16 Pneumococcal disease

Key information

<table>
<thead>
<tr>
<th>Mode of transmission</th>
<th>Contact with respiratory droplets.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incubation period</td>
<td>Asymptomatic nasopharyngeal carriage is common. The incubation period is variable and may be as short as 1–3 days.</td>
</tr>
<tr>
<td>Incidence and burden of disease</td>
<td>Highest at extremes of age (&lt;2 years and &gt;75 years), Māori and Pacific people, those with multiple comorbidities and with immunocompromise.</td>
</tr>
<tr>
<td>Funded vaccines</td>
<td>All children aged under 5 years: PCV10 (Synflorix). Children and adults with eligible conditions: • PCV13 (Prevenar 13) • 23PPV (Pneumovax 23).</td>
</tr>
<tr>
<td>Dose, presentation and route</td>
<td>All vaccines: • 0.5 mL per dose • pre-filled syringe • intramuscular injection (23PPV also be given subcutaneously).</td>
</tr>
<tr>
<td>Funded vaccine indications and schedule</td>
<td>PCV10 at ages 6 weeks, 5 months and 12 months, and age-appropriate catch-up for children &lt;5 years; or, PCV13 and 23PPV: • vaccination or re-vaccination at any age with eligible conditions • testing for primary immune deficiencies.</td>
</tr>
<tr>
<td>Vaccine efficacy</td>
<td>For pneumococcal conjugate vaccines: reductions in pneumococcal disease and carriage of vaccine serotypes in vaccinated populations, plus herd immunity effects reducing pneumococcal disease in other age groups; some increases in disease caused by non-vaccine serotypes.</td>
</tr>
<tr>
<td>Precautions and special considerations</td>
<td>Concomitant PCV13 and influenza vaccine may increase risk of fever and febrile convulsions in children aged 6 months to &lt;5 years. 23PPV should not be given to children aged under 2 years due to the reduced immune response associated with polysaccharide vaccines.</td>
</tr>
</tbody>
</table>

16.1 Bacteriology

*Streptococcus pneumoniae* is a gram-positive diplococcus. It is ubiquitous, and many individuals carry the organism asymptptomatically in their upper respiratory tract. There are over 90 identifiable serotypes of *S. pneumoniae*. Certain serotypes are more
invasive or more associated with antibiotic resistance, and dominant serotypes vary by age and geographical distribution.

See section 16.4.1 and Table 16.1 for a summary of the serotypes contained in the pneumococcal conjugate vaccines (PCV) and pneumococcal polysaccharide vaccine (PPV).

16.2 Clinical features

The human nasopharynx is the only natural reservoir of *S. pneumoniae*. Carriage rates in young children range from 21 percent in high-income settings to more than 90 percent in resource-limited countries. Transmission of *S. pneumoniae* is by contact with respiratory droplets. Although nasopharyngeal colonisation precedes disease, most who are colonised do not develop disease. The nasopharynx is a source of spread between individuals, so reduced nasopharyngeal carriage of *S. pneumoniae* vaccine serotypes in vaccinated children decreases transmission to adults. Transmission of pneumococci and invasive potential is increased by concomitant viral upper respiratory tract infection, especially influenza. Invasive pneumococcal disease (IPD) is defined by isolation of *S. pneumoniae* from a usually sterile site, such as blood, pleural fluid or cerebrospinal fluid, and represents the most severe end of the disease spectrum. The most common clinical syndromes in IPD are bacteraemic pneumonia, non-localised bacteraemia and meningitis. Older adults generally have bacteraemic pneumonia, while young children may have any of the three, with meningitis being the most severe.

Pneumonia without bacteraemia is up to five times more common than bacteraemic pneumonia, especially in older adults, where it also has high mortality. Other non-invasive infections include acute otitis media (predominantly in children) and sinusitis (predominantly older children and adults). The period between colonisation with *S. pneumoniae* and infection is variable but may be as short as one to three days.

16.3 Epidemiology

16.3.1 Global burden of disease

Pneumococcal disease is a common cause of morbidity and mortality worldwide. Rates of disease and death are highest in low-income countries with the majority of deaths occurring in sub-Saharan Africa and Asia. Along with the very old and very young, patients with underlying cardiorespiratory disease and congenital or acquired immunosuppression have the highest rates of disease.

Risk of disease increases with multiple comorbidities and lifestyle factors (this is described as risk-stacking, see section 16.5.4). The risk of IPD in children and adults with two or more comorbid conditions can be as high as in those with a recognised ‘high-risk’ condition. Lifestyle factors, such as passive smoking, environmental and workplace pollutions, smoking
and alcohol dependency, can increase the risk of severe pneumococcal disease, especially in those with chronic illnesses that predispose them to infection, such as asthma, diabetes, dementia and mental illness.\textsuperscript{5, 6} Socioeconomic deprivation, homelessness and overcrowding have also been associated with increased risk of IPD.\textsuperscript{7}

The WHO estimates that 300,000 (range 200–370,000) children aged under 5 years died from pneumococcal infections, representing around 5 percent of all-cause mortality in this age group, in 2015.\textsuperscript{8} An additional 23,000 (15–40,000) deaths were estimated to occur in children co-infected with HIV. On average 75 percent of IPD and 83 percent of pneumococcal meningitis cases are aged under 2 years but the incidence and age distribution vary by country and socioeconomic status.\textsuperscript{8} Importantly, at least one quarter of survivors of pneumococcal meningitis experience long-term sequelae such as hearing loss, seizures, mental and motor abnormalities.

In each geographical region globally, PCV10 and PCV13 were shown to cover more than 70 percent of the serotypes causing IPD under 5 years of age during 1980–2007 prior to PCV introduction (PCV10 range 70–94 percent and 74–88 percent for PCV13).\textsuperscript{8}

### 16.3.2 Global epidemiology since the introduction of pneumococcal conjugate vaccines

#### Direct impact of PCV programmes on IPD in children

Reductions in IPD among target cohorts of children in high income countries have been similar for PCV10 and PCV7/13 in reported studies. Québec (PCV10 and 13) and Finland (PCV10) both used 2+1 schedules and observed 83 percent and 79 percent reductions in IPD in vaccine-eligible children, respectively.\textsuperscript{9, 10} In England, using PCV7 then PCV13 in a 2+1 schedule, there was an estimated 5,000 (54 percent) fewer hospital admissions for bacteraemia, meningitis and pneumonia in children aged under 5 years over 12 years after the introduction of PCV7 and PCV13. The greatest reductions were seen in meningitis (by 71 percent) in children under 2 years age.\textsuperscript{11}

#### Direct impact of vaccination on non-invasive pneumococcal disease

The impact of pneumococcal conjugate vaccination on the large burden of non-invasive pneumococcal disease has been clearly demonstrated internationally in countries that have introduced these vaccines, particularly through reductions in childhood hospitalisations due to pneumonia.\textsuperscript{12, 13} Other impacts, such as on acute otitis media, are less clear and more difficult to measure accurately.\textsuperscript{14} However, a systematic review found PCVs were associated with large reductions in risk of pneumococcal acute otitis media, but there was no evidence of benefit against all-cause otitis media in high-risk children over 1 year of age or older children with a history of respiratory illness.\textsuperscript{15}
Herd immunity

The extent to which childhood PCV immunisation programmes provide indirect reductions in IPD among high-risk children and older adults varies between reports, settings and vaccine serotype (notably serotypes 3 and 19A). There is some good evidence for the indirect (herd) effects of infant PCV immunisation on vaccine serotype pneumococcal disease in the non-vaccinated population, especially in adults aged 65 years and older, and an all age-effect on non-bacteraemic pneumonia. This includes data showing reductions in the rates of IPD due to PCV7 and, more recently, PCV13 serotypes in non-vaccinated groups in many countries (for both pneumonia and IPD in adults) in North America and Europe. Reductions in adult pneumococcal pneumonia have also been observed in Western Kenya following the introduction of PCV10 in children and in Japanese community-dwelling older adults following the introduction of PCV13. These herd effects are predominantly due to decreased nasopharyngeal carriage of vaccine types in immunised children lowering transmission to unimmunised older children and adults.

Although many countries have reported significant decreases in vaccine-type IPD among children and the wider population following the introduction of PCVs to the childhood schedules, IPD due to non-PCV serotypes has increased in some, particularly in older adults. Therefore, for direct protection against a broad range of serotypes, 23PPV continues to be necessary for those at highest risk of IPD.

16.3.3 New Zealand epidemiology

Pneumococcal disease occurs throughout the year, but is more common in the autumn and winter months. In the pre-PCV era, incidence of IPD was highest in infants and the elderly, especially among Māori and Pacific peoples. Isolates from cases of IPD are serotyped at ESR and detailed information by age group is regularly updated on the ESR Public Health Surveillance website (available at www.surv.esr.cri.nz/surveillance/IPD.php).

Incidence and mortality

In 2019, there were 497 notified IPD cases and the overall notification rate was 10.1 cases per 100,000 population (ESR, 26 June 2020). The highest rates of IPD were in adults aged 85 years and older (46.4 per 100,000) and in children aged under 1 year (30.2 per 100,000), followed by adults aged 75–84 years (24.2 per 100,000) and 65–74 years (21.4 per 100,000). The age-standardised rates of IPD were highest for the Pacific peoples (37.0 per 100,000, 79 cases) and Māori (28.9 per 100,000, 113 cases) ethnic groups. These rates were 5.7 and 4.4 times higher than the age-standardised rate for the European/Other ethnic group (16.5 per 100,000, 431 cases). The incidence of IPD was 3.7-fold higher for those living in areas with the highest levels of deprivation than those living in low deprivation areas across all age groups (18.8 vs 5.0 per 100,000). IPD was recorded as the primary cause of death for 11 cases in 2019, including two children aged under 5 years. In 2019, the most reported risk factors in cases aged under 5 years were children attending day care (45.5 percent) followed by smoking in
the household (27.8 percent), and for cases aged 5 years and older it was having a chronic illness (63.9 percent) (ESR, 26 June 2020).

New Zealand epidemiology since the introduction of PCV

PCV7 was introduced in June 2008, PCV10 in July 2011 and PCV13 in July 2014, PCV10 replaced PCV13 in July 2017 on the routine Schedule (see Appendix 1). As of July 2020, the number of primary doses of PCV10 were reduced to two (at age 6 weeks and 5 months) and the booster dose was brought forward from 15 months to 12 months in October 2020.

IPD incidence

There have been dramatic reductions in the incidence of IPD in the vaccine-eligible age groups in New Zealand since the introduction of PCV to the Schedule in 2008 (see Figure 16.1).

In children aged under 2 years, the total rate of IPD has decreased by 87.7 percent since the introduction of PCV to the Schedule in 2008: from 100.3 per 100,000 for 2006–07\textsuperscript{16} to 22.4 per 100,000 in 2019 (ESR, 26 June 2020). The reduction in PCV7 serotypes was even greater (see Figure 16.2), with no cases of PCV7 serotype IPD were detected in children aged under 2 years during 2019 (ESR, 26 June 2020).

Similar reductions were seen for IPD caused by PCV10 and PCV13 serotypes under 2 years (see Figure 16.2). IPD incidence decreased in children aged 2–4 years, for all-cause IPD (50.5 percent; Figure 16.1) and IPD caused by PCV serotypes (77.6 percent; Figure 16.2) (ESR, 26 June 2020).

In 2019, 26.9 percent of cases in adults aged 65 years and over were PCV13 serotypes, and 69.9 percent were due to 23PPV serotypes. Of these, 12.4 percent (24/193 cases) were due to serotype 19A, and 43.0 percent were due to 23PPV-non-PCV13 serotypes (ESR, 26 June 2020).

Figure 16.1: Rate per 100,000 of invasive pneumococcal disease by age group and year, 2006–2017

![Graph showing rate per 100,000 of invasive pneumococcal disease by age group and year, 2006–2017]
Figure 16.2: Rate per 100,000 population of invasive pneumococcal disease due to PCV7 serotypes, additional PCV10 types, additional PCV13 types and non-PCV types, by age group and year, 2006–2017

Notes:
‘PCV7 serotypes’ are cases due to serotypes covered by PCV7 (4, 6B, 9V, 14, 18C, 19F and 23F); ‘Serotypes 1, 5, 7F and 19A’ are cases due to the additional serotypes covered by PCV10; ‘Serotypes 3 and 6A’ are cases due to the additional serotypes covered by PCV13; and ‘Other serotypes’ are all other culture-positive IPD cases.
IPD became a notifiable disease in 2008. Data presented from 2009 onwards is based on IPD notifications, and data prior to 2009 is from ESR’s national laboratory-based surveillance of IPD.

Pneumococcal serotypes

Of the 497 IPD cases notified in 2019, 466 isolates were referred to ESR for serotyping.
In children aged under 5 years, 65.8 percent (25/38) of cases were due to serotypes not covered by PCV, compared with 71.5 percent (171/239) and 72.5 percent (137/189) in the 5–64 years and 65 years and older age groups (ESR, 26 June 2020).

Serotype 19A was the most common serotype (65 cases) in 2019, increasing from 3 cases in 2015 to 10 cases in 2019 in children aged under 5 years. In adults aged 65 years or older, serotype 22F was the most prevalent non-vaccine serotype in 2019 (20 cases compared with 40 cases in 2015; ESR, 26 June 2020).

Herd immunity

The addition of PCV to the New Zealand schedule in 2008 was followed by significant reductions in IPD due to PCV7 serotypes in age groups not eligible for routine infant immunisation (Figure 16.2). Since notification-based surveillance began in 2009, the rate of IPD due to PCV7 serotypes in the 5–64 year age group decreased 87 percent
from 3.8 per 100,000 to 0.5 per 100,000 in 2019, and the rate in cases aged 65 years and over decreased 94 percent from 26.6 to 1.5 per 100,000 (ESR, 26 June 2020). However, the total rate of IPD in adults did not fall dramatically (rate for age 5–64 years: 6.1 to 6.7 per 100,000; age 65 years and over: 34.2 to 31.3 per 100,000).

Impact of vaccination on non-invasive pneumococcal disease

While hospitalisations for respiratory infections in children aged 5 years and under have been increasing in New Zealand, hospitalisations for all-cause pneumonia have declined significantly since the implementation of the pneumococcal conjugate vaccine programme in 2008. The largest reductions in all-cause pneumonia hospitalisations between 2006 and 2015 were in Māori (a 12 percent reduction) and Pacific children (a 21 percent reduction) and those living in areas of high deprivation.37 A 51 percent decline in otitis media hospitalisations was observed for Māori children aged under 6 years following PCV immunisation, compared with 8 percent decline in otitis media across all ethnicities.37

Antimicrobial resistance

Introduction of pneumococcal conjugate vaccination has reduced the circulation of resistant pneumococcal serotypes in the US,38 but little change has been seen in New Zealand since PCV introduction. *S. pneumoniae* resistance to penicillin (14.1–23.5 percent) and cefotaxime resistance (0.4–2.1 percent) has varied year-to-year over the last decade with no significant trend.39 In 2017, PCV7 serotypes accounted for 10.3 percent of the penicillin-resistant isolates compared with 92.8 percent in 2006/07, but the prevalence of penicillin resistance among serotype 19A isolates increased just over 4-fold from 15.8 percent in 2006/07 to 68.3 percent in 2017. Together types 19F, 19A, 15A and 15B accounted for 72.7 percent (16/22) of the multidrug-resistant invasive pneumococci (ESR, 26 June 2020).

16.4 Vaccines

16.4.1 Available vaccines

There are two types of pneumococcal vaccine registered (approved for use) and available (marketed) in New Zealand for use against *S. pneumoniae*: pneumococcal conjugate vaccine (PCVs) with 10 or 13 serotypes and a plain polysaccharide pneumococcal vaccine (PPV) containing 23 serotypes. In PCV vaccines, the pneumococcal surface polysaccharide is coupled to a carrier protein that induces increased production of type-specific antibodies, particularly in children aged under 2 years, and immunological memory, enabling booster responses with subsequent doses (see section 1.4.3). Table 16.1 summarises the polysaccharide serotypes contained within each vaccine.
Table 16.1: Summary of pneumococcal vaccine serotype content

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>PCV7</th>
<th>PCV10</th>
<th>PCV13</th>
<th>23PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV7</td>
<td>4</td>
<td>6B</td>
<td>9V</td>
<td>14</td>
</tr>
<tr>
<td>PCV10</td>
<td>1</td>
<td>4</td>
<td>5</td>
<td>6B</td>
</tr>
<tr>
<td>PCV13</td>
<td>1</td>
<td>4</td>
<td>5</td>
<td>6A</td>
</tr>
<tr>
<td>23PPV</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Note: PCV10 contains serotype 6B and 19F, which elicit cross-reactive opsonophagocytic antibodies against serotype 6A and 19A, respectively, but at a lower level than PCV13.8

Funded vaccines

**PCV10 (Synflorix, GSK)**

Each 0.5mL dose of PCV10 contains:

- 1 µg of pneumococcal polysaccharide serotypes 1, 5, 6B, 7F, 9V, 14 and 23F and 3 µg of serotype 4, conjugated to a total of 9–16 µg of non-typeable Haemophilus influenzae (NTHi) protein D, 3 µg of serotype 18C conjugated to 5–10 µg of tetanus toxoid, and 3 µg of serotype 19F conjugated to 3–6 µg of diphtheria toxoid, adsorbed onto 0.5 mg of aluminium phosphate
- 4.3 mg of sodium chloride and water for injection. PCV10 contains no preservative.

**PCV13 (Prevenar 13, Pfizer)**

Each 0.5 mL dose of PCV13 contains:

- 2.2 µg of pneumococcal purified capsular polysaccharides for serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F and 23F, and 4.4 µg of serotype 6B, conjugated to non-toxic diphtheria CRM197 protein and adsorbed onto aluminium phosphate (0.565 mg)
- succinic acid, polysorbate 80, aluminium phosphate, phosphate, and sodium chloride in water for injection.

**23PPV (Pneumovax 23, MSD)**

Each 0.5 mL dose of 23PPV contains:

- 25 µg of each capsular polysaccharide antigen (serotypes: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F)
- sodium chloride, water for injection, and phenol (0.25 percent) added as a preservative.
16.4.2 Efficacy and effectiveness

10-valent pneumococcal conjugate vaccine

IPD

Two key randomised controlled trials have demonstrated the protective efficacy of PCV10 against pneumococcal disease.\(^{40}\) The Finnish Invasive Pneumococcal disease (FinIP) study investigated a two- or three-dose infant series plus a toddler booster. Vaccine efficacy against vaccine-serotype IPD was 100 percent (95% CI: 83–100) for the 3+1 schedule and 92 percent (95% CI: 58–100) for the 2+1 schedule. Based on national hospital discharge register data, vaccine efficacy was 71 percent (95% CI: 52–83) for patient file-verified non-laboratory-confirmed IPD.\(^{41,42}\)

The Clinical Otitis Media and Pneumonia Study (COMPAS) showed PCV10 efficacy to be 100 percent (95% CI: 74.3–100) against vaccine-serotype IPD and 65 percent (95% CI: 11.1–86.2) against any IPD.\(^{43}\) In this study, approximately 24,000 infants received PCV10 or HepB at ages 2, 4 and 6 months with a booster at age 15–18 months as part of the phase III trial conducted in Latin America (Argentina, Colombia and Panama).

Two observational studies in Brazil examined effectiveness of PCV10 (as a 3+1 schedule) post-introduction in 2010. A matched case-control study of 316 cases of IPD and 1,219 neighbourhood age-matched controls showed adjusted vaccine effectiveness (VE) against vaccine-serotype IPD of 83.8 percent (95% CI: 65.9–92.3) for an age-appropriate PCV10 schedule.\(^{44}\) A study based on data obtained from the Information System on Notifiable Diseases from 2007 to 2012 found two years after the introduction of routine PCV10 vaccinations that there was a decrease in pneumococcal meningitis morbidity and mortality in children aged under 2 years.\(^{45}\)

Overall, the incidence of pneumococcal meningitis decreased by 50 percent from 3.7 per 100,000 population in 2007 to 1.84 per 100,000 in 2012. Mortality decreased by 69 percent from 1.3 to 0.4 per 100,000. The greatest impact of PCV10 vaccination was in infants aged 6–11 months, with a 73 percent reduction in pneumococcal meningitis incidence and an 85 percent reduction in mortality.\(^{35}\)

Non-IPD pneumonia

The FinIP trial found vaccine effectiveness against all hospital-diagnosed pneumonia was 25.2 percent (95% CI: 2.6–42.6) for the 3+1 PCV10 schedule and 27.6 percent (95% CI: 5.5–44.6) for the 2+1 schedule.\(^{40}\)

In Brazil, there was a significant decrease of 12.7 percent (p<0.001) in all-cause pneumonia hospitalisations of children aged under 4 years between the pre (2002–2009) and post-PCV10 (2011–2012) periods, in the absence of any reduction in non-respiratory-cause hospitalisations (p=0.39).\(^{46}\) Active population-based surveillance studies in Central Brazil (across 17 paediatric hospitals) found around a 25 percent reduction in the rate of X-ray-confirmed pneumonia in children aged 2–23 months.\(^{47}\) Five years after the introduction of PCV10 in Brazil, pneumonia hospitalisations significantly reduced, both in vaccine-targeted children (17.4–26.5 percent) and age groups not targeted for vaccination (11.1–27.1 percent for ages 10–49 years), but not in those aged 65 years or older.\(^{48}\)
Otitis media

In the COMPAS trial, a post-hoc intent-to-treat analysis found that vaccine efficacy against bacteriologically-confirmed acute otitis media (AOM) was 19.0 percent (95% CI: 4.4–31.4; p=0.007), increasing to 55.7 percent (95% CI: 21.5–75.0) against pneumococcal AOM and 69.9 percent (29.8–87.1) against vaccine-serotype pneumococcal AOM. Although PCV10 has been suggested to be protective against non-typeable *Haemophilus influenzae* (NTHi) confirmed-AOM, following the introduction of PCV10 in New Zealand, no reduction in NTHi density in the nasopharyngeal or middle-ear microbiology in children with established ear disease was observed; NTHi remained the dominant pathogen for otitis media.

In a follow-up of the FinIP study, vaccine efficacy of PCV10 against all respiratory tract infections (RTIs) in children aged under 2 years was 12 percent (95% CI: 2–22), 23 percent (95% CI: 0–40) against RTIs with AOM, and 10 percent (95% CI: 0–19) against RTIs without AOM. Most of these infections were caused by rhinovirus. Despite low efficacy against any AOM (7–13 percent), the high incidence rate of AOM meant that related factors (antimicrobial prescriptions and tympanostomy tube placements) contributed to 95 percent of the reduction in total disease burden post PCV10, compared with 0.6 percent for laboratory-confirmed IPD. Similarly in Iceland, PCV10 introduction was associated with a 5.8 percent (95% CI: 1.6–9.8) reduction in all-cause antimicrobial prescriptions and 21.8 percent (95% CI: 11.5–30.9) reduction in AOM-associated prescriptions in children up to 3 years of age.

13-valent pneumococcal conjugate vaccine

Individuals at increased risk of IPD

Few studies have investigated the immunogenicity and effectiveness of PCV13 in individuals at increased risk of IPD. Studies using pneumococcal vaccines with similar but fewer antigens have demonstrated vaccine efficacy in individuals with immunocompromising conditions (eg, HIV, sickle cell disease), but the duration of protection against IPD remains unknown. High IgG titres have been demonstrated following PCV13 vaccination of children with sickle cell disease, HIV infection and nephrotic syndrome.

WHO recommends that children with medical conditions that reduce humoral immune response to vaccines, such as HIV, sickle cell disease and primary immune deficiencies, to have a 3+1 schedule of PCV13. In children and adolescents with underlying medical conditions, such as type 1 diabetes, cancer, cystic fibrosis or asthma, the broader serotype protection provided by PCV13 can reduce nasopharyngeal carriage and the associated risk of IPD.

Use of pneumococcal conjugate vaccines in adults

PCV13 induces robust immune responses in adults, including elderly adults. Although the antibody titres vary with serotype and between age groups, particularly for those aged over 65 years, the clinical significance of this variation is unclear. PCV13 is at least as immunogenic as 23PPV in adults. Some studies suggest that 23PPV
attenuates the immune response to subsequent doses of PCV13, not seen if PCV13 is given before 23PPV; PCV13 may amplify the response to subsequent 23PPV vaccination.\textsuperscript{66, 67, 68}

With respect to clinical outcomes, the Community-Acquired Pneumonia Immunization Trial in Adults (CAPITA) was a large randomised placebo-controlled trial conducted in the Netherlands that assessed efficacy of PCV13 against pneumococcal community-acquired pneumonia (CAP) with and without IPD in adults aged 65 years and older. The efficacy of PCV13 against vaccine-type IPD was 75 percent (95% CI: 41.4–90.8) and 45.6 percent (95% CI: 21.8–62.5) against vaccine-type pneumococcal CAP; 45.0 percent (95% CI: 14.2–65.3) for both combined.\textsuperscript{69} Although this study showed individual protection for vaccine-type CAP, there was no significant reduction in all-cause pneumonia.\textsuperscript{69}

An important uncertainty is the extent of indirect protection in vaccine-type IPD cases stemming from childhood immunisation programmes, which varies between countries. Where vaccine serotypes are sufficiently prevalent, PCV13 would provide some protection against all-cause CAP and lobular pneumonia.\textsuperscript{70} Some of the non-PCV13 vaccine serotypes more likely to cause disease in adults are covered by 23PPV.

Data is limited for younger adults and specific at-risk adult populations.

### 23-valent vaccine pneumococcal polysaccharide

The polysaccharide vaccine (23PPV, Pneumovax 23) is made from the purified capsular polysaccharides of 23 serotypes of \textit{S. pneumoniae}. It is available in New Zealand for adults and children from age 2 years. The 23 serotypes included in 23PPV (see Table 16.1) are responsible for about 90 percent or more of IPD in high-income countries.

See recent IPD surveillance reports from ESR for prevalence of serotypes covered by 23PPV in New Zealand (available at surv.esr.cri.nz/surveillance/IPD.php).

A meta-analysis of IPD in adults aged from 65 years in 10 European countries showed that incidence of PCV7 serotypes had declined by 77 percent and for additional PCV13 serotypes by 38 percent after 5 years of PCV13/PCV10 immunisation programmes. The incidence rate of 23PPV-non-PCV13 serotypes had increased by around 50 percent with these 11 serotypes causing 22–54 percent of IPD.\textsuperscript{71} In 2016, more than two-thirds of IPD cases in adults age 65 years or older were 23PPV-non-PCV13 serotypes.\textsuperscript{39}

The efficacy of 23PPV varies depending on whether immune-competent or immunocompromised patients are studied, and whether the end point is pneumococcal pneumonia or bacteraemia.

The limitations of the polysaccharide vaccine have been summarised as:

- reduced efficacy in high-risk individuals
- uncertain efficacy against pneumonia
- it is only suitable for children aged 2 years and older.
- waning protection 2.5 to 5 years after vaccination.
A 2017 meta-analysis from Germany found pooled VE for 23PPV against any serotype IPD of 45 percent (95% CI: 15–65), 59 percent (95% CI: 35–74) or 73 percent (95% CI: 10–92) across cohort, case-control or clinical trial data; and pooled VE against any serotype pneumococcal pneumonia of 48 percent (95% CI: 25–63) and 64 percent (95% CI: 35–80) in cohort studies and clinical trials. For both outcomes, waning of protection was found between 2.5 years and 5 years of follow-up after PPV23. Other systematic reviews, with differing eligibility criteria, found lower pooled VE estimates against IPD or pneumococcal pneumonia for 23PPV. A Japanese prospective study found 23PPV to have moderate but variable effectiveness against vaccine-type pneumococcal pneumonia in adults aged 65 years or older. Hence, questions remain around the clinical effectiveness and intervals between repeat doses of PPV23 that provide continued protection.

16.4.3 Transport, storage and handling


Store at +2°C to +8°C. Do not freeze.

16.4.4 Dosage and administration

The dose of PCV10, PCV13 and 23PPV is 0.5 mL, administered by intramuscular injection (see section 2.2.3). 23PPV can also be administered by subcutaneous injection (see section 2.2.3), but there is an increased likelihood of injection-site reactions.

Co-administration with other vaccines

PCV10, PCV13 or 23PPV may be administered at the same time as other routine childhood vaccinations, in a separate syringe at a separate injection site (see section 2.2.7 for information about multiple injections at the same visit). The only exception is PCV13 with the quadrivalent meningococcal conjugate vaccine MenACWY-D, which should be given at least four weeks after PCV13. This is because, when these vaccines were administered concurrently during clinical trials, impairment of the antibody response to some of the pneumococcal serotypes (serotypes 4, 6B and 18C) was reported.

PCV13 has been associated with increased risk of fever over 39°C and febrile convulsions when co-administered with inactivated influenza vaccine in children aged 6 months to under 5 years. Separation of the vaccines by two days can be offered but is not essential (see section 16.6.2). Systemic reactions have been noted in adults aged over 65 years.
Herpes zoster vaccine can be concomitantly delivered with 23PPV (see also section 23.4.4). 80, 81

16.5 Recommended immunisation schedule

16.5.1 Usual childhood schedule (PCV10)

PCV10 for children aged under 5 years

PCV10 (Synflorix) vaccine is funded for all children aged under 5 years. Two doses of PCV10 are given as the primary course, with a booster at age 12 months (Table 16.2). Children who started their immunisation course with PCV13 can complete it with PCV10.

Table 16.2: Usual childhood PCV10 (Synflorix) schedule

<table>
<thead>
<tr>
<th>Age</th>
<th>Vaccine</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 weeks</td>
<td>PCV10</td>
<td>Primary series</td>
</tr>
<tr>
<td>5 months</td>
<td>PCV10</td>
<td>Primary series</td>
</tr>
<tr>
<td>12 months</td>
<td>PCV10</td>
<td>Booster</td>
</tr>
</tbody>
</table>

Where a previously unimmunised child aged under 5 years presents late for pneumococcal vaccination, the age-appropriate catch-up schedules in Appendix 2 should be followed.

16.5.2 Extended pneumococcal immunisation for high-risk groups

As part of the extended immunisation programme for high-risk groups, PCV13 and 23PPV are funded for eligible individuals, as shown in Table 16.3, Table 16.4 and Table 16.5. Because the recommended schedule depends on the age of the individual at diagnosis, the tables have been organised into age groups (under 5 years, 5–18 years and 18 years and older).

The PCV13 and 23PPV funding restrictions are as follows. See Table 16.3, Table 16.4 and Table 16.5 for the eligible conditions and dosing requirements.
PCV13

All high-risk infants are recommended to receive at least three doses of a PCV vaccine, with at least one dose after 12 months of age. Change from PCV10 to PCV13 as soon as the infant is diagnosed as being at high risk.

- Two doses of PCV13 are funded for high-risk children aged from 12 months and under 18 years who have previously received two or three doses of PCV10.
- Up to four doses of PCV13 are funded for vaccination or re-vaccination of high-risk children aged under 5 years.
- Up to four doses of PCV13 are funded for vaccination or re-vaccination of eligible individuals aged 5 years and older.

23PPV

- Up to three doses of 23PPV are funded for individuals with eligible conditions.
- Up to two doses of 23PPV are funded for high-risk children aged under 18 years.

See also section 16.5.3 '(Re)vaccination'. See sections 4.2 and 4.3 for more information about immunocompromised infants, children and adults, including additional vaccine recommendations and schedule tables for certain conditions.
Table 16.3: Extended pneumococcal immunisation for children aged under 5 years – funded PCV13 and 23PPV indications and schedules

See the Pharmaceutical Schedule (www.pharmac.govt.nz) for any changes to funding decisions.

<table>
<thead>
<tr>
<th>PCV13 (Prevenar 13) and 23PPV (Pneumovax 23) are funded for children aged under 5 years:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• prior to planned immunosuppressive therapy or radiotherapy, including prior to solid organ transplantation</td>
</tr>
<tr>
<td>• on immunosuppressive therapy or radiotherapy (vaccinate when there is expected to be a sufficient immune response)</td>
</tr>
<tr>
<td>• with primary immune deficiencies</td>
</tr>
<tr>
<td>• with HIV infection</td>
</tr>
<tr>
<td>• with renal failure or nephrotic syndrome</td>
</tr>
<tr>
<td>• who are immunosuppressed following organ transplantation (including HSCT)</td>
</tr>
<tr>
<td>• with cochlear implants or intracranial shunts</td>
</tr>
<tr>
<td>• with cerebrospinal fluid leaks</td>
</tr>
<tr>
<td>• who are receiving corticosteroid therapy for more than 2 weeks, and who are on an equivalent daily dosage of prednisone of 2 mg/kg per day or greater, or children who weigh more than 10 kg on a total daily dosage of 20 mg or greater</td>
</tr>
<tr>
<td>• with chronic pulmonary disease (including asthma treated with high-dose corticosteroid therapy)</td>
</tr>
<tr>
<td>• who were preterm infants, born before 28 weeks’ gestation</td>
</tr>
<tr>
<td>• with cardiac disease, with cyanosis or failure</td>
</tr>
<tr>
<td>• with diabetes</td>
</tr>
<tr>
<td>• with Down syndrome</td>
</tr>
<tr>
<td>• who are pre- or post-splenectomy, or with functional asplenia.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age at diagnosis</th>
<th>Vaccine</th>
<th>Recommended vaccine schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;12 months</td>
<td>PCV13</td>
<td>PCV13&lt;sup&gt;a&lt;/sup&gt; at ages 6 weeks, 3, 5&lt;sup&gt;b&lt;/sup&gt; and 12 months or an age-appropriate catch-up schedule. For those who have not been immunised at age 7–11 months – give 2 doses of PCV13 (8 weeks apart) and a further dose 8 weeks later, from age 12 months. For children aged 7–11 months who have completed a 2-dose primary course with PCV10, give 1 dose of PCV13 as soon as possible and another dose (of PCV13) 8 weeks later, from age 12 months.</td>
</tr>
<tr>
<td>23PPV</td>
<td>Following the completion of the PCV course, give 1 dose of 23PPV at age ≥2 years. There must be at least 8 weeks between the last PCV dose and the 23PPV dose. If risk persists, revaccinate once with 23PPV, 5 years after the first 23PPV.</td>
<td></td>
</tr>
<tr>
<td>12 months to &lt;5 years</td>
<td>PCV13</td>
<td>For children who have not yet received any PCV13, give 2 doses of PCV13 at least 8 weeks apart&lt;sup&gt;c,d&lt;/sup&gt;.</td>
</tr>
<tr>
<td>23PPV</td>
<td>Give 1 dose at least 8 weeks after the last PCV13 dose, from age 2 years. If risk persists, revaccinate once with 23PPV, 5 years after the first 23PPV.</td>
<td></td>
</tr>
</tbody>
</table>

---

<sup>a</sup> A three-dose primary series plus a booster dose of PCV13 replaces PCV10 on the usual Schedule.

<sup>b</sup> Additional dose of PCV13 given at 3 months, differing from PCV10 Schedule.

<sup>c</sup> If 23PPV has already been given (prior to any doses of PCV13) to children aged under 5 years, wait at least 8 weeks before administering PCV13 (note: this timing differs in adults, see footnote in Table 16.5).

<sup>d</sup> There are no safety concerns, regardless of the interval between the last dose of PCV10 and the first dose of PCV13.
### Table 16.4: Extended pneumococcal immunisation for children aged from 5 to under 18 years – funded PCV13 and 23PPV indications and schedules

PCV13 (Prevenar 13) and 23PPV (Pneumovax 23) are funded for children aged 5 to under 18 years:
- with HIV infection
- who are pre- or post-HSCT\(^a\) or chemotherapy\(^d\)
- who are pre- or post-splenectomy or with functional asplenia
- who are pre- or post-solid organ transplant
- undergoing renal dialysis
- with complement deficiency (acquired or inherited)
- with cochlear implants
- with primary immunodeficiency\(^d\)

<table>
<thead>
<tr>
<th>Age at diagnosis</th>
<th>Vaccine</th>
<th>Recommended vaccine schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 years to &lt;18 years</td>
<td>PCV13</td>
<td>For children who have not previously received PCV13 – give 1 dose of PCV13, even if fully vaccinated (^b,c)</td>
</tr>
<tr>
<td></td>
<td>23PPV</td>
<td>1 dose of 23PPV at least 8 weeks after the PCV13 dose. If risk persists, revaccinate once with 23PPV, 5 years after the first 23PPV.</td>
</tr>
</tbody>
</table>

\(^a\) PCV13 is funded pre- or post-HSCT or chemotherapy. 23PPV is only funded post-HSCT or chemotherapy.

\(^b\) If 23PPV has already been given (prior to any doses of PCV13) to children aged under 18 years, wait at least 8 weeks before administering PCV13.

\(^c\) There are no safety concerns, regardless of the interval between the last dose of PCV10 and the first dose of PCV13.

\(^d\) See section 4.3.3 for children with Down syndrome.

### Table 16.5: Extended pneumococcal immunisation for adults aged 18 years and older – funded PCV13 and 23PPV indications and schedules

PCV13 (Prevenar 13) and 23PPV (Pneumovax 23) are funded for (re)vaccination of patients:
- with HIV infection
- who are pre- or post-HSCT\(^a\) or chemotherapy\(^d\)
- who are pre- or post-splenectomy or with functional asplenia
- who are pre- or post-solid organ transplant
- undergoing renal dialysis
- with complement deficiency (acquired or inherited)
- with cochlear implants
- with primary immunodeficiency.

<table>
<thead>
<tr>
<th>Age at diagnosis</th>
<th>Vaccine</th>
<th>Recommended vaccine schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥18 years</td>
<td>PCV13</td>
<td>1 dose of PCV13.(^b)</td>
</tr>
<tr>
<td></td>
<td>23PPV</td>
<td>Give a maximum of 3 doses of 23PPV in a lifetime, a minimum of 5 years apart. The first 23PPV dose is given at least 8 weeks after PCV13, the 2nd a minimum of 5 years later, and the 3rd dose at age ≥65 years.</td>
</tr>
</tbody>
</table>

\(^a\) PCV13 is funded pre- or post-HSCT or chemotherapy. 23PPV is only funded post-HSCT or chemotherapy.

\(^b\) If 23PPV has already been given (prior to any doses of PCV13) to adults aged 18 years and older, wait at least 1 year before administering PCV13.
16.5.3 (Re)vaccination

Up to an additional four doses of PCV13 are funded:

1. For vaccination or re-vaccination of high-risk children aged under 5 years (as listed in Table 16.3)

2. For (re)vaccination of children and adults aged 5 years and older:
   - with HIV
   - who are pre- or post-HSCT or chemotherapy
   - who are pre- or post-splenectomy, or with functional asplenia
   - who are pre- or post-solid organ transplant
   - undergoing renal dialysis
   - with complement deficiency (acquired or inherited)
   - with cochlear implants
   - with primary immune deficiency.

See also sections 4.3 and 4.6.

16.5.4 Recommended but not funded

Risk stacking

Two classifications of IPD risk are recognised: ‘high-risk’ conditions for which there is significant risk of IPD and ‘at-risk’ conditions, which on their own may not significantly increase risk, but when combined together or with lifestyle risk factors increase an individual’s risk of IPD. This is described as ‘risk stacking’ – IPD incidence substantially increases with the accumulation of concurrent risk factors or conditions.\(^3\),\(^4\) The risk of pneumococcal infections in those with two or more at-risk conditions may be as high as the risk for those with a recognised high-risk condition.\(^82\),\(^83\),\(^84\)

Recommendations

PCV13 and 23PPV are recommended but not funded for the following individuals:

- immune-competent adults (aged 18 years and older) at increased risk of pneumococcal disease or its complications because of chronic illness (eg, chronic heart, renal, liver or pulmonary disease, diabetes or alcohol dependency)
- adults with cerebrospinal fluid leak
- immunocompromised adults at increased risk of pneumococcal disease (eg, those with nephrotic syndrome, multiple myeloma, lymphoma and Hodgkin’s disease)
- individuals of any age who have had one episode of IPD
- smokers.
For those individuals who choose to purchase PCV13 and 23PPV vaccines, providers may follow the age-appropriate schedules in Table 16.4 and Table 16.5.

**Adults aged 65 years and older with no other risk factors**

Give one dose of PCV13 followed at least eight weeks later with 23PPV (not funded).

### 16.5.5 Pregnancy and breastfeeding

Pneumococcal vaccines are not routinely recommended for pregnant women.

Women of childbearing age who are eligible for funded PCV13 and 23PPV should be vaccinated before a planned pregnancy or as soon as possible after delivery (see Table 16.5). Administration of these vaccines in pregnancy is unlikely to result in serious adverse effects and may be considered in individuals at the very high risk of IPD who were not vaccinated prior to pregnancy.85

PCV13 and 23PPV may be given to breastfeeding women.85

### 16.6 Contraindications and precautions

See section 2.1.3 for pre-vaccination screening guidelines and section 2.1.4 for general contraindications for all vaccines.

#### 16.6.1 Contraindications

There are no specific contraindications to pneumococcal polysaccharide or conjugate vaccines apart from a severe reaction to a previous dose or known hypersensitivity to any components of either vaccine.

#### 16.6.2 Precautions

Systemic reactions (chills, rash and myalgia) may occur when PCV13 and influenza vaccine are administered at the same time. PCV13 has been associated with a slightly higher risk of fever over 39°C and febrile convulsions when co-administered with inactivated influenza vaccine in infants and young children, compared to when administered separately.86 Febrile convulsion history is not a contraindication to PCV13 immunisation. If indicated, PCV13 and influenza vaccines may be given to a child aged under 5 years at the same visit.85 Parents/guardians should be informed of the small
risk of febrile convulsions, and separation of vaccines by two days can be offered. If the child has a history of febrile convulsions, separation of the vaccines is recommended.

23PPV should not be given to children aged under 2 years due to the reduced immune response associated with polysaccharide vaccines (see section 1.4.3).

16.7 Potential responses and AEFIs

16.7.1 Pneumococcal conjugate vaccines

Pneumococcal conjugate vaccines have excellent safety profiles. A 2016 systematic review found that pneumococcal conjugate vaccines are considered safe for use in children, and serious adverse events are detected very rarely by post-marketing surveillance.87

PCV10

Pooled evaluation of data derived from several clinical trials found PCV10 to be very well tolerated and safe with a similar safety profile to other PCVs.87 After primary immunisation of infants, mild to moderate irritability and injection-site redness were most commonly reported, occurring after 55 percent and 41 percent of all doses, respectively. Fever occurred in 30–35 percent of children, regardless of the dose. Injection-site pain increased with age, reported by more than 39 percent of younger children and 58 percent of the older subjects. Severe adverse events were exceptionally rare.

When PCV10 was co-administered with DTaP-containing vaccines, fever of 38°C or higher was reported after about one-third of primary or booster vaccine doses.88 These are similar results to those seen following co-administration of PCV7 and DTaP-containing vaccines.88

PCV13

The most commonly reported adverse reactions are injection-site reactions, fever, irritability, decreased appetite and increased or decreased sleep.89 An increase in injection-site reactions was reported in children older than 12 months compared to rates observed in infants during the primary series with PCV13.

No serious adverse events have been identified in adults or children, associated with underlying disease or immunocompromise.90, 91, 92
16.7.2 Pneumococcal polysaccharide vaccine

Local discomfort, erythema and induration lasting a couple of days are potential responses. Local and systemic reactions, such as self-limiting mild fever, myalgia and decreased arm movement in injected limb, may occur after revaccination of adults, particularly when the second dose is given within five years of the first dose.

16.8 Public health measures

IPD is a notifiable condition, and if confirmed, the laboratory undertaking the testing must notify the local medical officer of health.

Local public health action is not expected in response to individual notifications of this disease. Passive surveillance for IPD and pneumococcal serotypes help to inform the immunisation schedule.

Antimicrobial prophylaxis is not indicated for close contacts of cases of IPD. For those at high risk of pneumococcal disease where response to vaccination may be poor, antimicrobial prophylaxis may be indicated. Discuss with an appropriate specialist.


16.9 Variations from the vaccine data sheets

The PCV10 (Synflorix) vaccine data sheet recommends that infants and children who receive a first dose of PCV10 complete the full vaccination course with PCV10. The Ministry of Health recommends that those who started with PCV10 may complete with PCV13 if they are subsequently diagnosed with a PCV13-eligible condition (see section 16.5).

The PCV13 (Prevenar 13) data sheet states that there is no data on the interchangeability of PCV13 with other pneumococcal conjugate vaccines containing a protein carrier different from CRM197. The Ministry of Health recommends that those who started with PCV13 may complete with PCV10 (see section 16.5).

The 23PPV (Pneumovax 23) data sheet states that 23PPV and the herpes zoster vaccine (Zostavax) should not be given concurrently. The Ministry of Health recommends that 23PPV and the herpes zoster vaccine may be given concurrently (see section 23.4.4).
References


50. de Gier C, Granland CM, Pickering JL, et al. PCV7- and PCV10-vaccinated otitis-prone children in New Zealand have similar pneumococcal and *Haemophilus influenzae* densities in their nasopharynx and middle-ear. *Vaccines (Basel)*, 2019. 7(1).


78. Pina LM, Bassily E, Machmer A, et al. Safety and immunogenicity of a quadrivalent meningococcal polysaccharide diphtheria toxoid conjugate vaccine in infants and...


