

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 (CRM₁₉₇) 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 data²⁴ and the US examining vaccine effectiveness²⁵ 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, <i>Catch-up</i> , 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, <i>Catch-up</i> , 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, <i>Catch-up</i> , 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 23vPPV³¹ 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>.