervals between either immunoglobulins or blood products and MMR, MMRV or varicella vaccination*. Rubella-containing vaccines may be administered concomitantly with, or at any time in relation to, anti-D immunoglobulin, but at a separate injection site. However, women who have received anti-D immunoglobulin should be serologically tested 8 weeks after vaccination to ensure that seroconversion has occurred.[1,23]

(iv) Pregnant women

MMR and monovalent rubella vaccines should not be given to a woman known to be pregnant, and pregnancy should be avoided for 28 days after vaccination (see 'Use in pregnancy' below).[1,32] Data on the use of MMRV vaccines in individuals >12 years of age are not available.

Precautions

- If MMR or monovalent rubella vaccine is not given simultaneously with other live viral parenteral vaccines (eg. varicella vaccine), they should be given at least 4 weeks apart.
- Breastfeeding is not a contraindication to rubella vaccination. The rubella vaccine virus may be secreted in human breast milk, and there have been rare cases of transmission of vaccine virus through breast milk reported. However, these infections have been mild.[1]
- There is no risk to pregnant women from contact with recently vaccinated individuals. The vaccine virus is not transmitted from vaccinees to susceptible contacts.[1]

For precautions related to MMR and MMRV vaccines, see Chapter 3.11, *Measles* and Chapter 3.24, *Varicella*.

Adverse events

Mild adverse events such as fever, sore throat, lymphadenopathy, rash, arthralgia and arthritis may occur after vaccination.[1,23] Symptoms most often begin 1 to 3 weeks after vaccination and are usually transient. Joint symptoms are more common in adults, especially women (10 to 25%, very common) than in children (0.3%, uncommon).[1,23] Thrombocytopenia, that is usually self limiting, has been

reported rarely after rubella vaccine.[23] Very rarely, neurological symptoms have been reported, but a causal relationship has not been established.[23]

For adverse events related to MMR and MMRV vaccines, see Chapter 3.11, *Measles* and Chapter 3.24, *Varicella*.

The public health management of rubella

All cases of suspected rubella infection should be laboratory tested and false positive results excluded. Infected individuals should be excluded from school/work/institution and should avoid contact with women of child-bearing age for at least 4 days after the onset of the rash.[26]

All contacts should be identified, especially those who are pregnant. If a contact is pregnant, see 'Rubella infection in pregnancy' above. All contacts >12 months of age without adequate proof of immunity should receive 1 dose of MMR (or MMRV, when available, in those 12 months to 12 years of age). This will not prevent rubella disease if already exposed. If vaccination is refused, the contact should avoid further contact with cases until at least 4 days after onset of the rash in the case.

Exposed healthcare workers without adequate proof of immunity should be excluded from work for 21 days from exposure or for at least 4 days after the onset of a rash.[26]

Use in pregnancy

Vaccination should be avoided in early pregnancy.[1] However, active surveillance in the USA, UK and Germany indicates that no case of vaccine-induced congenital rubella syndrome occurred among more than 500 women inadvertently vaccinated with rubella vaccine during pregnancy, whose pregnancies continued.[33] In a recent Iranian study performed after mass vaccination with a measles-rubella vaccine, 117 susceptible women were inadvertently vaccinated while pregnant or became pregnant ≤3 months after vaccination. There were no CRS-related abnormalities among the infants born to these women.[34] Based on this evidence, the vaccine cannot be considered to be teratogenic, and termination of pregnancy following inadvertent vaccination is not indicated[1,24] (see Section 2.3.2, *Vaccination of women planning pregnancy, pregnant or breastfeeding women, and preterm infants*).

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.[23] 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.[23] 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.[35]

Variations from 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, MMR or MMRV vaccines, whereas NHMRC recommends 28 days.[32]

The product information for Meruvax II 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 individuals 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 or MMRV to children.

References

Full reference list available on the electronic *Handbook* or website http://immunise.health.gov.au.

3.20 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.[1]

Clinical features

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.[1] 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 nucleic 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 after 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 among 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 after admission of one patient with unrecognised smallpox.[3]

Vaccines

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.[4-6]

Australia has stocks of smallpox vaccine for use in an emergency situation only.[4-6]

The USA smallpox vaccine Dryvax, has been used to vaccinate Australian laboratory personnel working with poxviruses. This vaccine contains vaccinia which produces cross-immunity against variola. Dryvax is a freeze-dried formulation.

The duration of immunity is uncertain. A recent review, examining the frequency of adverse events after vaccination with different vaccinia strains, reported that the Lister strain vaccine is associated with a higher risk of severe adverse events, in particular postvaccinal encephalopathy.[7]

Transport, storage and handling

Transport according to *Guidelines for smallpox outbreak, preparedness, response and management*.[4] Smallpox vaccine should be kept frozen at –30°C. The shelf life of the vaccine is 24 hours once thawed and, once thawed, the vaccine should be stored at +2°C to +8°C.

Dosage and administration

Only trained healthcare 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.[4-6,8]

Personal protective equipment must be used while performing smallpox vaccination.

Smallpox vaccines *must not* be injected subcutaneously, intramuscularly or intravenously.

Intradermal inoculation with smallpox vaccine 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.[4-6]

Recommendations

The only current indication for vaccination in Australia is for workers using live pox virus in recombinant gene research, in order to prevent infection at sites of accidental inoculation. Currently, 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.[4]

Australian guidelines for smallpox outbreak, preparedness, response and management may be found at http://www.health.gov.au/internet/wcms/publishing.nsf/Content/health-pubhlth-publicat-others.htm.[4]

Contraindications

The vaccine is contraindicated in:[4,5]

- people with diseases that cause impaired immunity such as human immunodeficiency virus (HIV) infection, acquired immune deficiency syndrome (AIDS), leukaemia, lymphoma, generalised malignancy, agammaglobulinaemia,
- those undergoing therapy with alkylating agents, antimetabolites, radiation or large doses of steroids,
- those who have ever been diagnosed with eczema, even if the condition is mild or not presently active,
- those with a history of neurological disorder,
- women who are either pregnant or trying to become pregnant,
- women who are breastfeeding,
- children aged <1 year,
- anyone living in a household with a member who has any of the conditions listed above,
- people with serious, life-threatening allergies to the antibiotics polymyxin B, streptomycin, tetracycline or neomycin (this may depend on brand of vaccine used),
- those vaccinated in the past 30 days with a live vaccine,
- those with a history of cardiac disease, including:
  - previous myocardial infarction,
  - angina,
  - congestive heart failure,
  - cardiomyopathy,
  - valvular disease, including rheumatic heart disease,
  - stroke or transient ischaemic attack,
  - chest pain or shortness of breath with activity,
  - other heart conditions under the care of a doctor.

Precautions[4-6]

Individuals with acute or chronic skin conditions, such as atopic dermatitis, impetigo and varicella-zoster (chickenpox and shingles), should not be vaccinated until the condition resolves.

Individuals with eczema should live apart from recently vaccinated family members who may have skin lesions.

Women should be advised to avoid pregnancy for 3 months after smallpox vaccination.

Anyone who receives a smallpox vaccination should not receive another live vaccine for 1 month afterwards.

Adverse events[4-6,8]

Smallpox vaccines have well described adverse events, which vary in frequency according to the virus present in the seed stock. They include:

- postvaccinal encephalitis (PVE) or encephalomyelitis (PVEM), a demyelinating disease which occurs at a rate of 1 per 300 000 vaccinations; PVE is generally seen in those aged <1 year and PVEM in those aged >2 years;
- progressive vaccinia (vaccinia gangrenosa) at the site of inoculation, in vaccinees with immune impairment;
- eczema vaccinatum, being vaccinial skin disease at sites of previous or current eczema; occurs at a rate of about 1 in 26 000 vaccinations;
- generalised vaccinia, a self-limiting condition resulting from blood-borne dissemination of the virus to other skin sites; more serious in people with impaired immunity; occurs at a rate of 1 in 5000 vaccinations;
- inadvertent inoculation of either the vaccinee or vaccinator in sites such as the face, eyes or hands; occurs at a rate of 1 in 20 000 primary vaccinations;
- various skin rashes, usually self-limiting but can progress to Stevens-Johnson Syndrome;
- fetal vaccinia is rare (<50 reported cases), greatest risk occurs during the third trimester;
- cardiac adverse events including myocarditis, pericarditis and, possibly, dilated cardiomyopathy.

Use in pregnancy

Smallpox vaccine is contraindicated in women who are either pregnant or trying to become pregnant. Women should be advised to avoid pregnancy for 3 months after vaccination.

Vaccinia immune globulin[4,5]

Vaccinia immune globulin (VIG) is a sterile solution of the immunoglobulin fraction of plasma containing antibodies to the vaccinia virus, from individuals who were previously vaccinated with smallpox vaccine. VIG and the nucleoside analogue active against poxviruses, cidofovir, may be used to treat vaccine complications such as inadvertent inoculation of the eye or eyelid without vaccinal keratitis, severe generalised vaccinia if patient is toxic, eczema

vaccinatum and progressive vaccinia. VIG is not indicated for treatment of vaccinal keratitis or postvaccinal encephalitis.

VIG is contraindicated in those with a history of anaphylactic sensitivity to thiomersal or to other humanised monoclonal antibodies.

There are currently limited stocks of VIG and cidofovir available in Australia. Contact the Australian Government Department of Health and Ageing or your State/Territory Health Department for further information regarding these products (see Appendix 1, *Contact details for Australian, State and Territory Government health authorities and communicable disease control*).

References

Full reference list available on the electronic *Handbook* or website http://immunise.health.gov.au.

3.21 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 2 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 3 to 21 days (range 1 day to several months), with a median time of onset after injury of 10 days. Generally, a shorter incubation period is associated with a more heavily contaminated wound, more severe disease and a worse prognosis. Generalised tetanus, the most common form of the disease, is characterised by increased muscle tone and generalised spasms. Early symptoms and signs include increased tone in the masseter muscles (trismus, or lockjaw), dysphagia, 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 is rare in people who have received 5 doses of a tetanus-containing vaccine (1 in 90 cases in the United Kingdom from 1984–2000).[1] However, individual cases have been reported[2,3] and clinicians should consider tetanus when there are appropriate symptoms and signs, irrespective of the person's vaccination record. A high level of diagnostic awareness of tetanus is particularly important in the elderly in industrialised countries, including Australia, as most deaths occur in people over 70 years of age, especially women, and may be associated with apparently minor injury.[1,4]

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 primarily in older adults who have never been vaccinated or were vaccinated in the remote past. There were 18 notified cases of tetanus during 2001–2005, but 120 hospitalisations (July 2000–June 2005) where tetanus was the principal diagnosis.[4,5] This discrepancy suggests under-notification. During 2001–2005, there were 2 deaths from tetanus.[4,5] The case-fatality rate in Australia is about 3%. Neonatal tetanus is a frequent cause of infant mortality in parts of Asia, Africa and Latin America.

Effective protection against tetanus can be provided only 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.[1] A completed course of vaccination provides protection for many years.

Vaccines

The acronym DTPa, using capital letters, signifies child formulations of diphtheria, tetanus and acellular pertussis-containing vaccines. The acronym dTpa is used for adolescent/adult formulations which contain substantially lesser amounts of diphtheria toxoid and pertussis antigens (see formulations).

Formulations for children aged <8 years

- **Infanrix hexa** – GlaxoSmithKline (DTPa-hepB-IPV-Hib; diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliomyelitis vaccine-*Haemophilus influenzae* type b (Hib)). The vaccine consists of *both* a 0.5 mL pre-filled syringe containing 30 IU diphtheria toxoid, 40 IU tetanus toxoid, 25 µg pertussis toxoid (PT), 25 µg filamentous haemagglutinin (FHA), 8 µg pertactin (PRN), 10 µg recombinant HBsAg, 40 D-antigen units inactivated polioviruses type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett) adsorbed onto aluminium hydroxide/phosphate; phenoxyethanol as preservative; traces of formaldehyde, polymyxin and neomycin *and* a vial containing a lyophilised pellet of 10 µg purified Hib capsular polysaccharide (PRP) conjugated to 20–40 µg tetanus toxoid. The vaccine *must be reconstituted* by adding the entire contents of the syringe to the vial and shaking until the pellet is completely dissolved. May also contain yeast proteins.

- **Infanrix-IPV** – GlaxoSmithKline (DTPa-IPV; diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis vaccine). Each 0.5 mL pre-filled syringe contains 30 IU diphtheria toxoid, 40 IU tetanus toxoid, 25 µg PT, 25 µg FHA, 8 µg PRN, 40 D-antigen units inactivated polioviruses type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett) adsorbed onto aluminium hydroxide; phenoxyethanol as preservative; traces of formaldehyde, polymyxin and neomycin.
- **Infanrix Penta** – GlaxoSmithKline (DTPa-hepB-IPV; diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliomyelitis vaccine). Each 0.5 mL pre-filled syringe contains 30 IU diphtheria toxoid, 40 IU tetanus toxoid, 25 µg PT, 25 µg FHA, 8 µg PRN, 10 µg recombinant HBsAg, 40 D-antigen units inactivated polioviruses type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett) adsorbed onto aluminium hydroxide/phosphate; phenoxyethanol as preservative; traces of formaldehyde, polymyxin and neomycin. May also contain yeast proteins.

Formulations for people aged ≥8 years

Adsorbed diphtheria-tetanus vaccine

- **ADT Booster –** Statens Serum Institut/CSL Biotherapies (dT; diphtheria-tetanus, adult formulation). Each 0.5 mL pre-filled syringe or monodose vial contains ≥2 IU diphtheria toxoid and ≥20 IU tetanus toxoid adsorbed onto 0.5 mg aluminium hydroxide.

Combination vaccines

- **Adacel** – Sanofi Pasteur Pty Ltd (dTpa; diphtheria-tetanus-acellular pertussis). Each 0.5 mL monodose vial contains ≥2 IU diphtheria toxoid, ≥20 IU tetanus toxoid, 2.5 µg PT, 5 µg FHA, 3 µg PRN, 5 µg pertussis fimbriae (FIM) 2+3; 1.5 mg aluminium phosphate; phenoxyethanol as preservative; traces of formaldehyde.
- **Adacel Polio** – Sanofi Pasteur Pty Ltd (dTpa; diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis vaccine). Each 0.5 mL monodose vial contains ≥2 IU diphtheria toxoid, ≥20 IU tetanus toxoid, 2.5 µg PT, 5 µg FHA, 3 µg PRN, 5 µg FIM 2+3, 40 D-antigen units inactivated polioviruses type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett); 1.5 mg aluminium phosphate; phenoxyethanol as preservative; traces of formaldehyde, polymyxin, neomycin and streptomycin.

- **Boostrix** – GlaxoSmithKline (dTpa; diphtheria-tetanus-acellular pertussis). Each 0.5 mL monodose vial or pre-filled syringe contains ≥2 IU diphtheria toxoid, ≥20 IU tetanus toxoid, 8 µg PT, 8 µg FHA, 2.5 µg PRN, adsorbed onto 0.5 mg aluminium hydroxide/phosphate; 2.5 mg phenoxyethanol as preservative. May contain traces of formaldehyde.
- **Boostrix-IPV** – GlaxoSmithKline (dTpa-IPV; diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis vaccine). Each 0.5 mL pre-filled syringe contains ≥2 IU diphtheria toxoid, ≥20 IU tetanus toxoid, 8 µg PT, 8 µg FHA, 2.5 µg PRN, 40 D-antigen units inactivated polioviruses type 1 (Mahoney), 8 D-antigen units type 2 (MEF-1) and 32 D-antigen units type 3 (Saukett) adsorbed onto aluminium hydroxide/phosphate; traces of formaldehyde, polymyxin and neomycin.

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

Complete immunisation (5 doses) induces protective levels of antitoxin lasting throughout childhood but, by middle age, about 50% of vaccinees have low or undetectable levels.[6-8] A single dose of tetanus toxoid produces a rapid anamnestic response in such vaccinees.[9-11]

Tetanus toxoid is available in combination with other antigens. Production of the previously available tetanus toxoid vaccine was discontinued by the manufacturer in February 2006. Production of the previous DT (CDT vaccine), registered for use in children <8 years of age, ceased in June 2005. ADT Booster can be used for the booster dose of dT in people aged ≥8 years or, if necessary, for the primary dT course (see 'Variations from product information' below).

Transport, storage and handling

Transport according to *National Vaccine Storage Guidelines: Strive for 5*.[12] Store at +2°C to +8°C. Protect from light. Do not freeze.

Dosage and administration

The dose of tetanus-containing vaccine is 0.5mL by IM injection.

Do not mix DTPa-containing vaccines, dTpa or dT vaccine with any other vaccine in the same syringe, unless specifically registered for use in this way.

Recommendations

(i) Vaccination in childhood

Vaccination against tetanus is part of the National Immunisation Program (NIP) schedule, with tetanus toxoid being given in combination with diphtheria toxoid and acellular pertussis as DTPa vaccine. The recommended primary course of vaccination is at 2, 4 and 6 months of age. A booster dose of DTPa is given at 4 years of age. Immunity to tetanus will not be compromised before the booster dose, as the serological response to the primary course of vaccination is usually sufficient for those years. A second booster, using the adolescent/adult formulation, dTpa, at 12–17 years of age, is essential for maintaining immunity to tetanus in adults. 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 experienced a tetanus-prone wound during childhood.

For details on the management of children who have missed doses in the NIP schedule, see Section 1.3.5, *Catch-up*.

(ii) Vaccination of adults

Booster vaccination

Routine 10-yearly booster doses in adults who have previously received 5 doses of a tetanus-containing vaccine have *not* been recommended in Australia since 2000. All adults who reach the age of 50 years and have not received a booster dose of a tetanus-containing vaccine in the previous 10 years should be given dT or dTpa vaccine. This stimulates further production of circulating tetanus antibodies at an age when waning of diphtheria and tetanus immunity is commencing in the Australian population.[6] The adolescent/adult formulation dTpa is preferred, if not given previously, as it provides additional protection against pertussis (see Chapter 3.14, *Pertussis*).

Primary vaccination

Where an adult has not received a primary course of tetanus toxoid previously, 3 doses of dT should be given, at minimum intervals of 4 weeks, followed by booster doses at 10 and 20 years after the primary course. Give the first of these doses as dTpa, to provide boosting to natural immunity from exposure to pertussis, which is almost universal in unvaccinated adults. In the event that dT vaccine is *not* available, dTpa can be used for all primary doses. However, this is not recommended routinely because there are no data on the safety, immunogenicity or efficacy of dTpa in multiple doses for primary vaccination.

Tetanus-prone wounds

Adults who have sustained injuries deemed to be tetanus prone should receive a booster dose of dT, if more than 5 years have elapsed since the last dose. In the event that dT vaccine is *not* available, dTpa can be used (see Table 3.21.1 below).

(iii) Other people at special risk

Adults who were born in countries without adequate vaccination programs may never have received primary vaccination against tetanus. Older adults may have inadequate antitoxin levels, due to incomplete primary vaccination against tetanus. Injecting drug users are at risk of tetanus, particularly if skin 'popping' is practised.[13]

Travellers to countries where health services are difficult to access should be adequately protected against tetanus before departure. They should receive a booster dose of dT, if more than 10 years have elapsed since the last dose, or dTpa if not given previously.

Tetanus-prone wounds

In the event of a tetanus-prone injury (defined below), a booster dose of vaccine should be given if more than 5 years have elapsed since the last dose. If there is any doubt about the adequacy of previous tetanus immunisation, tetanus immunoglobulin (see below) should be given as well as tetanus toxoid (see Table 3.21.1). In children <8 years of age, this dose of vaccine should be given as DTPa or a DTPa-combination vaccine, consistent with the child's vaccination history and the NIP schedule. For details on the management of children who have missed doses in the NIP schedule, see Section 1.3.5, *Catch-up.*

The definition of a tetanus-prone injury is not straightforward, as tetanus may occur after apparently trivial injury, such as from a rose thorn, or with no history of injury. However, there are certain types of wounds likely to favour the growth of tetanus organisms. These include compound fractures, bite wounds, deep penetrating wounds, wounds containing foreign bodies (especially wood splinters), wounds complicated by pyogenic infections, wounds with extensive tissue damage (eg. contusions or burns) and any superficial wound obviously contaminated with soil, dust or horse manure (especially if topical disinfection is delayed more than 4 hours). Reimplantation of an avulsed tooth is also a tetanus-prone event, as minimal washing and cleaning of the tooth is conducted to increase the likelihood of successful reimplantation.

General measures for treatment of tetanus-prone wounds[14-19]

Table 3.21.1: Guide to tetanus prophylaxis in wound management

History of tetanus vaccination	Time since last dose	Type of wound	DTPa, DTPa-combinations, dT, dTpa, as appropriate	Tetanus immunoglobulin* (TIG)
≥3 doses	<5 years	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.

† Individuals who have no documented history of a primary vaccination course (3 doses) with a tetanus toxoid-containing vaccine should receive all missing doses. See Section 1.3.5, *Catch-up*.

As an alternative to dT vaccine after a tetanus-prone wound, adults can receive a single dose of dTpa vaccine to provide additional protection against pertussis (providing they have not received a dose of dTpa previously).[20]

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 3.21.1. These should be administered as soon as possible after the injury.

Tetanus immunoglobulin

Tetanus immunoglobulin (human) for intramuscular use

- **Tetanus Immunoglobulin-VF (TIG)** – CSL Bioplasma. 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 3 or more doses of a tetanus toxoid-containing vaccine or where there is doubt about their tetanus vaccination status. TIG provides immediate protection, for a period of 3 to 4 weeks.

(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-VF** (human, for intravenous use) – CSL Bioplasma. 60 mg/mL solution of immunoglobulin fraction of selected human plasma with high concentration of antibodies to 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.

Contraindications

The only absolute contraindications to tetanus vaccine are:

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

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.

Precautions

In previously vaccinated people, administration of more than 1 dose of a tetanus-containing vaccine in a 5-year period may provoke adverse events.

Adverse events

Mild discomfort or pain at the injection site persisting for up to a few days is common. Uncommon general adverse events following dT vaccine include headache, lethargy, malaise, myalgia and fever. Anaphylaxis, urticaria and peripheral neuropathy very rarely occur (brachial neuritis occurs in 0.001% of

cases). For specific adverse events following combination vaccines containing both tetanus and pertussis antigens, see Chapter 3.14, *Pertussis*.

Use in pregnancy

Refer to Chapter 2.3, *Groups with special vaccination requirements*, Table 2.3.1 *Vaccinations in pregnancy*.

Variations from product information

The product information for both Infanrix hexa and Infanrix Penta states that these vaccines may be given as a booster dose at 18 months of age. NHMRC recommends that a booster dose of DTPa (or DTPa-containing vaccines) is not necessary at 18 months of age. However, DTPa-containing vaccine may be used for catch-up of the primary schedule in children <8 years of age.

The product information for Infanrix-IPV states that this vaccine may be used as a booster dose for children ≤6 years of age who have previously been vaccinated against diphtheria, tetanus, pertussis and poliomyelitis. NHMRC recommends that booster doses of DTPa and IPV be given at 4 years of age; however, this product may be used for catch-up of the primary schedule or as a booster in children <8 years of age.

The product information for ADT Booster states that this vaccine is indicated for a booster dose only in children aged ≥5 years and adults who have previously received at least 3 doses of diphtheria and tetanus vaccines. NHMRC recommends that, where a dT vaccine is required for any person ≥8 years of age, ADT Booster can be used, including for primary immunisation against diphtheria and tetanus.

The product information for adolescent/adult formulations of dTpa-containing vaccines states that these vaccines are indicated for booster doses only. NHMRC recommends that, where dT is unavailable for the primary course, dTpa can be used.

The product information for Adacel and Boostrix (adolescent/adult formulations of dTpa) states that these vaccines are recommended for use in those aged >10 years. However, NHMRC recommends that they may be used in people aged ≥8 years. The product information also states that dTpa should not be given within 5 years of a tetanus toxoid-containing vaccine. However, NHMRC recommends that dTpa vaccines can be administered at any time following receipt of a diphtheria and tetanus toxoid-containing vaccine.

References

Full reference list available on the electronic *Handbook* or website http://immunise.health.gov.au.

3.22 TUBERCULOSIS

Bacteriology

Tuberculosis (TB) is caused by organisms of the *Mycobacterium tuberculosis* complex (M.TB complex), that are slow-growing, aerobic, acid-fast bacilli. The M.TB complex consists of *Mycobacterium tuberculosis*, *M. bovis*, *M. microti*, *M. canetti* and *M. africanum*.[1] *M. tuberculosis* is the cause of almost all TB in Australia, whereas *M. bovis*, *M.canetti* and *M. africanum* are rare.[2]

Clinical features

As infection is usually air-borne, lung disease is the most common form of tuberculosis, accounting for approximately 60% of notified TB cases in Australia.[3] Cough, fever, sweats, weight loss and haemoptysis are common symptoms of pulmonary TB. TB lymphadenitis is the most common extrapulmonary manifestation, but the disease can occur in any part of the body, including the meninges, bone and kidneys. Disseminated disease (miliary TB) and meningeal TB are the most serious forms, particularly in children.[1]

Most individuals infected with *M. tuberculosis* remain asymptomatic, but there is a 10% lifetime risk of developing clinical illness, sometimes many years after the original infection. Infants, the elderly and patients with impaired immunity due to drugs or disease or as a result of adverse socioenvironmental circumstances (eg. malnutrition, alcoholism) are more prone to rapidly progressive or generalised infection.[1,4]

Epidemiology

The World Health Organization (WHO) declared tuberculosis a global emergency in 1993, and recent reports have reaffirmed the threat to human health.[5] About 1000 cases of TB are notified to Australian health authorities each year. The annual notification rate for TB has been relatively stable at approximately 5 to 6 cases per 100 000 population since 1985, and multi-drug resistance remains rare, occurring in less than 2% of notified cases.[2] Tuberculosis in animals (*M. bovis*) has been eradicated by screening and culling programs. In Australia, most TB cases (greater than 80%) occur in people born overseas, particularly in Asia, southern and eastern European countries, the Pacific Islands, and north and sub-Saharan Africa. The rates of TB in the overseas-born population have been slowly increasing over the past decade.[3] High TB rates seen in people from Ethiopia, Somalia and the Sudan reflect recent changes in the composition of Australia's migrant and refugee intake.[3,6] Rates of TB are also high in Aboriginal and Torres Strait Islander people and in Papua New Guineans living in some parts of Australia.[3,7]

Patients with impaired immunity are at high risk of developing active TB if they are infected with *M. tuberculosis*.[4,5] Screening programs in Australia now concentrate on those at high risk, including contacts of notified patients.

Vaccine

- **BCG vaccine** – Sanofi Pasteur Pty Ltd (freeze-dried live vaccine prepared from an attenuated strain of *Mycobacterium bovis*). When reconstituted with accompanying buffered saline diluent, vaccine contains between 8–32 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] Protective efficacy ranges from 0 to 80% in controlled trials. The variation has been attributed to differences in vaccine strains, local prevalence of (protective) environmental mycobacteria, and host factors such as age at vaccination and nutritional status. Geographic latitude and vaccine strains explain most of the variation in efficacy. However, it should be noted that BCG is highly effective in children, particularly those <5 years of age, for whom it is primarily intended. The efficacy of BCG in adolescents and adults is less.

BCG is primarily intended for children as meta-analyses have found the protective efficacy for preventing serious forms of TB in this group is over 80%.[9] Protective efficacy in all age groups is about 50%.[10,11] An Australian study reported a protective efficacy of 30%, at best, in school-aged children.[12] Protective efficacy is difficult to quantify and may vary from 10 years to 50 years.[13,14] The WHO does not recommend repeat vaccination.

In some studies, BCG has been shown to offer some protection against leprosy.[15]

Transport, storage and handling

Transport according to *National Vaccine Storage Guidelines: Strive for 5*.[16] Store reconstituted vaccine 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. 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. It should be given only by specially trained medical or nursing staff who are fully conversant with the following procedures:

Tuberculin test all individuals, except infants <6 months of age, before vaccination. Read the test 48 to 72 hours later and, where 5 tuberculin units has been given, give BCG only to those who have <5 mm of induration.

- Give 0.1 mL of BCG to children and adults, and 0.05 mL to infants <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.
- Wear protective eye-wear. The patient and parent holding the patient (if patient is a small child requiring restraint) should also wear protective eye-wear. Eye splashes may ulcerate, so if an eye splash occurs, wash the eye with saline or water immediately.
- Inject BCG into the skin over the region of the insertion of the deltoid muscle into the humerus. This is just above the mid-point of the upper arm. This site is recommended to minimise the risk of keloid formation. By convention, the left upper arm is used wherever possible to assist those who subsequently look for evidence of BCG vaccination.
- Stretch the skin between a finger and thumb and insert the bevel into the dermis, bevel uppermost, to a distance of about 2 mm. The bevel should be visible through the transparent epidermis.
- If the injection is not intradermal, withdraw the needle and try again at a new site. A truly intradermal injection should raise a blanched bleb of about 7 mm in diameter with the features of peau d'orange. Considerable resistance will be felt as the injection is given. If this resistance is not felt, the needle may be in the subcutaneous tissues.
- Advise the subject of adverse events which may follow the injection.

A tuberculin reaction induced by BCG usually ranges from 0 to 15 mm, but clinical trials have not shown a consistent relationship between the size of tuberculin reactions and the protection provided. For this reason, tuberculin skin testing of BCG vaccinees is not routinely recommended. Because of waning hypersensitivity, most adults who were vaccinated with BCG in early childhood will have a negative tuberculin test.

BCG is available from State/Territory tuberculosis services.

Response to BCG vaccination

A small red papule forms and eventually ulcerates, usually within 2 to 3 weeks of vaccination. The ulcer heals with minimal scarring over several weeks. There may be swelling and tenderness in local lymph nodes. 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:[17]

- Aboriginal and Torres Strait Island neonates living in regions of high TB incidence,
- neonates born to parents with leprosy or a family history of leprosy,
- children <5 years of age 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 – see http://www.who.int/tb/en/),
- embalmers,
- healthcare workers involved in conducting autopsies.

(iii) State and Territory guidelines should be consulted for advice on vaccination of the following groups of individuals:[17]

- healthcare workers who may be at high risk of exposure to drug-resistant cases,
- neonates weighing <2.5 kg,
- children ≥5 years and <16 years of age who will be travelling or living for extended periods in countries with a high prevalence of tuberculosis.

Contraindications

The use of BCG vaccine is contraindicated in the following:

- individuals with impaired immunity due to HIV infection, corticosteroids or other immunosuppressive agents, congenital immunodeficiencies and malignancies involving bone marrow or lymphoid systems (because of the risk of disseminated BCG infection) (see also Chapter 2.3, *Groups with special vaccination requirements*),
- individuals with a high risk of HIV infection where HIV antibody status is unknown,
- individuals with any serious illness including the malnourished,
- individuals with generalised septic skin diseases and skin conditions such as eczema, dermatitis and psoriasis,
- 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 or a large (≥5 mm) tuberculin (Mantoux) reaction,
- individuals with significant febrile illness (administer 1 month from the time of recovery).

Precautions

BCG should be deferred in the following:

- neonates with a birth weight <2.5 kg or those who may be relatively malnourished,
- neonates of mothers who are HIV-positive,
- children who are currently on isoniazid preventive therapy for latent TB infection (as the therapy can inactivate the BCG),
- a 4-week interval should be allowed after administration of another live vaccine (MMR, varicella [and MMRV when available], yellow fever vaccine) unless given concurrently with the BCG.

Adverse events

About 5% (common) of vaccinees experience adverse events. 2.5% develop injection site abscesses and 1% lymphadenitis. About 1% (uncommon) may need medical attention including surgery as a result of the adverse event.[18] 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.

Use in pregnancy

Use of BCG in pregnancy is not recommended. BCG has never been shown to cause fetal damage, but use of live vaccines in pregnancy is contraindicated.

The tuberculin skin test (TST)

(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 past infection for epidemiological purposes, (b) to detect latent TB infection (LTBI), especially in contacts of TB patients, (c) as an aid in diagnosing disease due to TB, and (d) as a pre-vaccination screen before BCG to prevent vaccine reactions.

(ii) Most tuberculin testing in Australia is performed using the Mantoux technique. The PPD preparation for this test is currently supplied by Sanofi Pasteur Pty Ltd. The product, Tubersol, comes in multidose vials and has 5 Tuberculin units (TU)/0.1 mL (10 doses per 1 mL vial). For routine testing, 0.1 mL of PPD (ie. a dose of 5 TU) is injected intradermally into the skin of the upper third of the flexor surface of the left forearm, producing a peau d'orange bleb 4 to 10 mm in diameter. The reaction is examined 48 to 72 hours later, and the diameter of the palpably indurated skin is measured across the long axis of the forearm and recorded in millimetres. In certain circumstances, 2-step skin testing may be required. It is used to detect individuals previously infected who may

test negative to tuberculin testing initially, but who show a strong reaction to tuberculin if the same procedure is repeated 1 to 2 weeks later. The 2-step 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. Detailed information can be accessed in the Tubersol product information and relevant State/Territory guidelines.

(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 strongly positive reactions to previous testing should not be retested.

(iv) The reaction to PPD may be suppressed by recent surgery, sarcoidosis, immunosuppressant drugs and illnesses, such as Hodgkin's disease, lymphoma and HIV infection that result in impaired immunity. The reaction also wanes with increasing age, so that most adults vaccinated with BCG in childhood have negative tuberculin reactions.

(v) The reaction to PPD may be unreliable for 4 weeks after administration of other live vaccines including MMR, varicella and yellow fever vaccines unless given concurrently. The tuberculin skin test should be deferred for patients with major viral infections or live-virus vaccination in the past month. Oral typhoid and oral polio (OPV is no longer used in Australia but may have been received overseas) vaccines do not necessitate a delay in testing.

(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 healthcare staff who should be made aware that subsequent tuberculin skin testing may be difficult to interpret.

(viii) New interferon-gamma release assays (blood tests) using specific antigens for *M. tuberculosis* are now available in some laboratories. Interferon-gamma based assays are increasingly being used to diagnose latent TB and, particularly, to distinguish latent TB from post-BCG vaccine skin reactivity. There are relatively few data on the sensitivity and specificity of these tests in children, particularly those <2 years of age, or in people with impaired immunity.[19]

Variations from 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.

References

Full reference list available on the electronic *Handbook* or website http://immunise.health.gov.au.

3.23 TYPHOID

Bacteriology

Typhoid fever is a clinical syndrome caused by a systemic infection with *Salmonella enterica* subspecies *enterica* serovar Typhi (*S*. Typhi). Paratyphoid fever, caused by infection with *S*. *enterica* serovar Paratyphi A or B, is similar to, and often indistinguishable from, typhoid fever. The two infections are collectively known as enteric fever; there is no vaccine against paratyphoid fever.

NB. *S*. Paratyphi B biovar Java does not cause typhoid-like enteric fever but rather causes a typical gastroenteritis; it can be acquired through handling aquarium fish.[1]

Clinical features

Typhoid fever has a usual incubation period of 7 to 14 days (range 3 to 60 days).[2] Although clinical presentations of typhoid fever can be quite variable, a typical case presents with a low-grade fever, dull frontal headache, malaise, myalgia, anorexia and a dry cough.[2] The fever tends to increase as the disease progresses; constipation (more typically diarrhoea in young children), abdominal tenderness, relative bradycardia and splenomegaly are common. Complications occur in 10 to 15% of patients and tend to occur in patients who have been ill for >2 weeks. The more important complications include gastrointestinal bleeding, intestinal perforation and typhoid encephalopathy.[2]

Relapse occurs in 5 to 10% of patients, usually 2 to 3 weeks after the initial fever resolves. Chronic asymptomatic biliary carriage of *S*. Typhi occurs in up to 5% of patients with typhoid fever, even after treatment. Chronic carriage is defined by the continued shedding of the organism for >1 year, and is a public health risk (eg. if a carrier works in the food industry).[2]

Because travellers are likely to seek medical advice relatively early in the illness, severe typhoid fever with complications is rarely seen in this group of patients. Nevertheless, travellers can still become chronic carriers of *S*. Typhi.

Epidemiology

Humans are the sole reservoir of *S*. Typhi. It is shed in the faeces of those acutely ill and those who are chronic asymptomatic carriers of the organism; transmission usually occurs via the ingestion of faecally-contaminated food or water.

The vast majority of typhoid fever cases occur in less-developed countries where poor sanitation, poor food hygiene and untreated drinking water all contribute to endemic disease with moderate to high incidence and considerable mortality.[3] Geographic regions with high incidence (>100 cases per 100 000 population

per year) include the Indian subcontinent, most southeast Asian countries and several south Pacific nations, including Papua New Guinea.

In developed countries, typhoid fever is predominantly a travel-related disease, with a considerably greater risk following travel to the Indian subcontinent than to other regions.[4,5] Those who travel to endemic regions to visit friends and relatives (ie. immigrants who travel to their former homelands) appear to be at considerably greater risk of acquiring typhoid fever than other travellers.[4,5] There are approximately 50 to 80 cases of typhoid fever reported in Australia each year, with most following travel to regions with endemic disease.

Vaccines

- **Vivotif Oral** – CSL Biotherapies/Berna Biotech Ltd (oral live attenuated typhoid vaccine). Each enteric-coated capsule contains not less than 2 x 10^9 viable organisms of attenuated *S.* Typhi strain Ty21a Berna. 3 capsules in a blister pack.
- **Typherix** – GlaxoSmithKline (purified Vi capsular polysaccharide vaccine). Each 0.5 mL pre-filled syringe contains 25 µg Vi polysaccharide of *S.* Typhi; phenol as preservative; phosphate buffer. 10 dose packs are also available.
- **Typhim Vi** – Sanofi Pasteur Pty Ltd (purified Vi capsular polysaccharide vaccine). Each 0.5 mL pre-filled syringe contains 25 µg Vi polysaccharide of *S.* Typhi; phenol as preservative; phosphate buffer.

Combination vaccine that includes both typhoid and hepatitis A (see Chapter 3.5, *Hepatitis A*)

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

The attenuated non-pathogenic *S.* Typhi strain Ty21a was derived by chemical treatment attenuation of a wild-type strain. Attenuated features of Ty21a include the absence of the enzyme, UDP-galactose-4-epimerase, and the Vi capsular polysaccharide antigen (an important virulence determinant of *S.* Typhi). These features partially contribute to the non-pathogenicity and, therefore, the safety of the oral live vaccine.[6]

The oral vaccine Ty21a strain cannot be detected in faeces more than 3 days after administration of the vaccine. It stimulates vigorous secretory intestinal IgA and cell-mediated immune responses.[6] Clinical trials, with different formulations of

the vaccine and with a variety of schedules, have been undertaken in several countries (Egypt, Chile, Indonesia) with endemic typhoid fever. These have documented varying degrees of protection against the disease.[2,6]

The parenteral Vi polysaccharide vaccine is produced by fermentation of the Ty2 strain followed by inactivation with formaldehyde, and then extraction of the polysaccharide from the supernatant using a detergent.[6] The vaccine elicits prompt serum IgG anti-Vi responses in 85 to 95% of adults and children >2 years of age. The vaccine has also been used in clinical trials in endemic regions (Nepal, South Africa, China), indicating moderate protection against typhoid fever.[2,6]

Neither the oral nor the parenteral vaccines have been studied in prospective clinical trials in travellers to endemic regions. Because many travellers do not have any naturally-acquired immunity, the protection conferred through typhoid vaccination may be less than that documented in the clinical trials mentioned above. However, there is circumstantial evidence that the vaccines do provide protection to travellers to endemic regions,[4,5] and that 3-yearly revaccination is necessary to prolong the protection.[7]

Transport, storage and handling

Transport according to *National Vaccine Storage Guidelines: Strive for 5*.[8] Store all typhoid vaccines at +2°C to +8°C. Protect from light. Do not freeze.

Because the vaccinee will be responsible for looking after the course of the oral live attenuated vaccine, details of how it should be transported (from the pharmacy to the home) and stored in the refrigerator (at home) must be carefully explained.

Dosage and administration

Oral live attenuated vaccine

The vaccine is registered for use in individuals ≥6 years of age; it is presented in a pack of 3 capsules. The dose (a whole capsule) is the same for both adults and children.

It may be administered at the same time as either OPV (no longer used in Australia), or yellow fever vaccine.[6] It may also be given concurrently with mefloquine or with atovaquone/proguanil combination (Malarone).

The vaccination schedule consists of 1 capsule of vaccine on days 1, 3, and 5, taken 1 hour before food. The capsule must be swallowed whole with water and must not be chewed since the organisms can be killed by gastric acid. Do not give the vaccine concurrently with antibiotics, or other drugs that are active against *Salmonellae*. If possible, antibiotics and other relevant drugs should be delayed for 3 days after the last dose of the vaccine.

A fourth capsule taken on day 7 has been shown (in a single study[9]) to result in a lower incidence of typhoid fever than 3 doses. However, the use of a fourth dose requires partial use of a second pack and, therefore, may involve considerable extra expense.

Oral live attenuated typhoid vaccine should be separated from the administration of inactivated oral cholera vaccine by an interval of at least 8 hours (see 'Precautions' below).

Parenteral Vi polysaccharide vaccines

Both vaccines (Typherix and Typhim Vi) are registered for use in individuals ≥2 years of age; the dose (0.5 mL) is the same for both adults and children. (The dose of the combined Vi polysaccharide and hepatitis A vaccine is 1 mL.) The vaccines are given by IM injection.

Booster doses

The optimal timing of revaccination against typhoid fever is uncertain and, therefore, international recommendations can vary considerably.[2,5,6]

However, if continued exposure to *S.* Typhi exists (such as occurs with either prolonged travel or residence in an endemic region) it is reasonable to recommend a dose of the parenteral vaccine 3 years after the initial primary parenteral vaccination. If a 3-dose schedule of the oral live attenuated vaccine was used initially, a repeat 3-dose course can be given after 3 years; if a 4-dose schedule of the oral vaccine was used initially, a repeat 4-dose course can be given after 5 years.[6]

Recommendations

Typhoid vaccination is recommended for all travellers ≥2 years of age going to endemic regions, where food hygiene may be suboptimal and drinking water may not be adequately treated. Travellers include the military. Vaccination should be completed at least 2 weeks before travel.

Individuals travelling to endemic regions to visit friends and relatives are probably at considerable risk of acquiring typhoid fever, and vaccination is strongly recommended for them.

NB. Travellers must also be advised about personal hygiene, food safety and about drinking boiled or bottled water only. They should be advised that raw (or undercooked) shellfish, salads, cold meats, untreated water and ice (in drinks) are all potentially 'high-risk', as are short (day) trips away from higher quality accommodation venues.

Laboratory personnel routinely working with *S.* Typhi should also be considered for vaccination.

Contraindications

The only absolute contraindications to typhoid vaccines are:

- anaphylaxis following a previous dose of a typhoid vaccine, or
- anaphylaxis following any component of a particular typhoid vaccine.

Oral live attenuated vaccine

The oral live attenuated vaccine should *not* be administered

- to pregnant women; parenteral Vi polysaccharide vaccine should be used instead;
- to individuals with impaired immunity, including those known to be infected with HIV; parenteral Vi polysaccharide vaccine should be used instead; or
- to individuals taking antibiotics; parenteral Vi polysaccharide vaccine should be used instead.

Parenteral Vi polysaccharide vaccines

There are no other contraindications to these vaccines.

Precautions

There should be an interval of at least 8 hours between the administration of the inactivated oral cholera and oral typhoid vaccines, as the buffer in the cholera vaccine may affect the transit of the capsules of oral typhoid vaccine through the gastrointestinal tract.

The Vi polysaccharide vaccines should not be administered to children <2 years of age.

The oral live attenuated vaccine should not be administered to children <6 years of age; parenteral Vi polysaccharide vaccine should be used instead in children 2–5 years of age.

Adverse events

Typhoid vaccines, both oral and parenteral, are associated with very few adverse events and, when adverse events do occur, they tend to be mild and transient.[10]

Oral live attenuated vaccine

Abdominal discomfort, diarrhoea, nausea, vomiting and rashes have occasionally been reported.

Parenteral Vi polysaccharide vaccines

Local adverse events such as erythema, swelling and pain at the injection site are very common (10 to 20%). Systemic adverse events are common and include fever (3%), malaise and nausea.

Public health management of typhoid fever

Typhoid fever is a notifiable disease in all States and Territories in Australia.

Upon notification, the relevant public health authority should ascertain the likely source of infection, and determine if the case has an occupation (eg. as a food handler or carer of children, the elderly or of those with impaired immunity) where there might be the potential for the spread of *S.* Typhi.[11] Cases in such occupations should be excluded from work until 2 consecutive faecal samples, collected a week apart after the completion of antibiotic treatment, are negative for *S.* Typhi.[11] Cases not in such occupations should also be proved to have cleared the organism from 2 consecutive faecal samples, but they can return to work once they have recovered and any diarrhoea has ceased.

All those who have been in close contact with a case of typhoid fever in the 30 days before the clearance of *S.* Typhi from the case's faeces should have their occupation assessed (as above). Contacts in 'risk' occupations should be excluded from work until 2 faecal samples, collected at least 24 hours apart, have proved negative for *S.* Typhi.[11] Contacts not in such occupations can remain at work, but should have at least 1 faecal sample collected. Further instructions about the management of cases of typhoid fever, and their contacts, should be obtained from State/Territory public health authorities (see Appendix 1, *Contact details for Australian, State and Territory Government health authorities and communicable disease control*).

Use in pregnancy

The oral live attenuated vaccine should not be given in pregnancy. However, pregnancy is not a contraindication to vaccination with a parenteral Vi polysaccharide vaccine. Refer to Chapter 2.3, *Groups with special vaccination requirements,* Table 2.3.1 *Vaccinations in pregnancy*.

Variations from product information

The product information for the oral live attenuated vaccine does not mention the use of a 4-dose course of the vaccine for either primary or booster vaccination.

Although NHMRC considers pregnancy a contraindication to the oral live attenuated typhoid vaccine, the product information does not include pregnancy among the listed contraindications.

The Typhim Vi product information recommends a booster dose every 2 to 3 years. However, revaccination with a dose of Vi polysaccharide vaccine 3 years after an initial dose is recommended by NHMRC.

References

Full reference list available on the electronic *Handbook* or website http://immunise.health.gov.au.

3.24 VARICELLA

Virology

Varicella-zoster virus (VZV) is a DNA virus within the herpes virus family.[1] Primary infection with VZV causes varicella (chickenpox). Following primary infection, VZV establishes latency in the dorsal root ganglia. Reactivation of the latent virus manifests as herpes zoster (shingles)[2] (see Chapter 3.26, *Zoster*).

Clinical features

Varicella is a highly contagious infection spread by air-borne transmission of droplets from the upper respiratory tract or from the vesicle fluid of the skin lesions of varicella or zoster infection.[1] Varicella is usually a mild disease of childhood. However, complications occur in approximately 1% of cases.[3] It is more severe in adults and in individuals of any age with impaired immunity, in whom complications, disseminated disease, and fatal illness can occur.[1]

The average incubation period is 14 to 16 days (range 10–21 days), but may be longer in those with impaired immunity, especially after receipt of zoster immunoglobulin (ZIG).[2] The period of infectivity is from 48 hours before the onset of rash until crusting of all lesions has occurred. A short prodromal period of 1 to 2 days may precede the onset of the rash, especially in adults.[1,2] In otherwise healthy children, skin lesions usually number between 200 and 500.[1,2] Acute varicella may be complicated by secondary bacterial skin infection, pneumonia, acute cerebellar ataxia (1 in 4000 cases), aseptic meningitis, transverse myelitis, encephalitis (1 in 100 000 cases), and thrombocytopenia. In rare cases, it involves the viscera and joints.[1]

Congenital varicella syndrome has been reported after varicella infection in pregnancy and may result in skin scarring, limb defects, ocular anomalies, and neurologic malformations.[1,4] There is a higher risk to the fetus if maternal infection occurs in the second trimester compared with infection in the first trimester (1.4% vs 0.55%).[5] Infants with intrauterine exposure also risk developing herpes zoster in infancy (0.8–1.7%) with the greatest risk following exposure in the third trimester.[4] Severe neonatal varicella infection can result from perinatal maternal varicella.[6] 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.[7]

Reactivation of latent VZV as a result of waning cellular immunity results in herpes zoster (HZ), a localised vesicular rash. HZ can occur at any age, but is more common in older adults and individuals with impaired immunity. Complications may include post-herpetic neuralgia, and disseminated zoster with visceral, central nervous system and pulmonary involvement[1] (see Chapter 3.26, *Zoster*).

There is no specific therapy for uncomplicated varicella infection. Antiviral therapy is used in the treatment of complicated or severe disease or varicella in people with impaired immunity. An increased risk of Reye syndrome following varicella infection has been reported in association with aspirin or other salicylate use[8-12] (see 'Precautions' below). Aspirin or other salicylates should not be used in the management of varicella infection.

Epidemiology

In an unimmunised population in temperate climates, the annual number of cases of varicella approximates the birth cohort.[13] Tropical regions have a higher proportion of cases in adults. Approximately 5% of cases are subclinical. A serosurvey conducted in 1997–1999 found that 83% of the Australian population were seropositive by 10–14 years of age.[14] Before the introduction of a varicella vaccination program in Australia there were about 240 000 cases, 1500 hospitalisations and an average of 7 to 8 deaths each year from varicella in Australia.[15-17] The highest rates of hospitalisation occur in children <4 years of age.[18]

In the USA, universal varicella vaccination since 1995 has resulted in a decline in varicella disease by 85% and hospitalisations have declined by 70 to 88%.[19-21] The greatest decline in hospitalisation rates has been in 0–4-year-olds, who were most likely to be vaccinated. However, a reduction in hospitalisation rates also occurred in older children and adults, due to herd immunity.[19] Surveillance of varicella and HZ in the USA, conducted between 1992 and 2002, demonstrated that, as vaccination coverage increased to 65% in 2002, the incidence of varicella decreased by 65% across all age groups, and the incidence of HZ remained stable.[22]

Vaccines

Live attenuated varicella vaccine (VV) is currently available as a monovalent vaccine. It is anticipated that quadrivalent combination vaccines containing measles, mumps, rubella and varicella vaccines (MMRV) will be available in the near future (see Chapter 3.11, *Measles* for information on MMRV vaccines). All available varicella-containing vaccines are derived from the Oka VZV strain, but have some genetic differences.[23]

Monovalent VVs have been available in Australia since 2000, and from November 2005, a single dose of VV has been funded under the NIP for all children at 18 months of age, with a catch-up dose funded for children 10–<14 years of age.[24] At the time of implementation of a universal varicella vaccination program in Australia, a single dose was considered adequate for protection of infants and children <14 years of age. However, recent data from the USA suggests that a second dose of varicella-containing vaccine in children is optimal to provide an immune response more like natural infection, reducing the risk of vaccine failure and increasing population immunity.[7] Vaccine failure is known as 'breakthrough varicella' and is defined as a case of wild-type varicella ≥42 days post vaccination. A majority of cases of breakthrough varicella are

mild with fewer lesions than natural infection. However, breakthrough varicella infections can be contagious.[25]

Post-licensure studies in the USA have estimated the effectiveness of 1 dose of VV in children to be 80 to 85% against any disease and 95 to 98% against severe varicella.[25-29] Although earlier data suggested persistence of immunity in most healthy vaccinees,[1] recent long-term data from the United States has shown that, >5 years after vaccination, rates of vaccine failure increased by 2.6 times in children who received only 1 dose of vaccine, compared with those who had received the vaccine within 5 years.[30] Data from a randomised controlled trial in varicella-negative children 12 months to 12 years of age, comparing 1 with 2 doses of VV over a 10-year period, showed significantly higher protection with 2 doses (94.4% vs 98.3%).[31] Based on current evidence, 2 doses of a varicella-containing vaccine in children from 12 months of age will minimise the risk of breakthrough varicella (see 'Recommendations' below).

Healthy adolescents (≥14 years of age) and adults require 2 doses of varicella vaccine, 1 to 2 months apart, as the response to a single dose of VV decreases progressively as age increases and is insufficient to provide adequate protection.[32]

Monovalent varicella vaccines

- **Varilrix** – GlaxoSmithKline (lyophilised preparation of live attenuated Oka strain of varicella-zoster virus). Each 0.5 mL monodose of the reconstituted, lyophilised vaccine contains not less than $10^{3.3}$ plaque-forming units of attenuated varicella-zoster virus; human serum albumin; lactose; neomycin; polyalcohols. Single and 10 pack of monodose vials also available.
- **Varivax Refrigerated** – CSL Biotherapies/Merck & Co Inc (lyophilised preparation of live attenuated Oka/Merck strain of varicella-zoster virus). Each 0.5 mL monodose of the reconstituted, lyophilised vaccine contains not less than 1350 plaque-forming units; 18 mg sucrose; 8.9 mg gelatin; 3.6 mg urea; 0.36 mg monosodium glutamate; residual components of MRC-5 cells; trace amounts of neomycin and fetal bovine serum from MRC-5 culture media. Single and 10 pack of monodose vials also available.

Transport, storage and handling

Varicella vaccines are less stable than other commonly used live viral vaccines, and the storage temperature requirements are critical. Available monovalent VVs have different storage requirements.

Varilrix – store at +2°C to +8°C. Protect from light. Do not freeze. After reconstitution, use within 90 minutes at ambient temperature or for up to 8 hours at +2°C to +8°C.

Varivax Refrigerated – store at +2°C to +8°C. Protect from light. Do not freeze. After reconstitution, use within 30 minutes at ambient temperature (+20°C to +25°C) to maintain potency.

Transport according to *National Vaccine Storage Guidelines: Strive for 5*.[33]

Dosage and administration

The dose of monovalent VV is 0.5 mL, administered by SC injection.

If VV is given at the same time as MMR, it should be given using separate syringes and injection sites. MMR and monovalent VV should not be mixed before injection.

VV can be given at the same time as other vaccines (including MMR, DTPa, hepatitis B and MenCCV), using separate syringes and injection sites. If VV is not given simultaneously with other live viral parenteral vaccines (eg. MMR), they should be given at least 4 weeks apart (see 'Precautions' below).

Recommendations

(i) Children

It is recommended that at least 1 dose of a varicella-containing vaccine be given to all non-immune children from the 2nd year of life to <14 years of age. Children in this age group with a reliable history of varicella infection, either by confident clinical diagnosis or with laboratory confirmation, may be considered immune and do not require vaccination.

Routine varicella-containing vaccine should be administered as follows (and as per Table 3.24.1):

- One dose of monovalent VV at 18 months of age.
- When MMRV vaccines become available, 1 dose of varicella-containing vaccine should be given as MMRV at 12 months of age.

The change in the recommended age of administration of varicella vaccine is influenced by moving the second dose of MMR to 18 months of age, and the anticipated availability of MMRV vaccines in the near future. The available evidence now suggests that the administration of varicella vaccine at the earlier age of 12 months, compared with 18 months, does not reduce vaccine effectiveness or lead to increased rates of breakthrough varicella.[34] Administration of varicella vaccine at 12 months of age will provide earlier protection from varicella. However, until MMRV vaccines are available in Australia, it is recommended that administration of monovalent VV at 18 months of age continue to avoid schedule crowding (4 injections) at 12 months of age.

Receipt of 2 doses of varicella-containing vaccine provides increased protection and minimises the chance of breakthrough varicella in children.[31] However, at this time, routine administration of 2 doses of varicella-containing vaccine at <14 years of age is not included on the NIP schedule. If parents/carers wish to

minimise the risk of breakthrough varicella, a second dose of varicella-containing vaccine to children <14 years of age is recommended (see 'Vaccines' above). When available, use of MMRV at 18 months of age is a suitable means to provide a *second* dose of varicella-containing vaccine. (For further information, see also Chapter 3.11, *Measles*.) The minimum approved interval between doses of varicella-containing vaccine in children <14 years of age is 4 weeks.

Table 3.24.1: Recommendations for varicella vaccination with monovalent VV (currently available), and once MMRV vaccines are available

	12 months	18 months	Catch-up requirements*
Monovalent varicella vaccine	MMR	MMR + VV†	No requirement for varicella catch-up
MMRV when available	MMRV	MMR‡	Use MMRV at 18 months for children who have not yet received at least 1 dose of varicella vaccine

* If catch-up is required for MMR, see Chapter 3.11, *Measles*.

† Give in separate syringes and at separate injection sites (preferably the other arm).

‡ When available, use of MMRV at 18 months of age is a suitable means to provide a second dose of varicella-containing vaccine.

(ii) Adolescents (≥14 years of age) and adults

Vaccination is recommended in non-immune adolescents (≥14 years of age) and adults. Immune responses are reduced in adolescents and adults compared with young children.[32,35] Therefore, adolescents and adults must receive 2 doses of VV to achieve adequate protection from varicella. The 2 doses should be administered at least 4 weeks apart. However, a longer interval between vaccine doses is acceptable. Lack of immunity to varicella should be based on a negative history of previous varicella infection and can be supplemented by serological testing (see 'Serological testing before varicella vaccination' below).

VV is particularly indicated for those in the following categories:

- non-immune people in high-risk occupations where exposure to varicella is likely (such as healthcare workers, teachers and workers in childcare centres) (see Section 2.3, Table 2.3.6 *Recommended vaccinations for those at risk of occupationally acquired vaccine-preventable diseases*),[36]
- non-immune women before pregnancy to avoid congenital or neonatal varicella,
- seronegative women immediately after delivery,
- non-immune parents of young children, and
- non-immune household contacts of all ages of people with impaired immunity.

MMRV vaccines are not recommended for use in adolescents and adults because data are currently available only for children ≤12 years of age.

(iii) Serological testing before varicella vaccination

Vaccination is well tolerated in previously infected individuals and can be administered if there is uncertainty regarding immunity. Serological testing before varicella vaccination of children with a reliable history of varicella infection, either by confident clinical diagnosis or with laboratory confirmation, is not warranted. Reliable history of varicella infection correlates highly with serological evidence of immunity.[37,38] Those who have an uncertain history should be considered susceptible and offered vaccination.

In adolescents and adults with a negative history of varicella infection, serological testing before vaccination is more likely to be cost-effective, as a majority of those with a negative history may be immune.[36,39] However, vaccination can proceed without testing (provided there are no contraindications), as the vaccine is well tolerated in seropositive people.

(iv) Serological testing after varicella vaccination

Testing to check for seroconversion after varicella vaccination is not recommended. Commercially available laboratory tests are not always sufficiently sensitive to detect low antibody levels following vaccination and, in addition, the presence of detectable antibody shortly after vaccination does not necessarily indicate complete immunity to varicella.[40,41]

(v) Post-exposure prophylaxis and outbreak control

Several studies have shown that VV is effective in preventing varicella infection, particularly moderate to severe disease, following exposure. This is generally successful when given within 3 days, and up to 5 days, after exposure, with earlier administration being preferable.[42-46] Vaccination of exposed individuals during outbreaks has also been shown to prevent further cases and control outbreaks (see also 'The public health management of varicella' below). When available, vaccination with MMRV in children 12 months to 12 years of age could be used for vaccination in this setting if MMR vaccination is also indicated.

In the event of an outbreak, seek advice from local public health authorities before proceeding with vaccination of a large number of individuals (see Appendix 1, *Contact details for Australian, State and Territory Government health authorities and communicable disease control*).

(vi) Household contacts of people with impaired immunity

Vaccination of household contacts of people with impaired immunity is strongly recommended. This recommendation is based upon evidence that transmission of varicella vaccine virus strain is extremely rare and it is likely to cause only mild disease that can be treated with acyclovir. This compares with the relatively high risk of severe disease in people with impaired immunity following

exposure to wild-type varicella-zoster virus.[41,47] If vaccinees develop a rash, they should cover the rash and avoid contact with people with impaired immunity for the duration of the rash. Zoster immunoglobulin (ZIG) need not be given to an immune impaired 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.

(vii) Vaccination of healthcare workers (HCW)

(Refer to Table 2.3.6 *Recommended vaccinations for those at risk of occupationally acquired vaccine-preventable diseases*)

Pre-exposure vaccination of HCWs:

- A HCW with a negative or uncertain history of varicella infection should undergo serological testing. If seronegative, vaccination should be offered in a 2-dose schedule[48] (see 'Recommendations (ii)' above).
- If a rash develops during the 6 weeks after administration of the vaccine, the HCW should cover the rash and be reassigned to duties that require no patient contact, or placed on sick leave.[48] Reassignment or leave should be only for the duration of the rash[48] (see 'Variations from product information' below).
- VV-associated rash may be atypical and may not be vesicular (see 'Adverse events' below). A VV-associated rash is likely to occur in less than 5% of vaccinees, and to last for less than 1 week.[49,50]
- Testing to check for seroconversion after VV is not recommended (see 'Serological testing after varicella vaccination' above).

Post-exposure management of HCWs:

- 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. If HCW vaccinees develop a rash, cover the rash, reassign duties (no patient contact) or place on sick leave until no new lesions appear and all lesions have crusted.
- If a HCW is exposed to varicella and is unvaccinated and has a negative or uncertain history of varicella infection, 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 rapid testing are available, it may be possible to identify those with pre-existing immunity before vaccination. However, serological testing should not delay vaccination beyond the recommended 3 to 5 days after exposure. Vaccination in the absence of serological results is acceptable (see 'Serological testing after varicella vaccination' above).

- If the HCW is vaccinated after exposure, as above, he/she can work but should watch daily for any rash for 6 weeks after exposure. Note that the VV-associated rash 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, cover the rash, 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 days 10 to 21 from the time of first exposure.

Contraindications

(i) Allergy to vaccine components

Varicella vaccination is contraindicated where there has been:

- anaphylaxis following a previous dose of any of the varicella vaccines, or
- anaphylaxis following any vaccine component.

(ii) Pregnant women

VV should not be given during pregnancy and vaccinees should not become pregnant for 28 days after vaccination. Since wild-type VZV poses only a very small risk to the fetus, the risk to the fetus of the attenuated VV virus, if any, should be even lower. Data from a registry, established in the USA to monitor the maternal-fetal outcomes of pregnant women who were inadvertently administered VV 3 months before or at any time during pregnancy, revealed that no birth defects compatible with congenital varicella syndrome occurred in 254 known pregnancy outcomes.[51,52] The rate of occurrence of congenital anomalies from prospective reports in the registry was similar to what is reported in the general USA population (3.2%) and the anomalies showed no specific pattern or target organ.

A non-immune pregnant household contact is *not* a contraindication to vaccination with VV of a healthy child or adult in the same household. The benefit of reducing the exposure to varicella by vaccinating healthy contacts of non-immune pregnant women outweighs any theoretical risks of transmission of vaccine virus to these women.

Data on the use of MMRV vaccines in individuals >12 years of age are not available.

(iii) People with impaired immunity

Varicella-containing vaccines are contraindicated in subjects with primary or acquired impaired immunity, including:

- people with impaired immunity due to HIV/AIDS. Vaccination with live attenuated vaccine can result in a more extensive vaccine-associated rash or disseminated infection in individuals with AIDS.[53] However, varicella vaccination of asymptomatic or mildly symptomatic HIV-infected children

may be considered (see Table 2.3.4 *Immunological categories based on age-specific CD4 counts and percentage of total lymphocytes*). Since studies have not been performed using combination MMRV vaccines in asymptomatic or mildly symptomatic HIV-infected children, it is recommended that only MMR and monovalent VV be considered for use in such children;[54]

- people with conditions in which normal immunological mechanisms may be impaired;
- people suffering from malignant conditions of the reticuloendothelial system (such as lymphoma, leukaemia, Hodgkin's disease); and
- people receiving high-dose systemic immunosuppressive treatment, such as general radiation, x-ray therapy or oral corticosteroids. Varicella-containing vaccines are contraindicated in those taking high-dose oral corticosteroids (in children equivalent to either >2 mg/kg per day prednisolone (≥20 mg per day total) for >1 week or >1 mg/kg per day for >4 weeks) (see Section 2.3.3, *Vaccination of individuals with impaired immunity due to disease or treatment*). 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 1 month.[55] (See also Chapter 2.3, *Groups with special vaccination requirements* and Chapter 3.11, *Measles*).

Precautions

(i) Vaccination with MMR

If VV is not given simultaneously with other live viral parenteral vaccines (eg. MMR), they should be given at least 4 weeks apart.

(ii) Vaccination after immunoglobulin or blood products

NHMRC recommends that varicella-containing vaccines should not be given for between 3 and 9 months after the administration of immunoglobulin-containing blood products. The interval between receipt of the blood product and vaccination depends on the amount of antibody in each product, and is indicated in Table 2.3.5 *Recommended intervals between either immunoglobulins or blood products and MMR, MMRV or varicella vaccination*. For further information, see Section 2.3.5, *Vaccination of patients following receipt of other blood products including blood transfusions,* and 'Variations from product information' below.

(iii) Administration of immunoglobulin or blood-derived products after vaccination

After vaccination with varicella-containing vaccines, immunoglobulin-containing products should not be administered for 3 weeks unless the benefits exceed those of vaccination. If immunoglobulin-containing products are administered within this interval, the vaccinee should either be revaccinated later at the appropriate time following the product, as indicated in Table 2.3.5, or tested for immunity 6 months later and then revaccinated if seronegative.

(iv) Long-term aspirin or salicylate therapy

Individuals receiving long-term salicylate therapy should be vaccinated if indicated, as the benefit is likely to outweigh any possible risk of Reye syndrome occurring after vaccination. Natural varicella infection and salicylate use has been associated with an increased risk of developing Reye syndrome. However, there have been no reports of an association between Reye syndrome and varicella vaccination (see 'Variations from product information' below).

Adverse events

- Adverse events following administration of VV are generally mild and well tolerated.[56] Fever >39°C has been observed in 15% (common) of healthy children, but this was comparable to that seen in children receiving placebo.[55] In adults and adolescents, fever has been reported in 10% (common) of VV vaccinees. Injection site adverse events (pain, redness or swelling) are the most common adverse events reported after varicella vaccination, occurring in 7 to 30% (common to very common) of vaccinees, but are generally well tolerated.[2,56] Slightly higher rates of fever were observed in the clinical trials of MMRV vaccines, as compared with giving MMR and monovalent varicella vaccine at the same time but at separate sites.[57,58] It is recommended that parents/vaccine recipients be advised about possible symptoms, and given advice for reducing fever, including the use of paracetamol for fever in the period 5 to 12 days after vaccination.
- A maculopapular or papulovesicular rash may develop after vaccination (usually within 5 to 26 days). Rashes typically consist of 2 to 5 lesions and may be generalised (3–5%, common), or occur at the injection site (3–5%, common).[55] Most varicelliform rashes that occur within the first 2 weeks after vaccination are due to wild-type VZV, with median onset 8 days after vaccination (range 1–24 days), while vaccine-strain VZV rashes occur at a median of 21 days after vaccination (range 5–42 days).[59] (See also 'Transmission of vaccine virus…' below.)
- No serious adverse events were reported from pre-licensure trials of VV.[1] A post-licensure study reported that serious adverse events, such as encephalitis, ataxia, thrombocytopenia and anaphylaxis, were reported following vaccination at a rate of 2.9 per 100 000 doses distributed. However, this does not necessarily imply a causal relationship.[41]
- Transmission of vaccine virus to contacts of vaccinated individuals is rare. In the USA, where more than 56 million doses of VV were distributed between 1995 and 2005, there have been only 6 well documented cases of transmission of the vaccine-type virus from 5 healthy vaccinees.[55,60] Contact cases have been mild and associated with a rash in the vaccinee.[55,60-62]

Risk of herpes zoster (shingles)

Herpes zoster (HZ) has been reported rarely in vaccine recipients and has been attributed to both the vaccine strain and to wild-type varicella virus reactivation.[59] The risk of developing HZ is currently thought to be lower after vaccination than after natural varicella virus infection, and reported cases have been mild.[2] HZ is uncommon before the age of 45 years, and incidence increases with age.[63] Rates of herpes zoster in children 0–9 years of age after natural VZV infection were estimated to be 30 to 74 per 100 000 per year.[64,65] Vaccination results in a lower rate of zoster with a rate of 22 per 100 000 person-years reported in a 9-year follow-up of 7000 varicella vaccinated children (Jane Seward, US Centers for Disease Control and Prevention (CDC), personal communication) (see Chapter 3.26, *Zoster*).

Zoster immunoglobulin

High-titre zoster immunoglobulin (ZIG) is available from the Australian Red Cross Blood Service on a restricted basis for the prevention of varicella in high-risk subjects. ZIG has no proven use in the treatment of established varicella or zoster infection. ZIG must be given early in the incubation period (within 96 hours of exposure). ZIG is highly efficacious, but is often in short supply. Normal human immunoglobulin (NHIG) can be used for the prevention of varicella if ZIG is unavailable.

Zoster immunoglobulin should be given only by IM injection.

- **Zoster Immunoglobulin-VF (human)** – CSL Bioplasma (160 mg/mL immunoglobulin (IgG) preparation from human plasma containing high levels of antibody to the varicella-zoster virus). Vials contain 200 IU, with the actual volume stated on the label on the vial. Also contains glycine.

The public health management of varicella

'Significant exposure' is defined as living in the same household as a person with active varicella or HZ, or direct face-to-face contact with a person with varicella or HZ for at least 5 minutes, or being in the same room for at least 1 hour. In the case of varicella infection, the period of infectivity is from 48 hours before the onset of rash until crusting of all lesions has occurred.

Immunocompetent varicella contacts should be tested for varicella-zoster antibodies. However, this should not delay ZIG administration after initial contact with a case.

ZIG should be given to individuals in the following categories within 96 hours of significant exposure to either varicella or HZ:

- Pregnant women who are presumed to be susceptible to varicella infection. If practicable, they should be tested for varicella-zoster antibodies before ZIG is given.[4]

- 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 up to 30% in this setting. ZIG must be given as early as possible in the incubation period.
- 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.
- Premature infants (born at <28 weeks' gestation or <1000 g birth weight) exposed to VZV while still hospitalised should be given ZIG *regardless of maternal history of varicella*.
- Patients suffering from primary or acquired diseases associated with cellular immune deficiency, and those receiving immunosuppressive therapy. While it is recommended that varicella contacts with impaired immunity be tested for varicella-zoster antibodies, this should not delay ZIG administration, preferably within 96 hours and up to 10 days after initial contact with a case.[66,67]

NB. If a contact with impaired immunity 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 3.24.2: Zoster immunoglobulin-VF (ZIG) dose based on weight

Weight of patient (kg)	Dose (IU)
0–10	200
11–30	400
>30	600

A dose of ZIG may be repeated if a second exposure occurs more than 3 weeks after the first dose of ZIG. However, testing for varicella antibodies is also recommended (see above). Normal human immunoglobulin can be used for the prevention of varicella if ZIG is unavailable (see Chapter 3.8, *Immunoglobulin preparations*). Patients receiving monthly high-dose intravenous NHIG are likely to be protected and probably do not require ZIG if the last dose of NHIG was given 3 weeks or less before exposure.

Use in pregnancy

Varicella vaccine is contraindicated during pregnancy (see 'Contraindications (ii) Pregnant women' above, and Chapter 2.3, *Groups with special vaccination requirements,* Table 2.3.1 *Vaccinations in pregnancy)*.

Pregnancy should be avoided for at least 28 days after vaccination.

Variations from product information

Varilrix vaccine is approved for use in healthy children from 9 months of age. NHMRC recommends that routine vaccination of children against varicella should occur at ≥12 months of age.

Varilrix and Varivax Refrigerated are registered for use as 2 doses of 0.5 mL (1–2 months apart) in adolescents ≥13 years of age and adults. NHMRC recommends a single dose of varicella vaccine for children <14 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 at least 4 weeks after the first dose.

For both varicella vaccines, the product information states that pregnancy should be avoided for 3 months after vaccination. NHMRC recommends that pregnancy be avoided for at least 28 days after vaccination.

For both varicella vaccines, the product information recommends that vaccinees should avoid contact with people with impaired immunity for up to 6 weeks after vaccination. NHMRC recommends that healthcare 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 'Vaccination of healthcare workers (HCW)' above).

For both varicella vaccines, the product information states that salicylates should be avoided for 6 weeks after varicella vaccination, as Reye syndrome has been reported following the use of salicylates during natural varicella infection. NHMRC recommends that non-immune individuals receiving long-term salicylate therapy should receive VV as the benefit is likely to outweigh any possible risk of Reye syndrome occurring after vaccination.

The product information for Varivax Refrigerated recommends delaying vaccination for 5 months after receipt of NHIG by IM injection or blood transfusion. The NHMRC recommends that VV should not be given for at least 3 months in subjects who have received immunoglobulin-containing blood products according to the intervals contained in Table 2.3.5.

The dosage of ZIG recommended in the product information differs with that in Table 3.24.2, which has been revised in order to minimise wastage of ZIG.

References

Full reference list available on the electronic *Handbook* or website http://immunise.health.gov.au.

3.25 YELLOW FEVER

Virology

Yellow fever is a viral haemorrhagic fever caused by a flavivirus that is transmitted by mosquitoes. *Aedes aegypti*, a highly domesticated mosquito found throughout the tropics, is the vector responsible for person-to-person transmission of the yellow fever virus in urban and inhabited rural areas in endemic countries.

Clinical features

The clinical spectrum of yellow fever varies from a non-specific febrile illness to a fatal haemorrhagic fever.[1] After an incubation period of 3 to 6 days, the disease begins abruptly with fever, prostration, myalgia and headache. The patient appears acutely ill with congestion of the conjunctivae; there is an intense viraemia during this 'period of infection' which lasts 3 to 4 days.[1] This may be followed by the 'period of remission' in which the fever and symptoms settle over 24 to 48 hours during which the virus is cleared by immune responses.[1]

Approximately 15 to 25% of patients may then relapse with a high fever, vomiting, epigastric pain, jaundice, renal failure and haemorrhage: 'the period of intoxication'.[1] These complications can be severe, and reflect the viscerotropic nature of the yellow fever virus (its ability to infect the liver, heart and kidneys). The case-fatality rate varies widely, but can be as high as 20% in local populations.

Epidemiology

Yellow fever occurs in tropical regions of Africa and Central and South America. In both regions the virus is enzootic in rainforest monkeys and canopy mosquito species; sporadic human cases occur when people venture into these forests ('sylvatic or jungle yellow fever').[1]

In moist savannah regions in Africa, especially those adjacent to rainforests, tree hole-breeding *Aedes* mosquito species are able to transfer yellow fever virus from monkeys to people and then between people, leading to small-scale outbreaks ('intermediate yellow fever').

Aedes aegypti occurs in both heavily urbanised areas and settled rural areas in tropical Africa and the Americas.[1] Epidemics of 'urban yellow fever' occur when a viraemic individual (with yellow fever) infects local populations of *Ae. aegypti*; such epidemics can be large and very difficult to control. Although *Ae. aegypti* also occurs throughout much of tropical Asia and Oceania (including north Queensland), yellow fever has never been reported from these regions.

Although yellow fever is undoubtedly markedly under-reported, it is clear that there has been a considerable increase in the reported number of outbreaks, and therefore cases, of yellow fever in recent decades.[2] Most of this increase has been in Africa, particularly in West African countries.[2,3] Between 2000 and 2004, 18 of the 25 countries at risk in Africa reported cases of yellow fever, with 13 of the 14 countries at risk in West Africa reporting cases.[3] During this time, West Africa experienced 5 epidemics of urban yellow fever, 3 of which affected capital cities (Abidjan (Côte d'Ivoire, 2001), Conakry (Guinea, 2002), Dakar and Touba (Senegal, 2002) and Bobo-Dioulasso (Burkina Faso, 2004)).[3]

The risk of susceptible travellers acquiring yellow fever varies considerably with season, location, duration of travel and utilisation of mosquito avoidance measures. There have been at least 6 reported cases of yellow fever, all fatal, in unvaccinated travellers to Africa and South America since 1996.[3]

Vaccine

- **Stamaril** – Sanofi Pasteur Pty Ltd (live attenuated yellow fever virus (17D-204 strain) lyophilised vaccine). Each 0.5 mL monodose of reconstituted, lyophilised vaccine contains not less than 1000 mouse LD_{50} units; lactose; sorbitol. May contain traces of egg proteins. The vaccine 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 cultured in, and harvested from, embryonated chicken eggs. The vaccine contains neither antibiotics nor preservatives, and does not contain gelatin.

Vaccination elicits protective levels of neutralising antibodies in approximately 90% of adult vaccinees by day 14, and in virtually all by day 28.[4] Immunity is long-lasting and perhaps life-long; regardless, revaccination is required after 10 years under International Health Regulations for a valid International Certificate of Vaccination. Because the vaccine produces a transient very low level viraemia in healthy adult recipients, they cannot serve as a source of infection for mosquitoes.[4]

Although the efficacy of the yellow fever vaccine has never been determined in prospective clinical trials, there is considerable observational evidence that it is very effective in preventing the disease.[4]

Transport, storage and handling

Transport according to *National Vaccine Storage Guidelines: Strive for 5*.[5] The vaccine and diluent should be stored at +2°C to +8°C. Do not freeze. Protect from light. The vaccine should be used within 1 hour of reconstitution.

Dosage and administration

The vaccine can be given to those ≥9 months of age. The dose is 0.5 mL of reconstituted vaccine regardless of age, given by either IM or SC injection.

Recommendations

Yellow fever is considered to be endemic in 32 African and 11 Central and South American countries (Table 3.25.1). Of these, 25 African and 9 South American countries are currently considered at risk because they have reported cases since 1950; of particular concern are the countries in West Africa (Table 3.25.1).[3,6]

Table 3.25.1: Yellow fever endemic countries

West African countries	Other endemic countries	
Benin *	Angola*	Guyana*
Burkina Faso *	Bolivia*	Kenya*
Côte d'Ivoire *	Brazil*	Niger
Gambia *	Burundi	Panama
Ghana *	Cameroon*	Peru*†
Guinea *	Central African Republic*	Rwanda
Guinea-Bissau *	Chad	Sao Tome and Principe
Liberia *	Colombia*	Somalia
Mali *	Congo*	Sudan*
Mauritania *	Democratic Republic of the Congo*	Suriname*
Nigeria *	Ecuador*	Trinidad and Tobago
Senegal *	Equatorial Guinea*	Uganda*
Sierra Leone *	Ethiopia*	United Republic of Tanzania
Togo *	French Guiana*	Venezuela*
	Gabon*	

* Countries with cases reported since 1950.

† Travellers who will visit only the cities of Cuzco and Machu Picchu do not need vaccination.

The yellow fever vaccine is recommended for:

- those ≥9 months of age travelling or living in any country in West Africa (see Table 3.25.1), regardless of where they will be in that country,
- those ≥9 months of age travelling or living outside urban areas of all other yellow fever endemic countries (see Table 3.25.1), and
- laboratory personnel who routinely work with yellow fever virus.

All those travelling or living in endemic countries should be informed that the mosquito vectors of yellow fever usually bite during the day, and they should be advised of the necessary mosquito avoidance measures. These include the use of insect repellents, coils and sprays, the use of mosquito nets (preferably those that have been treated with an insecticide), and adequate screening of residential (and work) premises.

As well as the above recommendations, many countries outside the endemic regions require evidence of vaccination for those travellers arriving from endemic countries. Because *Ae. aegypti* exists in many of these non-endemic countries, there is a potential for yellow fever virus transmission; a listing of these countries is available in an annex at www.who.int/ith/en/.

Travellers >1 year of age arriving into Australia within 6 days of leaving a yellow fever endemic country are required to have a valid International Certificate of Vaccination against Yellow Fever (see below). Such travellers who do not have a valid certificate are placed under quarantine surveillance until 6 days have passed after leaving the endemic country. Quarantine surveillance does not place restrictions on the traveller's movements, but does require prompt medical assessment should the traveller develop relevant symptoms.

Yellow fever vaccine can be administered only by Yellow Fever Vaccination Centres approved by the relevant State or Territory health authorities. Each yellow fever vaccination is to be recorded in an International Certificate of Vaccination against Yellow Fever; the certificate must include the vaccinee's name and signature (or the signature of a parent or guardian if the vaccinee is a child), and the signature of a person approved by the relevant health authority. The date of the vaccination must be recorded in day-month-year sequence with the month written in letters, and the official stamp provided by the State or Territory health authority must be used. The certificate becomes valid 10 days after vaccination, and remains valid for 10 years.

NB. People with a true contraindication to yellow fever vaccine (see below) who intend to travel to endemic countries (as recommended above) should obtain a letter from a doctor, clearly stating the reason for withholding the vaccine. The letter should be formal, signed and dated, and on the practice's letterhead.

Contraindications

(i) Known anaphylactic sensitivity

The yellow fever vaccine is contraindicated in those who have had either:

- anaphylaxis following a previous dose, or
- anaphylaxis following any of the vaccine components.

In particular, the vaccine is contraindicated if there is a known anaphylaxis to eggs.

(ii) Infants

Yellow fever vaccine is contraindicated in infants <9 months of age.

(iii) Altered immune status

As with all live virus vaccines, the yellow fever vaccine should not be given to people with impaired immunity due to either disease or medical treatment (see Chapter 2.3, *Groups with special vaccination requirements*).

(iv) Thymus disorders

People with a history of any thymus disorder, including myasthenia gravis, thymoma, thymectomy and DiGeorge syndrome, should not be given the yellow fever vaccine.

Precautions

(i) Adults ≥60 years of age

The risk of severe adverse events following yellow fever vaccine is considerably greater in those aged ≥60 years than in younger adults.[7,8]

Adults ≥60 years of age should be given yellow fever vaccine only if they intend to travel to endemic countries (as recommended above) and they have been informed about the (albeit very low) risks of developing a severe complication.

(ii) Pregnancy

As with all live virus vaccines, unless there is a risk of exposure to the virus, yellow fever vaccine should not be given to pregnant women. Pregnant women should be advised against going to the rural areas of yellow fever endemic areas (and to urban areas of West African countries as well). However, pregnant women who insist on travelling, against medical advice, to endemic countries should be vaccinated.

The yellow fever vaccine has been given to considerable numbers of pregnant women[4,9] with no evidence of any adverse outcomes. Therefore, women vaccinated in early pregnancy can be reassured that there is no evidence of risk to themselves and very low (if any) risk to the fetus; there are no grounds for a termination of pregnancy.[4]

(iii) Administration of other vaccines on the same day

The administration of other live virus vaccines (MMR, varicella vaccine [and MMRV when available]) should be on the same day as yellow fever vaccine, or separated by a 4-week interval. Other vaccines relevant to travel can be given with, or at any time before or after, yellow fever vaccine.

Adverse events

(i) Common adverse events

Adverse events following yellow fever vaccine are generally mild. Vaccinees often report mild headaches, myalgia and low-grade fevers or other minor symptoms for 5 to 10 days post vaccination. In clinical trials in which symptoms are actively elicited, up to 25% of vaccinees report mild adverse events and up to 1% curtail regular activities.[4,10]

(ii) Immediate hypersensitivity reactions

Immediate hypersensitivity reactions, including anaphylaxis, following yellow fever vaccine are very rare with an incidence of less than 1 in 1 million and occur principally in people with anaphylactic sensitivity to eggs.[4] Although it has been suggested that an anaphylactic sensitivity to gelatin (added as a stabiliser to some yellow fever vaccines) may also precipitate anaphylaxis following vaccination,[11] Stamaril does not contain gelatin.

(iii) Vaccine-associated neurotropic adverse events

At least 25 cases of meningoencephalitis following yellow fever vaccination have been reported.[4] However, 15 of these cases occurred in the 1950s in infants ≤7 months of age; following recommendations in the early 1960s not to vaccinate young infants, the incidence of vaccine-associated meningoencephalitis declined considerably.[4] Nevertheless, these adverse events, albeit very rare, still occur in adults; the risk is greater in vaccinees ≥60 years of age.[7,8]

(iv) Vaccine-associated viscerotropic adverse events

Recently, an apparently very rare (and often fatal) complication, characterised by multiorgan system failure, has been recognised following yellow fever vaccination; it appears that overwhelming infection with the 17D vaccine-virus is responsible for these viscerotropic adverse events.[4] Up to October 2004, 25 such cases had been reported worldwide; the exact incidence is unknown but may be less than 1 in 400 000 doses of vaccine.[4]

Vaccine-associated viscerotropic adverse events do not appear to be caused by altered virulence of the vaccine-virus, but rather appear to be related to host factors. Although cases have occurred in younger people, it is apparent that the risk is increased with advanced age, in particular in those aged ≥60 years.[7,8] Another host factor associated with an increased risk of a viscerotropic adverse event is pre-existing thymus disease. Four of the 25 reported cases had a history of thymic tumour and thymectomy, both uncommon conditions.[12]

Use in pregnancy

Pregnant women, who insist on travelling to either a West African country, or outside urban areas of any other endemic country, should be vaccinated (see 'Precautions' above).

Variations from product information

The product information states that pregnancy is a contraindication to the yellow fever vaccine. However, NHMRC recommends that pregnant women who insist on travelling, against medical advice, to endemic countries, should be vaccinated.

The product information suggests that a 0.1 mL test dose of yellow fever vaccine can be used intradermally to assess an individual with suspected allergy to the vaccine. However, NHMRC states that (with the exception of Q fever vaccine) test doses should never be used.

References

Full reference list available on the electronic *Handbook* or website http://immunise.health.gov.au.

3.26 ZOSTER (HERPES ZOSTER)

Virology

Varicella-zoster virus (VZV) is a DNA virus that is a member of the herpesvirus family. Herpes zoster (HZ) or 'shingles' is caused by reactivation of latent VZV which typically resides in the dorsal root or trigeminal ganglia following primary infection with VZV.[1] Primary infection with VZV is known as varicella or 'chickenpox'.[1]

Clinical features

Reactivation of VZV causing HZ is thought to be due to a decline in cellular immunity to the virus, and presents clinically as a unilateral vesicular rash in a dermatomal distribution in the majority of cases. It is often painful and lasts 10 to 15 days.[1,2] A prodromal phase occurs 48 to 72 hours before the appearance of the lesions in 80% of cases.[3] Associated symptoms may include headache, photophobia, malaise, and an itching, tingling, or severe pain in the affected dermatome.[2,4] In the majority of patients, HZ is an acute and self-limiting disease. However, complications can occur, especially with increasing age.

Post-herpetic neuralgia (PHN), the most frequent debilitating complication of HZ, is a neuropathic pain syndrome that persists or develops after the dermatomal rash has healed or persists longer than 3 months after the onset of the rash.[5,6] Other complications associated with HZ, such as ophthalmic disease and neurological complications, may occur depending on the site of reactivation. Rarely, disseminated HZ may develop with visceral, central nervous system, and pulmonary involvement. Disseminated disease is more common in people with impaired immunity.[4] Dermatomal pain without the appearance of rash is also documented (zoster siné herpéte). Antiviral therapy, intiated within 3 days after the onset of HZ, reduces the severity and duration of HZ and may reduce the risk of developing PHN.[7-11] However, in many cases, PHN may persist for years, and may be refractory to treatment.[12]

Epidemiology

HZ occurs most commonly with increasing age (>50 years), impaired immunity, and a history of varicella in the first year of life. The lifetime risk of reactivation of VZV causing HZ is estimated to be approximately 20 to 30%, and it affects half of those who live to 85 years.[1,13-15] Second attacks of HZ occur in less than 5% of immunocompetent individuals, but are more frequent in individuals with impaired immunity.[2,16] Internationally, average incidence rates of HZ in the total population vary from 130 to 405 per 100 000 person-years depending on the study population.[17,18] Australian data on the incidence of HZ in the community are limited. However, using general practice and other data, approximately

5 cases per 1000 population (range 3.3–8.3 per 1000) are estimated to occur annually.[19-21]

Overall, an estimated 13 to 26% of HZ patients develop complications. Complications occur more frequently with increasing age, and with impaired immunity.[22,23] PHN occurs infrequently in young people but, in patients >50 years of age, it complicates HZ in 25 to 50% of cases.[1]

Modelling the outcomes of the introduction of a universal infant vaccination schedule for varicella has predicted a rise in the incidence of HZ based on the assumption that exposure to VZV boosts immunity.[24] It has been suggested that an increase in HZ incidence rates (in the population previously infected with wild-type VZV) will occur for approximately 40 years, based on a varicella vaccine coverage rate of 90% and boosting preventing HZ for an average of 20 years.[21,24] Surveillance in the USA has not suggested a change in the incidence of HZ since the introduction of a universal varicella vaccination program in 1995.[18] The incidence of HZ in children vaccinated with varicella vaccine is less than in those infected with wild-type virus.[1,25]

In most states of Australia, surveillance for varicella and HZ is currently being implemented in order to track the burden of disease from VZV before and after the introduction of the varicella vaccination program.[26] South Australia has conducted passive surveillance of varicella and HZ since January 2002.

Vaccine

A frozen formulation of a live attenuated zoster vaccine is currently registered in Australia but is not marketed. The zoster vaccine is formulated from the same VZV strain (Oka/Merck) as the licensed varicella (chickenpox) vaccine, Varivax, but is of higher potency (at least 14 times greater). The higher viral titre in the zoster vaccine is required in order to elicit a sufficient cellular immune response in adults who usually remain seropositive to VZV but have declining cellular immunity with increasing age. The licensed varicella vaccines are not suitable for use in the prevention of zoster in older people.

Several randomised placebo-controlled trials conducted during the clinical development of the zoster vaccine confirmed that a vaccine at potencies above 19 400 plaque forming units (PFU) stimulated both VZV-specific antibodies and a cell-mediated immune response.[27,28] A large randomised, double-blind, placebo-controlled efficacy and safety trial of the zoster vaccine (known as the "Shingles Prevention Study") was conducted among 38 546 primarily healthy adults aged ≥60 years, and demonstrated that the zoster vaccine was safe and generally well tolerated. Vaccination significantly reduced the burden of both HZ and PHN.[27] Overall, compared with placebo, vaccination reduced the incidence of HZ by 51.3% (95% CI: 44.2–57.6%), the incidence of PHN by 66.5% (95% CI: 47.5–79.2%), and the burden of illness associated with pain from HZ by 61.1% (95% CI: 51.1–69.1%) over a median of 3.12 years of follow-up.[27]

No product is currently marketed in Australia (see Appendix 3, *Products registered in Australia but not currently available*).

References

Full reference list available on the electronic *Handbook* or website http://immunise.health.gov.au.