

16 Pneumococcal Disease

16.1 Introduction

Streptococcus pneumoniae (pneumococcus) is a lance shaped gram-positive diplococcus. It is ubiquitous, with many asymptomatic individuals carrying the organism in the upper respiratory tract. There are some 90 identifiable serotypes of *S. pneumoniae*. Some more commonly affect children, while others are of greater significance in adults.

16.2 The illness

Transmission of the pneumococcus is from person to person, usually by droplet contact. The pneumococcus is the most common bacterial cause of otitis media in children and a frequent cause of sinusitis and pneumonia in all age groups. It also gives rise to meningitis and bacteraemia, especially in the very young, and is often the cause of bacteraemia with no obvious primary site of infection. The pneumococcus may also cause endocarditis, and, less commonly, sites such as joints, the peritoneal cavity and the fallopian tubes are affected. The incubation period of *S. pneumoniae* infection is variable but may be as short as one to three days. Illness usually occurs within one month of acquiring a new serotype in the upper respiratory tract. Illness does not usually result in prolonged carriage of the organism.

16.3 Epidemiology

Pneumococcal disease occurs throughout the year, but is more common in the autumn and winter months.¹ The risk of disease is much higher in infants and elderly people, and more frequent in individuals with predisposing conditions such as viral upper respiratory tract infections, or underlying conditions such as immune deficiency states. Mortality is highest in patients with underlying conditions, where infection may lead to meningitis or bacteraemia. These conditions include congenital or acquired immune deficiency, splenic dysfunction or asplenia (see section 1.8), sickle cell anaemia, Hodgkin's disease, human immunodeficiency virus (HIV) infection, cochlear implants, or following organ transplantation. Other conditions that increase the risk of pneumococcal infection include diabetes mellitus, congestive heart failure, chronic pulmonary disease and renal failure. Patients with cerebrospinal fluid (CSF) leakage due to a fracture at the base of the skull or following a neurosurgical procedure are at risk of recurrent pneumococcal meningitis.

The World Health Organization (WHO) estimates² that pneumococcus causes over one million deaths per year, mostly in children under five years of age in non-industrialised countries. In industrialised countries it causes an estimated 100 cases of pneumonia, 15–19 cases of febrile bacteraemia and 1–2 cases of meningitis per 100,000 people per year. Even in industrialised countries the mortality rate from

bacteraemic pneumococcal pneumonia averages 10–20 percent, and may exceed 50 percent in the high risk groups.³ Many studies have identified pneumococcus as the commonest cause of community acquired pneumonia⁴, in adults causing between 30 and 50 percent of all cases. Many cases of pneumonia that do not have the causative organism identified are likely to be pneumococcal. *S. pneumoniae* is the major bacterial cause of otitis media in children, accounting for 30–60 percent of culture positive episodes.⁵

New Zealand epidemiology

An analysis of hospitalisation data from 1986 to 1996⁶ found that pneumonia is an important illness in the first year of life, with high rates for children up to five years of age. After this the incidence declines over the first decade of life and remains at low levels until the age of 50, then starts rising steeply from 65 years of age. The hospitalisation data also shows that only 18 percent of the 8995 hospitalisations with pneumonia in 1995 had a cause identified, with pneumococcal pneumonia the most commonly coded organism in 734 (8 percent) of hospitalisations. This may underestimate the proportion of cases of pneumonia caused by *S. pneumoniae* as the organism is not identified in all cases, and not all are coded accurately where the organism is found.

A population based Auckland review of invasive pneumococcal disease (IPD) in children from 1984 to 1992 found an average annual incidence of 22 per 100,000 for children under 15 years, 56 per 100,000 in children under five years and 110 per 100,000 in children under two years.⁷ The rates were higher in Māori and Pacific children. The rates of invasive disease for Māori and Pacific children under 15 years were 28 per 100,000 and 49 per 100,000, and the rate was especially high in Pacific children under two years of age with a rate of 215 per 100,000. Rates of pneumococcal meningitis in all children under the age of two years was 23 per 100,000, and was 46 per 100,000 in Pacific children.

Further data from Auckland prospective surveillance during 2000/01 found the rate of invasive disease in all children under the age of two years was 191 per 100,000.⁸ For Māori children the rate was 217 per 100,000 and for Pacific 296 per 100,000. The rate of pneumococcal meningitis in children under the age of two years in Auckland remains high with a rate of 30 per 100,000 in all children, and rates of 43 per 100,000 and 49 per 100,000 in Māori and Pacific children. Lower rates for all New Zealand of 80 per 100,000 are likely to reflect less than complete referral of isolates in a passive surveillance system, and different rates of disease through the country.

More recent information comes from isolates from invasive disease, which are serogrouped and serotyped at the Institute of Environmental Science and Research (ESR) reference laboratory. The most common serogroups/serotypes in 2003/04 were 14, 9, 19, 4 and 23F. Table 16.1 below shows the proportion of invasive pneumococcal isolates that would be covered by either a seven-valent conjugate vaccine or a 23-valent polysaccharide vaccine at different ages. Note that although

the table gives the percentage of isolates covered by the 23-valent polysaccharide vaccine in children under five years, this vaccine is not effective in children under the age of two years when disease rates are highest. Although not all isolates from invasive disease are sent for reference testing, these results do provide an assessment of the burden of severe disease caused by *S. pneumoniae* in New Zealand and the likely benefit from vaccines directed against specific serogroups/serotypes.

Table 16.1: Number of isolates of invasive pneumococcal disease, and serotypes covered by a vaccine, by age

Year	Number of isolates from children < 5 years	Percent covered by PCV7 and 23PPV vaccines:		Number of isolates from children 5–15 years	Percent covered by 23PPV vaccine	Number of isolates from adults 15+	Percentage covered by 23PPV vaccine
		PCV7	23PPV				
2003	176	77%	95%	21	81%	325	95%
2004	161	79%	95%	20	95%	363	95%

Key: PCV7 = pneumococcal conjugate vaccine; 23PPV = pneumococcal polysaccharide vaccine

In New Zealand, as in other countries, there has been concern at the increase in the prevalence of antimicrobial resistance in *S. pneumoniae*. Antibiotic resistance data is collected and collated by ESR,⁹ and the antibiotic resistance of New Zealand isolates of *S. pneumoniae* is given in Table 16.2.

Table 16.2: Increase in antibiotic resistance of *Streptococcus pneumoniae* disease isolates, 1988–2004

Year	1988–90	1997–99	2000	2004
Invasive isolates				
% resistance to:				
Penicillin	1	15	16.6	16.4
Cefotaxime	0.8	4.1	7.5	12.1
Non-invasive isolates				
% resistance to:				
Penicillin	1.8	19	25.7	27.6
Tetracycline	5.6	11.2	15.5	18.9

When the *S. pneumoniae* isolates from 2004 were analysed by serotype and by their resistance pattern, it was found that 98 percent of penicillin resistant serotypes would be covered by the serotypes of the seven-valent vaccine and 100 percent would be covered by the 23-valent vaccine. Similarly, 94 percent of the serotypes

resistant to third generation cephalosporins would be covered by serotypes in the seven-valent vaccine and 100 percent by the 23-valent vaccine.¹⁰ This suggests that if pneumococcal vaccines were more widely used in New Zealand, disease caused by resistant isolates would be reduced.

In a study of adults with community acquired pneumonia admitted to Christchurch and Waikato Hospitals in 1999/2000,¹¹ the pneumonia rate among Māori was 3.03 times higher than that among non-Māori. The age specific rates were significantly higher among Māori for each 10-year age band from 45 to 74 years, and the mean age of Māori who were admitted to hospital was lower at 50 years, compared with the mean age of non-Māori of 66 years. Overall, 58 percent of the participants in the study had a comorbidity such as chronic obstructive pulmonary disease, diabetes, heart failure or asthma, and 21 percent were smokers. The Māori participants were more likely to have a comorbid condition (63 percent compared with 57 percent in non-Māori), although the difference was not significant, and were more likely to be smokers (35 percent Māori compared with 19 percent of non-Māori). Both smoking and having a comorbid illness are known to be risk factors for pneumococcal disease.

16.4 Vaccines

There are two types of vaccine available against *S. pneumoniae*: the 23-valent polysaccharide vaccine licensed for adults and children from two years of age, and the newer seven-valent protein conjugate vaccine (Prevenar®) licensed for use in children aged six weeks to nine years.

From 2006 the pneumococcal conjugate vaccine and pneumococcal polysaccharide vaccine will be fully funded for a group of children at special risk of the disease (see section 16.5A); and the pneumococcal polysaccharide vaccine will be funded for individuals with asplenia and pre- and post-splenectomy (see section 16.5B).

16.4A Seven-valent conjugate vaccine (PCV7)

A seven-valent pneumococcal polysaccharide protein conjugate vaccine (PCV7, Prevenar®, Wyeth Lederle) is effective in infants and young children against *S. pneumoniae* and is licensed in New Zealand for infants and children aged six weeks to nine years.

The pneumococcal polysaccharide is conjugated to a carrier protein, as in the *Haemophilus influenzae* type b vaccines, and induces increased production of antibodies, immunological memory and maturation of the antibody response. The resulting antibodies have high avidity in contrast to the poor antibody response when polysaccharide vaccine alone is given. Each candidate polysaccharide is coupled individually to the protein, and this limits the number of serotypes covered. The seven-valent protein conjugate vaccine contains the saccharides of the capsular antigen of *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F and 23F individually

conjugated to diphtheria CRM₁₉₇ protein, a non-toxic variant of diphtheria toxin. These serotypes caused 88 percent of invasive disease in children under the age of five years in 2002.¹²

One dose (0.5 mL) contains 2 µg of saccharide for serotypes 4, 9V, 14, 18C, 19F and 23F, and 4 µg of serotype 6B per dose (16 µg total saccharide) conjugated to the CRM₁₉₇ carrier protein and adsorbed on aluminium phosphate (0.5 mg), and is administered intramuscularly. (See section 2.3 for needle sites and sizes.)

PCV7 was recommended for the infant schedule in the United States (US) in February 2000 for all children from two to 23 months of age, and for children from 24 to 59 months of age who are at increased risk of pneumococcal disease.¹³ Other countries are now including pneumococcal conjugate vaccine on their infant immunisation schedule, including Australia and the Scandinavian countries.

Efficacy of the seven-valent conjugate vaccine

In a large controlled trial among infants attending the Northern California Kaiser Permanente (NCKP) medical centres in the US,¹⁴ PCV7 had a 97.4 percent efficacy (95 percent confidence interval [CI]: 83–100 percent) against *S. pneumoniae* invasive disease in children who had completed a four-dose vaccine course at two, four, six and 12 to 15 months of age, and 85.7 percent efficacy (95 percent CI: 0–100 percent) in partially vaccinated children who had received one dose or more of vaccine against the seven vaccine serotypes.

It was also found that in children who had received one or more doses of PCV7 there were 11 percent fewer episodes of clinical pneumonia and a reduction of 33 percent of episodes of pneumonia confirmed by X-ray. Among children who had clinical pneumonia and X-ray evidence of consolidation (≥ 2.5 cm), the efficacy of PCV7 was estimated at 73 percent.¹⁵ In the same trial there was a 7 percent reduction overall in episodes of acute otitis media.

A further efficacy study¹⁶ with PCV7 against IPD in American Indian children showed a primary efficacy of 76.8 percent (95 percent CI: 9.4–95.1 percent), and the intention to treat analysis was 82.6 percent (95 percent CI: 21.4–96.1 percent). Importantly, there was no increase in disease from non-vaccine serotypes.

In the US further studies have been published examining the effect of introducing pneumococcal vaccine to the infant schedule. In one large study,¹⁷ the rate of IPD decreased after the vaccine was introduced (in early 2000) from 24.3 per 100,000 persons to 17.3 per 100,000 in 2001. The largest decrease was in children less than two years of age, where the disease rate decreased 69 percent in 2001 compared to the baseline. The rate of disease from vaccine serotypes decreased by 78 percent, and the rate of disease from vaccine related serotypes decreased by 50 percent. The rates of IPD also decreased in adults (unimmunised) by 32 percent in those aged 20–39 years, by 8 percent in those aged 40–64 years, and by 18 percent in those

aged 65 years and older. Disease from penicillin resistant strains decreased by 35 percent. Ongoing monitoring is in place to monitor both this decline in disease incidence and any shift to non-vaccine serotype disease.

Following the introduction of PCV7 into the infant immunisation schedule in Massachusetts,¹⁸ the rate of IPD in children under the age of five years declined by 69 percent: from 56.9 per 100,000 in 1990–2001 to 17.4 per 100,000 in 2001–03, in spite of some vaccine shortages. Infants under the age of one year had the highest rate of disease, at 36.5 per 100,000, a 7.8 fold risk compared with children older than one year. Immunised children who developed disease caused by one of the vaccine serotypes were more likely to have a comorbid disease, and the African-American and children of Hispanic descent in the study had a 2.3 and 1.9 fold greater incidence rate than whites.

The US and some European countries recommend three doses of PCV7 in the first year and a fourth dose in the second year of life. In contrast, the schedules in Sweden, Denmark, Norway and Italy, and in Finland from 2005, recommend primary vaccination with PCV7 at ages three and five months and a third dose at 12 months of age. The immunogenicity and tolerability of this regime was studied in Swedish children.¹⁹ The results suggest that a two-plus-one course of PCV7 may be sufficient, although follow up studies to assess ongoing efficacy are needed.

A study of Gambian children²⁰ has shown some evidence that children who are primed with two or three doses of a pneumococcal conjugate vaccine respond with a higher antibody response when the polysaccharide vaccine is given at age two years. This supports the use of a booster of polysaccharide vaccine.

Other conjugate pneumococcal vaccines, including a nine-valent vaccine, are being studied in clinical trials, and a significant effect on pneumonia was seen in the Gambia.²¹ In South Africa,²² a nine-valent pneumococcal conjugate vaccine was given at six, 10 and 14 weeks of age. Among children without HIV infection, the vaccine reduced the incidence of a first episode of invasive pneumococcal disease (caused by vaccine serotypes) by 83 percent (95 percent CI: 39–97 percent), and the efficacy among HIV infected children was 65 percent (95 percent CI: 24–86 percent). The vaccine also reduced the incidence of vaccine serotype and antibiotic resistant invasive pneumococcal disease among children both with and without HIV infection.

The South African study also reported the incidence of viruses associated with pneumonia.²³ The nine-valent vaccine prevented 31 percent (95 percent CI: 15–43 percent) of pneumonias associated with any of seven respiratory viruses, influenza A, respiratory syncytial virus, adenovirus and parainfluenza viruses types 1–3 in the hospitalised children. The results suggest that pneumococcus has a major role in the development of pneumonia associated with viruses, and that these viruses may contribute to the pathogenesis of bacterial pneumonia.

A study from Finland²⁴ suggested that boosting with polysaccharide vaccine at 12 months of age following priming doses of a conjugate vaccine in infancy was as effective as boosting with the conjugate vaccine in protection against acute otitis media. This raises the possibility of boosting with polysaccharide vaccine as a less costly option, though further studies are needed.

Administration with other vaccines

The pneumococcal conjugate vaccine PCV7 may be administered at the same time as other routine childhood vaccinations, in a separate syringe at a separate injection site.

16.4B Pneumococcal polysaccharide 23-valent vaccine (23PPV)

The polysaccharide vaccine (23PPV, PNEUMOVAX[®]23, MSD) is made from the purified capsular polysaccharide antigens of 23 serotypes of *S. pneumoniae*. It is available in New Zealand for adults and children from two years of age. PNEUMOVAX[®]23 includes the 23 serotypes responsible for about 90 percent or more of cases of invasive disease in industrialised countries: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F. The Auckland study of paediatric invasive disease²⁵ found that the 23-valent vaccine would cover 98 percent of serotypes, but because two-thirds of these children were under two years of age the vaccine would be of limited value. Cross reactivity may allow for protection against additional serotypes.

One dose (0.5 mL) contains 25 µg of each capsular polysaccharide antigen, dissolved in isotonic saline solution with phenol (0.25 percent) added as a preservative, and no adjuvant. The vaccine can be administered either intramuscularly or subcutaneously. (See section 2.3 for needle sites and sizes.)

Efficacy of the polysaccharide 23-valent vaccine

The assessment of the efficacy of pneumococcal vaccination depends on whether immune competent or immune compromised patients are compared, and whether the end point is pneumococcal pneumonia or bacteraemia.

Healthy adults

The early pneumococcal vaccine trials were performed in South African gold miners and US military recruits,^{26,27} and at least 90 percent of these healthy young adults responded to a single dose of vaccine. Results of a more recent trial with the 23-valent vaccine show that about 80 percent or more of young, healthy adults respond to the vaccine with type specific antibodies within two to three weeks.²⁸ A meta-analysis of trials with a total of over 21,000 participants confirmed that pneumococcal vaccine was effective in immunocompetent subjects under 65 years in preventing both all cause pneumonia, pneumococcal pneumonia and deaths and bacteraemias.²⁹ This meta-analysis failed to show any benefit for the elderly.

Children under the age of two years

Bacterial capsular polysaccharides induce antibodies primarily by T-cell independent mechanisms, which are not mature before two years of age, and so children less than two years of age respond poorly and inconsistently to the polysaccharide vaccine. Age specific immune responses also vary by serotype, and the response to some common paediatric pneumococcal serotypes (eg, 6A and 14) is decreased in children aged between two and five years of age.

Older people

Most healthy older people respond well to the vaccine, although there it is unclear how long the antibody response lasts. The consensus appears to be that most older people will require a second vaccination after five years.³⁰ In a large community based study³¹ of adults over the age of 65 years, the vaccine reduced the risk of pneumococcal bacteraemia (hazard ratio: 0.56; 95 percent CI: 0.33–0.93), there was no reduction in pneumonia. A meta-analysis confirmed that in observational studies there was a protective effect against bacteraemia, and a non-significant protective effect in the trial data. No benefit was demonstrated against pneumonia.³² A two-year retrospective cohort study of older people with chronic lung disease found that vaccination prevented 43 percent of pneumonia hospitalisations and 31 percent of deaths, resulting in both health and economic benefits.³³

Immune compromised people

Response to vaccination is generally less than normal in immune compromised individuals. Many will show no response, and antibody response in those who do respond often declines rapidly. Patients with advanced HIV disease are less likely to respond.³⁴ However, people with HIV are a high risk group for pneumococcal infection (the risk is 100 times greater than in non-HIV adults of a similar age³⁵), and it is felt that the risk of infection justifies vaccination. In a case control study of people with HIV infection, the vaccine was 70 percent effective against pneumonia.³⁶

Chronic conditions

The response to vaccination has been studied in patients with chronic cardiovascular and respiratory conditions, with diabetes, and in alcoholics. In these conditions most studies have reported adequate response to vaccination, although the response has been reduced in patients with chronic obstructive pulmonary disease.^{37,38}

Haematological neoplasm

Patients with Hodgkin's disease normally respond to vaccination if it is given prior to radiation or chemotherapy, but seldom respond after treatment is completed. The response to vaccination is poor in patients with multiple myeloma and almost non-existent in those with chronic lymphocytic leukaemia.³⁹

Other population studies

A 1999 meta-analysis that included 13 randomised or quasi-randomised controlled trials (RCTs) estimated that immunisation reduced invasive disease caused by the *S. pneumoniae* types in the vaccine by 83 percent, and invasive disease from all *S. pneumoniae* types by 73 percent, but had no effect on the other outcomes.⁴⁰ It has been argued that the failure of the controlled studies to show an effect was due to the studies being too small, and there being a lack of specificity and sensitivity in the diagnosis of pneumococcal pneumonia.

A Swedish RCT also failed to show an effect on preventing pneumonia in 691 non-immune compromised patients between 50 and 85 years of age who had received the vaccine and been treated as inpatients for community acquired pneumonia.⁴¹

The problems with the polysaccharide vaccine have been summarised as:⁴²

- reduced efficacy in high risk individuals
- uncertain efficacy against pneumonia
- only suitable for children two years of age and over (there is high pneumococcal disease burden in the first year of life).

Administration with other vaccines

The polysaccharide vaccine may be given with the influenza vaccine or the other childhood vaccines. If not given at the same time, there is no need for a minimum interval after any other vaccine.

16.5 Vaccine recommendations

Pneumococcal vaccine recommendations are given below and in the text.

Table 16.3: Individual recommendations for pneumococcal immunisation

Funded Vaccine* Recommendations		Not Funded but Recommended		
Splenectomy or functional asplenia	Children with high risk conditions (< 5 years)	Children with other risk conditions (<16 years)	Adults at higher risk (16 years)	Healthy children (<5 years)
Children (0–16 years) pre- or post-splenectomy or with functional asplenia	On immunosuppressive therapy or radiation therapy	Preterm infants, born at under 28 weeks' gestation	Adults over the age of 65 years	Particularly Māori and Pacific children
	Primary immune deficiencies	Pre-term infants with chronic lung disease discharged home on oxygen	Adults with chronic illness (eg, cardiac, renal or pulmonary disease, diabetes, alcoholism)	
Adults pre- or post-splenectomy	HIV	Cardiac disease with cyanosis or failure	CSF leaks, cochlear implants	All children attending early childhood services
	Renal failure or nephrotic syndrome	Bronchiectasis	Immune compromised (eg, nephrotic syndrome, myeloma, Hodgkin's disease or post-organ transplant)	
	Organ transplants	Insulin dependent diabetes	HIV infection	
	Cochlear implants or intracranial shunts	Down's syndrome	Previous pneumococcal invasive disease	
	With chronic CSF leaks	Children over age 5 years with a high risk condition		
	On corticosteroid therapy for more than 2 weeks, at daily dose of prednisone of 2 mg/kg or greater, or a total daily dosage of 20 mg or more			

* Vaccine administration is also funded

Key: CSF = cerebrospinal fluid

Table 16.4: Pneumococcal vaccine recommendations*

	Funded Vaccine Recommendations		Not Funded but Recommended		
	Pre- and post-splenectomy (all ages)	High risk children (< 5 years of age)	Children with other risk conditions (< 16 years)	Adults at higher risk (16 years)	Healthy children (< 5 years of age)
Children under the age of 5 years	PCV7** + 23PPV at age 2 years and 5 years	PCV7** + 23PPV at age 2 years and 5 years	PCV7** + 23PPV at age 2 years and 5 years		PCV7**
Children 5–9 years	PCV7 +23PPV		PCV7 +23PPV		
Older children (10–16 years)	23PPV		23PPV (note: some paediatricians may recommend a dose of PCV7 + 23PPV)	23PPV (note: some specialists may recommend for HIV infected people PCV7 + 23PPV)	
Adults (16 years and above)	23PPV			23PPV (note: some specialists may recommend for HIV infected people PCV7 + 23PPV)	

* See Table 16.5 for pneumococcal vaccine schedule.

** See age appropriate schedule (Table 16.5) for timing and dosage.

Key: PCV7 = pneumococcal conjugate vaccine; 23PPV = pneumococcal polysaccharide vaccine.

16.5A Seven-valent conjugate vaccine recommendations for children ⁴³

Pneumococcal conjugate vaccine (PCV7, Prevenar®) is not yet funded for all children and is not on the National Immunisation Schedule. However, a small number of doses of PCV7 have been purchased, so that from 2006 children with specific conditions that put them at greater risk of pneumococcal invasive disease may be offered vaccination.

Recommended and funded immunisation schedules for children at special risk

From 2006 pneumococcal conjugate vaccine (PCV7) and pneumococcal polysaccharide vaccine (23PPV) will be fully funded for a group of children at special risk of the disease. The vaccines are available on the recommendation of a paediatrician or other secondary care specialist, and will be delivered in primary care. A child in the risk group is eligible for the age appropriate vaccine schedule, and both the PCV7 and the 23PPV vaccine boosters are publicly funded (see Tables 16.5 and 16.6).

The PCV7 may be given at the same time as other vaccines on the National Immunisation Schedule.

Children of any age pre- or post-splenectomy or with functional asplenia

PCV7 and 23PPV, including boosters, are funded for those children aged six weeks to 16 years, pre- or post-splenectomy or with functional asplenia. Where possible the vaccine should be administered at least 14 days before splenectomy (see section 1.8). Use Table 16.5 below for the recommended vaccine schedules. Boosters of 23PPV are recommended five-yearly and are funded.

Table 16.5: Schedule for pneumococcal vaccines for adults pre- and post-splenectomy and children pre- and post-splenectomy or with functional asplenia

Age of child at start of course	Conjugate pneumococcal vaccine (PCV7)	Polysaccharide pneumococcal vaccine (23PPV)
6 weeks to 6 months	3 doses PCV7 at least 6–8 weeks apart, or at same time as the usual schedule; plus a 4th dose at age 15 months	One dose of 23PPV at age 2 years and a second dose at age 4–5 years Booster dose of 23PPV 5 yearly
7–11 months	2 doses of PCV7 at least 6–8 weeks apart; plus a 3rd dose at age 15 months	One dose of 23PPV at age 2 years and a second dose at age 4–5 years Booster dose of 23PPV 5 yearly
12–59 months	2 doses of PCV7 given at 6–8 weeks apart	One dose of 23PPV at age 2 years and a second dose at age 4–5 years Booster dose of 23PPV 5 yearly
5–9 years	One dose of PCV7	One dose of 23PPV 6–8 weeks after PCV7 Booster dose of 23 PPV 5 yearly
10–16 years	(A dose of PCV7 may be recommended for some children)	One dose of 23PPV Booster dose of 23PPV 5 yearly
Adults >16 years		One dose of 23PPV Booster dose of 23PPV 5 yearly

Note that for these individuals the quadrivalent meningococcal vaccine (ACYW135) and Hib vaccine are now publicly funded (vaccine and administration), and the meningococcal B vaccine MeNZB™ is publicly funded while the vaccine is available in New Zealand (see section 1.8 and individual vaccine chapters).

Children under the age of five years with specific risk conditions

Pneumococcal conjugate and polysaccharide vaccines are funded for the following children aged under five years:

- on immunosuppressive therapy or radiation therapy, when there is expected to be sufficient immune response
- with primary immune deficiencies
- with HIV infection
- with renal failure, or nephrotic syndrome
- immune suppressed following organ transplantation
- with cochlear implants or intracranial shunts
- with chronic cerebrospinal fluid leaks
- receiving corticosteroid therapy for more than two weeks, 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.

The pneumococcal vaccine schedules recommended for this group of children at higher risk of pneumococcal disease are shown in Table 16.6. These schedules are for children who have not previously received any pneumococcal vaccine.

Some children in these groups may have received a previous dose of a pneumococcal vaccine. For recommendations for catch up schedules for these children, see Appendix 2.

Table 16.6: Schedule for pneumococcal vaccines for children at higher risk of pneumococcal disease with no prior history of pneumococcal vaccines

Age of child at start of course	Conjugate pneumococcal vaccine (PCV7)	Polysaccharide pneumococcal vaccine (23PPV)
6 weeks to 6 months	3 doses PCV7 at least 6–8 weeks apart, or at same time as the usual schedule; plus a 4th dose at age 15 months	One dose of 23PPV at age 2 years and a second dose at age 4–5 years
7–11 months	2 doses of PCV7 at least 6–8 weeks apart; plus a 3rd dose at age 15 months	One dose of 23PPV at age 2 years and a second dose at age 4–5 years
12–59 months	2 doses of PCV7 given at 6–8 weeks apart	One dose of 23PPV at age 2 years and a second dose at age 4–5 years
Older children up to the age of 16 years in high risk groups*	One dose of PCV7	One dose of 23PPV 6–8 weeks after PCV7

* not currently funded

Recommendations for other children at increased risk of invasive pneumococcal disease (not funded)

Pneumococcal vaccine is recommended, but not yet funded, for the following children at increased risk of pneumococcal disease:

- preterm infants, born at under 28 weeks' gestation
- premature infants with chronic lung disease who are discharged home on domiciliary oxygen.
- children with cardiac disease associated with cyanosis or cardiac failure
- bronchiectasis
- insulin dependent diabetes
- Down's syndrome.

The vaccine programme will be extended when funds are available, and practitioners will be informed of any changes. The schedules in Table 16.6 should be used for these children.

Recommendations for healthy children not in the risk groups (not funded)

Māori and Pacific children have higher rates of pneumococcal disease than children of other ethnicities, and children attending early childhood services have also

been reported with higher rates of disease. The pneumococcal vaccine schedule for healthy children is detailed below. Pneumococcal vaccine is not funded except for children at special risk of disease, as in the special programme above. However, some parents may wish to pay for pneumococcal vaccine for their child. The vaccine may be given at the same time as the usual childhood immunisations.

The following schedule is for healthy children not at increased risk of pneumococcal disease.

Table 16.7: Schedule for pneumococcal vaccines for healthy children

Age of healthy child at start of course	Conjugate pneumococcal vaccine (PCV7) schedule
6 weeks to 6 months	3 doses PCV7 at least 6-8 weeks apart, or at the same time as the usual schedule; plus a booster 4th dose at age 12–15 months, at least 2 months after the primary series
7–11 months	2 doses of PCV7 at least 6–8 weeks apart; plus a third dose at age 12–15 months
12–23 months	2 doses of PCV7 given 6–8 weeks apart
24–59 months	One dose of PCV7

16.5B Pneumococcal polysaccharide 23-valent vaccine recommendations for children and adults

The polysaccharide vaccine is recommended for children two years of age and older, as below.

Funded programme for pneumococcal polysaccharide vaccine for adults pre- and post-splenectomy and children pre- and post-splenectomy or with functional asplenia

From 2006 pneumococcal polysaccharide 23-valent vaccine (23PPV, PNEUMOVAX®23) is funded (vaccine and administration) on the recommendation, or a prior recommendation, of a secondary care specialist (such as haematologist or infectious diseases physician) for:

- adults pre- and post-splenectomy – where possible the vaccine should be administered at least 14 days before splenectomy (see section 1.8 and 16.5)
- children and young people up to the age of 16 years pre- and post-splenectomy or with functional asplenia (see Table 16.5 above for recommendations for PCV7 and 23PPV)

Reimmunisation with pneumococcal polysaccharide vaccine for individuals with asplenia is recommended five-yearly. The booster doses are also funded.

Note that for these individuals, the quadrivalent meningococcal vaccine (ACYW135) and Hib vaccine are now publicly funded (vaccine and administration), and the meningococcal B vaccine (MeNZB™) is publicly funded while the vaccine is available in New Zealand (see section 1.8 and individual vaccine chapters).

Other recommendations for pneumococcal polysaccharide vaccine

Pneumococcal polysaccharide vaccine is recommended, but not publicly funded, for patients, at special risk, including:

- immune competent people at increased risk of pneumococcal disease or its complications because of chronic illness (eg, chronic cardiac, renal or pulmonary disease, diabetes, and alcoholism)
- people with chronic cerebrospinal fluid leaks
- immune compromised patients at increased risk of pneumococcal disease (eg, those with nephrotic syndrome, multiple myeloma, lymphoma and Hodgkin's disease, or those who are immune suppressed following organ transplantation)
- individuals with HIV infection, who are recommended to receive a dose of pneumococcal conjugate vaccine and a booster dose of the polysaccharide vaccine
- people who have had one episode of invasive pneumococcal disease
- people 65 years of age and over.

Reimmunisation/ booster doses

One time reimmunisation with polysaccharide vaccine should be considered after three to five years in children younger than 10 years of age when first immunised, and after five years in older children and adults belonging to particularly high risk groups, who frequently exhibit a poor immune response.⁴⁴ Examples of such high risk individuals include those with sickle cell anaemia, nephrotic syndrome and renal failure, and transplant recipients. Seek expert advice in such situations. Boosters are recommended five-yearly after a splenectomy.⁴⁵

Revaccination of immunocompetent individuals previously vaccinated with polysaccharide vaccine is not routinely recommended.

Special considerations

In patients with Hodgkin's disease or other malignant lymphomas, the vaccine should be given at least two weeks before any contemplated splenectomy (see section 1.8), and, if possible, before any significant chemotherapy or nodal irradiation. Similar considerations apply to patients undergoing organ transplantation. If a patient is immunised during chemotherapy, they should be reimmunised three months after the completion of chemotherapy.

Penicillin prophylaxis

Because of the relatively poor response to vaccination with pneumococcal vaccine in splenectomised children and individuals with nephrotic syndrome or sickle cell disease, it is recommended that such patients receive continuous penicillin prophylaxis in addition to pneumococcal vaccine (see section 1.8). The age at which prophylaxis can be discontinued must be decided empirically because no studies on this question have been carried out (see also section 16.8). Some experts continue prophylaxis throughout childhood and into adulthood for particularly high risk patients.

16.6 Expected responses and adverse events following immunisation (AEFI)

16.6A Seven-valent conjugate vaccine (PCV7)

Expected responses

Expected responses to PCV7 pneumococcal vaccine are generally mild and limited to local reactions of redness or swelling. There was no increase in reactogenicity through the primary series. In the NCKP vaccine trial⁴⁶ there was an increase in tenderness following the booster in 36 percent of children, and in 18.5 percent this affected limb movement.

This large US trial showed that local reactions to PCV7 were higher than local reactions to the diphtheria, tetanus and acellular pertussis vaccine (DTaP): around 10 percent of children had erythema at the site after PCV7 compared to 6.7 percent with erythema after DTaP. The rate of fever over 39°C in infants who received DTaP plus the second dose of PCV7 vaccine was 2.5 percent, compared with 0.8 percent of children who received a control vaccine.

Adverse events following immunisation

Rare events (≥ 0.01 percent and < 0.1 percent) included febrile seizures and hypotonic, hyporesponsive episode. Very rare events (< 0.01 percent) included urticaria, angioneurotic oedema, erythema multiforme, and hypersensitivity including anaphylaxis. For further information, see the manufacturer's data sheet.

Any severe or unexpected reactions should be reported to CARM, PO Box 913, Dunedin, using the prepaid postcard HP3442 (see section 2.4) or via online reporting at <http://carm.otago.ac.nz>. If the patient or parent/caregiver does not consent to being identified, the report should be made without personal identification.

16.6B Pneumococcal polysaccharide 23-valent vaccine (23PPV)

Pneumococcal polysaccharide vaccine is well tolerated. Expected responses following immunisation occur in small numbers of recipients (1–10 percent),⁴⁷ and consist primarily of local discomfort, erythema and induration lasting a couple of days. Side effects requiring a general practitioner consultation occur in approximately 8 per 1000 vaccinations, and more severe side effects in 1 per 100,000.⁴⁸

Revaccination with the current vaccine is not associated with an increase in systemic events.^{49,50} A recent study that compared rates in first time and repeat vaccination did find an increase in large (> 10 cm) local reactions (3 percent versus 11 percent), but no other differences. The reactions mostly did not cause limitation and lasted a few days. The reactions were associated with immune competence and high levels of antibody pre-immunisation. A large study compared hospitalisation rates after first or repeat vaccination and found no significant difference.⁵¹ Therefore, it appears that revaccination may be safely given, with a small increased risk of self limiting large local reactions.

Any severe or unexpected reactions should be reported to CARM, PO Box 913, Dunedin, using the prepaid postcard H3442 (see section 2.4) or via online reporting at <http://carm.otago.ac.nz>. If the patient or parent/caregiver does not consent to being identified, the report should be made without personal identification.

16.7 Contraindications to pneumococcal conjugate and polysaccharide vaccines

See section 1.9 for general contraindications for all vaccines. There are no specific contraindications to the polysaccharide or conjugate vaccines apart from a severe reaction to a previous dose or known hypersensitivity to any components of either vaccine.

Because the safety of pneumococcal polysaccharide vaccine has not been confirmed in pregnant women, deferral of immunisation is recommended unless the risk of infection is substantial.

16.8 Passive immunisation and prophylaxis

Intramuscular or intravenous immunoglobulin is recommended for the prevention of pneumococcal infection in individuals who have had recurrent pneumococcal infections and are unable to mount an immune response to vaccine because of congenital or acquired immune deficiency disease.

Antimicrobial prophylaxis with twice daily penicillin (co-trimoxazole or erythromycin for penicillin allergic people) should be considered for those likely to have a poor immune response to pneumococcal vaccine (see sections 1.8 and 16.5 for information about splenectomy).

References

- 1 Singh KP, Voolmann T, Lang SDR. 1992. Pneumococcal bacteraemia in South Auckland. *NZ Med J* 102: 394–5.
- 2 Pneumococcal vaccines: WHO position paper. 1999. *Wkly Epidemiol Rec* 74: 177–83.
- 3 Singh KP, Voolmann T, Lang SDR. 1992. Pneumococcal bacteraemia in South Auckland. *NZ Med J* 102: 394–5.
- 4 Klugman KP, Feldman C. 2001. *Streptococcus pneumoniae* respiratory tract infections. *Curr Opin Infect Dis* 14: 173–9.
- 5 Fedson DS, Musher DM, Eskola J. 1999. Pneumococcal vaccine. In: SA Plotkin, WA Orenstein (eds). *Vaccines* (3rd edition). Philadelphia: WB Saunders Company.
- 6 Mansoor O. 1999. Pneumococcal infections in New Zealand. *Vaccine* 17(Suppl 1): S122–3.
- 7 Voss L, Lennon D, Okasene-Gafa K, et al. 1994. Invasive pneumococcal disease in a pediatric population, Auckland, New Zealand. *Pediatr Infect Dis J* 13(10): 873–7.
- 8 Nua M, Lennon D, Martin D, et al. 2002. *Epidemiology of Invasive Pneumococcal disease in NZ children – Opportunities for Vaccine Prevention*. Paper presented at Paediatric Society of New Zealand meeting. Napier.
- 9 ESR. 2000. *Annual Surveillance Summary*. Report to the Ministry of Health, New Zealand.
- 10 Reported from laboratory data, ESR, 2005.
- 11 Chambers ST, Laing RTR, Murdoch DR, et al. 2005. *A prospective study of the incidence rates of community acquired pneumonia and pneumococcal pneumonia in Māori and Non-Māori*. In press.
- 12 ESR. 2003. Annual summaries 2002: Bacteriology, invasive infections. *Lablink* 10: 1–2.
- 13 US Centers for Disease Control and Prevention. 2000. Preventing pneumococcal disease among infants and young children: Recommendations of the Advisory Committee on Immunization Practices. *MMWR* 49(RR-9):1-29.
- 14 Black S, Shinefield H, Fireman B, et al. 2000. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. *Pediatr Infect Dis J* 19:187–95.
- 15 US Centers for Disease Control and Prevention. 2000. Preventing pneumococcal disease among infants and young children: recommendations of the Advisory Committee on Immunization Practices. *MMWR* 49(RR-9): 1-29
- 16 Whitney CG, Farley MM, Hadler J, et al. 2003. Decline in invasive pneumococcal disease after the introduction of protein polysaccharide conjugate vaccine. *N Engl J Med* 348: (18)1737–46.
- 17 O'Brien K, Moulton L, Reid R, et al. 2003. Efficacy and Safety of seven-valent conjugate pneumococcal vaccine in American Indian children: group randomised trial. *Lancet* 362: 355–61.
- 18 Hsu K, Pelton S, Karumuri S, et al. 2005. Population-based surveillance for childhood invasive pneumococcal disease in the era of conjugate vaccine. *Pediatr Infect Dis J* 24: 17–23.
- 19 Kayhty H, Åhman H, Eriksson K, et al. 2005. Immunogenicity and tolerability of a heptavalent pneumococcal vaccine administered at 3, 5 and 12 months of age. *Pediatr Infect Dis J* 24: 108-114.
- 20 Obaro SK, Huo Z, Banya WA, et al. 1997. A glycoprotein pneumococcal conjugate vaccine primes for antibody responses to a pneumococcal polysaccharide vaccine in Gambian children. *Pediatr Infect Dis J* 16(12): 1135–40.
- 21 Cutts F, Zaman SMA, Enwere G, et al for the Gambian Pneumococcal Trial Group. 2005. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. *Lancet* 365: 1139–46.

- 22 Klugman KP, Madhi SA, Huebner RE, et al. 2003. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. *N Engl J Med* 349: 1341–8.
- 23 Madhi SA, Klugman KP, Vaccine Trialist Group. 2004. A role for *Streptococcus pneumoniae* in virus-associated pneumonia. *Nature Medicine* 10(8): 811–13.
- 24 Kilpi T, Åhman H, Jokinen J, et al. 2003. Protective efficacy of a second pneumococcal conjugate vaccine against pneumococcal acute otitis media in infants and children: randomised controlled trial of a 7-valent pneumococcal polysaccharide-meningococcal outer membrane protein complex conjugate vaccine in 1666 children. *Clin Infect Dis* 31: 1155–64.
- 25 Voss L, Lennon D, Okasene-Gafa K, et al. 1994. Invasive pneumococcal disease in a pediatric population, Auckland, New Zealand. *Pediatr Infect Dis J* 13(10): 873–7.
- 26 Smit P, Oberholzer D, Hayden-Smith S, et al. 1977. Protective efficacy of pneumococcal polysaccharide vaccines. *JAMA* 238: 2613–16.
- 27 MacLeod CM, Hodges RG, Heidelberger M, et al. 1945. Prevention of pneumococcal pneumonia by immunisation with specific capsular polysaccharides. *J Exp Med* 82: 445–65.
- 28 Musher DM, Luchi M, Watson DA, et al. 1990. Pneumococcal polysaccharide vaccine in young adults and older bronchitics: determination of IgG responses by ELISA and the effect of adsorption of serum with non-type-specific cell wall polysaccharide. *J Infect Dis* 161: 728–35.
- 29 Moore RA, Wiffen PJ, Lipsky BA. 2000. Are the pneumococcal polysaccharide vaccines effective? Meta-analysis of the prospective trials. *BMC Family Practice* 1: 1.
- 30 Konradsen HB. 1995. Quantity and avidity of pneumococcal antibodies before and up to five years after pneumococcal vaccination of elderly persons. *Clin Infect Dis* 21: 616–20.
- 31 Jackson L, Neuzil KM, Yu O, et al. 2003. Effectiveness of pneumococcal polysaccharide vaccine in older adults. *NEJM*; 348: 174755
- 32 Mangtani P, Cutts F, Hall AJ. 2003. Efficacy of polysaccharide pneumococcal vaccine in adults in more developed countries: the state of the evidence. *Lancet Infect Dis*; 3: 71–8.
- 33 Nichol KL, Baken L, Wuorenma J, et al. 1999. The health and economic benefits associated with pneumococcal vaccination of elderly persons with chronic lung disease. *Arch Intern Med* 159: 2437–42.
- 34 Carson PJ, Schut RL, Simpson ML, et al. 1995. Antibody class and subclass responses to pneumococcal polysaccharides following immunization of human immunodeficiency virus-infected patients. *J Infect Dis* 172: 340–5.
- 35 Eskola J, Black S, Shinefield H. 2004. Pneumococcal vaccine. In: SA Plotkin, WA Orenstein (eds). *Vaccines* (4th edition). Philadelphia: WB Saunders Company.
- 36 Guerrero M, Kruger S, Saitoh A, et al. 1999. Pneumonia in HIV-infected patients: a case-control survey of factors involved in risk and prevention. *AIDS* 13: 1971–5.
- 37 Singh KP, Voolmann T, Lang SDR. 1992. Pneumococcal bacteraemia in South Auckland. *NZ Med J* 102: 394–5.
- 38 Eskola J, Black S, Shinefield H. 2004. Pneumococcal vaccine. In: SA Plotkin, WA Orenstein (eds). *Vaccines* (4th edition). Philadelphia: WB Saunders Company.
- 39 Carson PJ, Schut RL, Simpson ML, et al. 1995. Antibody class and subclass responses to pneumococcal polysaccharides following immunization of human immunodeficiency virus-infected patients. *J Infect Dis* 172: 340–5.
- 40 Hutchison BG, Oxman AD, Shannon HS, et al. 1999. Clinical effectiveness of pneumococcal vaccine: Meta-analysis. *Can Fam Physician* 45: 2381–93.

- 41 Ortvist A, Hedlund J, Burman LA, et al. 1998. Randomised trial of 23-valent pneumococcal capsular polysaccharide vaccine in prevention of pneumonia in middle-aged and elderly people. *Lancet* 351: 399–403.
- 42 Poland GA. 1999. The burden of pneumococcal disease: the role of conjugate vaccines. *Vaccine* 17(13-14): 1674–9.
- 43 US Centers for Disease Control and Prevention. 2000. Preventing pneumococcal disease among infants and young children: Recommendations of the Advisory Committee on Immunization Practices. *MMWR* 49 (RR-9): 1-35.
- 44 Torzill PJ. 1993. Pneumococcal vaccine: current status. *Aust NZ J Med* 23: 285–90.
- 45 Working Party of the British Committee for Standards in Haematology. 1996. Guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen. *BMJ* 312: 430–4.
- 46 Black S, Shinefield H, Fireman B, et al. 2000. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. *Pediatr Infect Dis J* 19: 187–95.
- 47 Bentley DW, Ita K, Moon D, et al. 1981. Pneumococcal vaccine in the institutional elderly: design of a non randomized trial and preliminary results. *Review of Infectious Diseases* (Suppl): 571.
- 48 Gable CB, Holzer SS, Englehart L, et al. 1990. Pneumococcal vaccine: efficacy and associated cost savings. *JAMA* 264: 2910–15.
- 49 Rodriguez R, Dyer PD. 1995. Safety of pneumococcal revaccination. *J Gen Intern Med* 10: 511–12.
- 50 Mufson MA, Hughey DF, Turner CE, et al. 1991. Revaccination with pneumococcal vaccine of elderly persons six years after primary vaccination. *Vaccine* 9: 403–7.
- 51 Snow R, Babish JD, McBean AM. 1995. Is there any connection between a second pneumonia shot and hospitalization among Medicare beneficiaries? *Public Health Rep* 110: 720–5.