

2012 Antigen Review for the New Zealand National Immunisation Schedule: Pneumococcal

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Executive summary

Streptococcus pneumoniae is a common cause of community-acquired pneumonia (CAP), bacterial meningitis, bacteraemia and otitis media (OM). Development of vaccines against *S. pneumoniae* began early in the 20th Century and the first vaccines were marketed in the 1940s. The development of conjugate vaccines was stimulated because of the poor immunogenicity of the polysaccharide vaccine in children under two years of age. Since the introduction of routine vaccination against pneumococcal disease significant herd immunity has been demonstrated by a clear reduction in invasive pneumococcal disease (IPD), in both vaccinated and community contacts. However, challenges for vaccine development and vaccine schedules have occurred with the increase of non-vaccine serotypes disease.

This review aims to evaluate the literature on vaccination against *S. pneumoniae* published from 2009 to 2012, since the writing of the New Zealand Immunisation Handbook 2011.

The recent New Zealand (NZ) epidemiology of IPD shows that there have been large reductions in the incidence of IPD caused by the vaccine serotypes since the introduction of 7-valent pneumococcal vaccine (PCV-7). However, alongside this, the incidence of IPD due to non-PCV-7 types has increased significantly in the population aged five years and over. The burden of IPD in New Zealand is now caused primarily by non-PCV-10 types, of which the most prevalent in 2011 were 19A, 3 and 22F. Although rates of serotype 19A are high, they have remained stable throughout the 2004-2011 period in the under-five age group. Serotype 3 is rare among children under five years of age. Ten-valent pneumococcal vaccine (PCV-10) has now been in use since late September 2011. As yet, there is no published data measuring the impact of PCV-10 on disease caused by the three additional serotypes (1, 5 and 7F) it covers, or any cross-protection it may provide against serotype 19A.

Overall, pneumococcal vaccines have demonstrated an excellent safety profile in all groups studied. There are no significant safety concerns with any of the vaccines. Both 13-valent pneumococcal vaccine (PCV-13) and PCV-10 have safety profiles similar to PCV-7 and are safely administered concomitantly with routine vaccines in infants and toddlers. PCV-13 appears safe in adults and the elderly. To date, no safety studies evaluating PCV-10 have included adults. Decades of safety data for have not identified safety concerns for the 23-valent pneumococcal vaccine (PPV-23). Local reactions are more common following subsequent doses and severe reactions have been reported, particularly with routine repeat doses.

A higher risk of febrile events has been associated with PCV-13 when co-administered with inactivated influenza vaccine in infants and children less than five years of age. However, the risk for severe febrile events following the co-administration of these vaccines is still very low.

Following clinical trials and its introduction into routine schedules, PCV-10 is associated with very high efficacy and effectiveness against IPD caused by vaccine serotypes and protection against clinical pneumonia in children. There is no data to support the effectiveness of PCV-10 in adults at this time. The replacement of vaccine serotypes with non-vaccine serotypes has the potential to erode the benefits of vaccination.

PCV-13 has been demonstrated to be highly immunogenic and effective in children against IPD, and immunogenic in adults aged over 50 years, including adults over 70 years. It is at least as immunogenic as PCV-7 in children and PPV-23 in adults, and performed well in clinical trials. Early data indicate a reduction in disease caused by PCV-13 serotypes following its introduction. There is no data yet on clinical efficacy. Priming adults with PCV-13 prior to any doses of PPV-23 vaccine seem well supported. However, more data is required to support its use in adult groups as well as the use of booster doses.

Effectiveness against acute otitis media (AOM) by conjugate vaccines is not fully established. PCV-7 has been shown to have some modest effect against AOM due to vaccine serotypes but no significant effect on all-cause AOM. PCV-11 (a precursor to PCV-10) was shown to have good effectiveness against AOM, but further studies will help clarify the effectiveness of PCV-10. There is little data to date on the effectiveness of PCV-13 against AOM, although, there is the potential for pneumococcal conjugate vaccines (PCV), particularly PCV-10, to reduce antibiotic usage in AOM.

The most recent analysis of the protective effect of PPV-23 in immunocompetent older adults indicates that PPV-23 is likely to be protective. Effectiveness in more fragile elderly is currently unsupported. However, immunogenicity data indicate that the elderly mount reasonable immune responses, particularly to the first dose. Diminished responses are seen in a repeat dose compared to a single dose. The use of a conjugate vaccine in these age groups may improve effectiveness; the results of studies are pending. To date, the data suggests that immune responses are blunted if PPV-23 is used prior to PCV vaccines. However, the use of PPV-13 prior to PPV-23 in a combination schedule provides significant immune responses.

There is very little evidence that immunosuppressed children in at risk groups mount responses to PPV-23. Immunosuppressed individuals do respond to PCV vaccines, however, responses are reduced and there is considerable heterogeneity in responses. There is no evidence to date that vaccinating in pregnancy will reduce neonatal infection.

Duration of protection is unclear for conjugates, and at least five to 10 years for PPV-23.

Age-specific questions reside primarily with the adult population. Efficacy data are still lacking in these groups, however, there is immunogenicity data that supports priming older adults and high risk groups with PCV-13 prior to using PPV-23. There is little evidence for use of PPV-23 in elderly. Effectiveness data for the use of PCV-13 in adults is anticipated in the coming years.

There is a question between the choice of PCV-10 or PCV-13 for the childhood schedule. Extrapolation from the current data suggests that PCV-13, instead of PCV-10, could reduce IPD by a 29% in children under two to four year olds and in other age groups by approximately 20%. These estimates do not take into account any potential cross-protection between serogroups. PCV-10 elicits superior cross-reactive antibodies against serotypes 6A and 19A as compared with PCV-7. The ability of these antibodies to protect against disease is not yet known. This data also does not take into account reductions in non-invasive pneumococcal disease, in particular non-bacteraemic pneumonia but also otitis media (OM).

While the current implementation strategy for NZ is the reduction in burden of IPD, a significant shift in the burden of OM as a result of the use of PCV-10 over PCV-13 would be important to consider in future cost-benefit analyses. Another consideration is the routine use of a single dose of PCV-13 in older adults either with or without a later dose of PPV-23.

There is literature to support either a 3+1 or a 2+1 schedule for infant and toddler immunisation with PCV. For adults, a schedule that uses PCV-13 as a priming dose prior to the use of PPV-23 is consistently supported. There is little data to support timing of booster doses for conjugate vaccines in adults. The use of PPV-23 does create potential for hyporesponsiveness to repeat doses.

Both PCV-10 and PCV-13 can be co-administered with a wide range of other vaccines. Primary courses for infants are suited to the NZ schedule at six weeks, three months and/or five months with a booster in the second year of life.

Internationally, there have been slightly different approaches to the use of pneumococcal vaccines. Overall, there is a move towards wide use of PCV-13 in place of first doses of PPV-23. The place and role of PPV-23 in high risk populations and for the elderly remains unclear; there is some positive immunogenicity data, but there is a lack of efficacy and effectiveness data. Also, questions remain around the use of both conjugate and polysaccharide vaccines in adults and high risk groups.

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Prepared as part of a Ministry of Health contract

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This review is one of a series of 18 antigen reviews presented in 15 individual reports.

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Abbreviations

ACIP	Advisory Committee on Immunisation Practices
AEFI	Adverse Event Following Immunisation
AOM	Acute otitis media
CAP	Community-acquired pneumonia
ESR	Institute of Environmental Science and Research (NZ)
GMC	Geometric mean concentration
GMT	Geometric mean titre
IPD	Invasive pneumococcal disease
NP	Nasopharyngeal
NPC	Nasopharyngeal carriage
NZ	New Zealand
OM	Otitis media
OPA	Opsonophagocytic activity
PCV	Pneumococcal conjugate vaccine
PCV-7	7-valent pneumococcal conjugate vaccine with serotypes 4, 6B, 9V, 14, 18C, 19F and 23F
PCV-10	10-valent pneumococcal conjugate vaccine with serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F
PCV-13	13-valent pneumococcal conjugate vaccine with serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F
PPV	Pneumococcal polysaccharide vaccine
PPV-23	23-valent pneumococcal polysaccharide vaccine with 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
RCT	Randomised controlled trials
SAE	Serious Adverse Event
UK	United Kingdom
US	United States
WHO	World Health Organization

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1. Background – pneumococcal disease and vaccination

Streptococcus pneumoniae is a Gram-positive diplococcus widely carried asymptotically in the upper respiratory tract. There are over 90 serotypes identified by the polysaccharide capsule that encloses the cell and contributes to virulence. *S. pneumoniae* is a common cause of community-acquired pneumonia, bacterial meningitis, bacteraemia and otitis media (OM). Development of vaccines against *S. pneumoniae* began early in the 20th Century and the first vaccines were marketed in the 1940s. Licensure of a 14-valent pneumococcal capsule polysaccharide vaccine occurred in the United States (US) in 1977 and a 23-valent polysaccharide vaccine followed in 1983.

The poor immunogenicity of the polysaccharide vaccine in children under two years of age stimulated the development of conjugate vaccines of which a seven-valent pneumococcal conjugate vaccine (PCV-7) was the first. The introduction of PCV-7 resulted in dramatic declines in disease due to vaccine types and demonstrated significant herd immunity.

Since the introduction of routine vaccination against pneumococcal disease, there has been an increase in the rates of disease caused by non-vaccine serotypes creating challenges for vaccine development.

The New Zealand (NZ) Immunisation Handbook 2011 contains a background summary of the data on this disease and associated vaccines in the NZ context. This review aims to evaluate the literature on vaccination against *S. pneumoniae* published from 2009 to 2012. During an edit of this review in 2014, reference updates were inserted where the data referenced had been published since 2013. A full review of data and vaccination schedules was not conducted.

2. Methodology for review

2.1 New Zealand Epidemiology

The NZ epidemiological information presented is based on national invasive pneumococcal disease (IPD) surveillance data to the end of 2011 (1). As PCV-7 was used for routine infant immunisation between June 2008 and late 2011, when it was replaced by PCV-10, any assessment of the impact in NZ of PCV on IPD caused by 'vaccine types' includes only PCV-7 serotypes (4, 6B, 9V, 14, 18C, 19F and 23F) and not the additional three PCV-10 serotypes (1, 5 and 7F).

2.2 Literature search strategy

The points below have formed the focus of the literature search:

- Safety
 - Of particular interest:
 - Safety of PCV-10 (Synflorix®) and PCV-13 (Prevenar® 13) in infants.
 - i. Anything new in safety over the past few years.
 - ii. Any differences in safety between them.
 - Safety of pneumococcal polysaccharide vaccine (PPV) and PCV-13 in older adults.
 - Effectiveness in disease control
 - Effect on invasive pneumococcal disease (IPD), pneumonia and otitis media (OM).
 - i. Particularly children.
 - ii. Adults.
 - iii. Differences between PCV-10 and PCV-13.
 - iv. Effect on nasopharyngeal carriage.
 - v. Indirect effects/herd immunity.
 - vi. Duration of protection.
 - Evidence of effectiveness of pneumococcal conjugate vaccine (PCV) on disease and carriage in older adults.
 - Update on PPV in adults.
 - Implementation issues (practicality of and possible impact on uptake).
 - Value of a catch-up/supplementary dose if a change from PCV-10 to PCV-13 is made in infant schedule.
- Differences that need to be considered for each age group, and groups with particular needs, for example, the variable severity of disease and immunisation concerns that differ with age.
 - High-risk groups – definition of which groups most likely to benefit and which vaccine/s.
- Different options for placement on the schedule, based on international findings and best practice.
 - 2+1 (and 3+0 as per Australia) vs. current 3+1, including dose intervals/timing, for routine immunisation of infants.
 - PPV schedule, including revaccination and how often, for older adults.
 - Possible PCV-13 schedule for older adults, or PCV-13 followed by PPV-23.
 - Schedules for high-risk children and younger adults.
- Different vaccine options for each disease and comparison between the options
 - Serotype coverage of PCV-10 vs. PCV-13 based on current disease epidemiology – most of the information will be based on up-to-date information on serotype distribution and serotype replacement from ESR's IPD surveillance.
 - Impact of PCV-10 on non-typeable H. influenzae disease and carriage.
 - PCV-10 versus PCV-13 – any differences in reduction in OM.
 - Cross-protection between the serotype 19F in PCV-10 and serotype 19A.
- Current international research and evidence around use of vaccines.
 - Consider this point is primarily covered in 1-6.

Other areas of special interest

- Consideration of the high-risk groups and whether the vaccine should be provided to them.
- Investigation of the implications for herd immunity.
- Investigation of strain shift and suitable vaccines.
- Investigation of whether the rate of strain 19A is sufficiently high that a change of vaccine is required.
- Duration of protection provided by vaccines.

2.2.1 Medline search terms and strategy

MeSH term: Pneumococcal Vaccines

2610

Limit to Humans, English, 2009 – current

872

NOT parent, physician, survey, interview, qualitative

818

NOT Costs and Cost analysis

746

MeSH term: Adverse Effects

214

Safety as keyword

68 (keep and view)

MeSH term: Effectiveness

84 (keep and view)

2.2.2 Cochrane Library search terms and strategy

Search term Pneumococcal Vaccin*

Limit to Cochrane Reviews, Other Reviews, Trials
2009-present

16 results (keep and view)

2.2.3 Scopus search terms and strategy

Pneumococcal AND Vaccin* Published 2011 – present

9921

Limit to: Medicine, humans, vaccination,
pneumococcus vaccine, journals

Exclude Letter, Short survey, Editorial and Erratum

670 (keep and view)

Reject social science articles. Delete duplicates

2.2.4 Grey literature

Conference abstracts were sought to include data that had not yet been published, particularly from the key infectious diseases conferences for 2011 and 2012 – European Society for Paediatric Infectious Diseases (ESPID), World Society for Paediatric Infectious Diseases (WSPID), and the International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD). A total of 34 conference abstracts and posters were accessed.

2.2.5 Additional searches

Where questions arose additional searches were undertaken to ensure there was no further available data. Where articles were missing they were accessed and added to the library. A further nine articles were accessed.

2.2.6 Final library

The final library includes 301 references. Where systematic reviews and/or meta-analysis were available, the preceding literature has been excluded from the review.

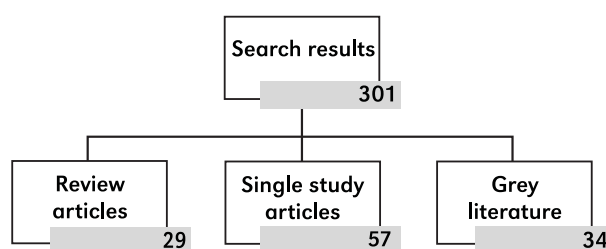


Figure 1. Flow of selection of articles for review

2.3 Participants/populations

The population for the universal programme are infants and children under two years of age. High risk groups cover all ages, and adult populations in this context are over 50 years of age.

High risk persons identified from the literature include:

- Children with immune deficiency, asplenia or dysfunction of the spleen, HIV, chemotherapy, systemic steroids > a month equivalent to > prednisone at 20mg per day (children under 20kg >1mg/kg/day).
- Chronic medical illness including bronchiectasis, cystic fibrosis, other respiratory diseases.
- Chronic heart disease.
- Chronic kidney disease, including nephritic syndrome, chronic renal failure and renal transplant.
- Chronic liver disease, including cirrhosis, biliary atresia, hepatitis.
- Diabetes requiring oral hypoglycaemic drugs.
- Cochlear implants.
- Indigenous background.
- Intracranial shunts.
- Cerebrospinal fluid leaks.
- Pre-term infants

2.4 Interventions

The interventions included are:

- PCV-10 in infants and young children as primary series or booster.
- PCV-13 in infants and young children as primary series or booster.
- PPV-23 in adults, including older adults.
- PCV and PPV in special groups at higher risk for disease.

The controls are placebo or another pneumococcal vaccine, usually PCV-7. Some studies have used an unrelated vaccine such as influenza vaccine. Figure 1 indicates the pneumococcal serotype covered by each vaccine.

2.4.1 Pneumococcal conjugate vaccine 10-valent (PCV-10)

PCV-10 (Synflorix®, GlaxoSmithKline) is a ten-valent polysaccharide-protein conjugate vaccine. Each dose contains 1µg each of pneumococcal polysaccharide serotypes 1, 5, 6B, 7F, 9V, 14 and 23F conjugated to Protein D derived from non-typeable *H. influenzae*, 3µg of serotype 4 conjugated to Protein D, 3µg of serotypes 18C conjugated to tetanus toxoid and 3µg of serotype 19F conjugated to diphtheria toxoid (CRM₁₉₇). Each dose contains aluminium phosphate adjuvant and 4.3mg of sodium chloride as a buffer with water for injection.

2.4.2 Pneumococcal conjugate vaccine 13-valent (PCV-13)

PCV-13 (Prevenar 13®, Wyeth Pharmaceuticals Inc.), a subsidiary of Pfizer Inc. contains polysaccharides of the capsular antigens of *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F, individually conjugated to a nontoxic diphtheria CRM₁₉₇ carrier protein. A 0.5mL PCV-13 dose contains approximately 2µg of polysaccharide from each of 12 serotypes and approximately 4µg of polysaccharide from serotype 6B; the total concentration of CRM₁₉₇ is approximately 34µg. The vaccine contains 0.125mg of aluminum as aluminum phosphate adjuvant and no thimerosal preservative.

2.4.3 Pneumococcal polysaccharide vaccine 23-valent (PPV-23)

PPV-23 (Pneumovax®23, Merck & Company, Inc.) is the 23-valent pneumococcal polysaccharide vaccine. Each dose contains 23 capsular polysaccharide antigens of *S. pneumoniae*: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F. One 0.5mL dose of PPV-23 contains 25µg of each polysaccharide in isotonic saline solution with 0.25% phenol as a preservative.

	1	2	3	4	5	6A	6B	7F	8	9N	9V	10A	11A	12F	14	15B	17F	18C	19A	19F	20	22F	23F	33F
PCV-7				Light blue			Light blue				Light blue				Light blue			Light blue		Light blue			Light blue	
PCV-10	Light blue			Light blue		Orange	Light blue	Light blue			Light blue				Light blue			Light blue	Orange	Light blue			Light blue	
PCV-13	Light blue		Light blue	Light blue		Light blue	Light blue	Light blue			Light blue				Light blue			Light blue		Light blue			Light blue	
PPV-23	Light blue	Light blue	Light blue	Light blue	Light blue		Light blue	Light blue	Light blue	Light blue	Light blue	Light blue	Light blue	Light blue	Light blue	Light blue	Light blue	Light blue	Light blue	Light blue	Light blue	Light blue	Light blue	Light blue

Light blue shading indicates protection

Orange shading indicates possible cross protection

Figure 2. Serotypes and coverage by vaccine

2.5 Study designs

The studies included in this update are meta-analysis, systematic reviews, reviews, randomised controlled trials, and observational studies using database matching. Conference abstracts have also been added.

3. Recent New Zealand epidemiology

According to the NZ Institute of Environmental Science and Research (ESR) surveillance data, since the introduction of PCV-7, as expected, there has been a strain shift, with reductions in the rates of IPD caused by PCV-7 types, almost to the point of elimination in the vaccine-eligible age group, with only three cases of IPD due to a PCV-7 type in under two year old infants in 2011. Conversely, there have been significant increases in the rates of IPD due to non-PCV-7 types in the population overall, and specifically, in the five to 64 and over 65 year age groups (see Table 1) (1).

Table 1. Increase in rates of culture-positive invasive pneumococcal disease due to non-PCV-7 serotypes between 2006/7 and 2011, by age group

Age group	Rate of IPD due to non-PCV-7 serotypes per 100 000 population		Percentage change between time periods	Significance of change (p value) ²
	2006/2007 (immediate pre-PCV years) ¹	2011		
<2 years	16.0	19.9	+24	0.428
2-4 years	5.3	5.3	0	1.000
5-64 years	2.5	4.8	+92	<0.001
≥65 years	12.0	25.7	+114	<0.001
All ages	4.2	8.0	+90	<0.001

¹ average rate across the 2 years 2006 and 2007; ² based on Fisher's exact test

Due to this strain shift following three to four years of infant PCV-7 immunisation, the serotypes causing the remaining burden of IPD in New Zealand have become the most relevant to any decisions about the most suitable PCV vaccine to use for infant immunisation. The number of IPD cases, proportion of IPD, and rate of IPD due to PCV-7, PCV-10, PCV-13 and non-PCV-13 serotypes in 2011 are shown in Table 2.

Based on this 2011 IPD data, and not taking into account any potential cross-protection between serogroups (i.e., between 19F and 19A and between 6B and 6A), then an additional 29% (8 of a total of 28 cases) of IPD in the <2 year age group would be covered by PCV-13 serotypes than are covered by PCV-10 serotypes. The extra coverage afforded by PCV-13 in the other age groups would be: 29% (5 of a total of 17 cases) in the two to four year old group, 20% (751 of a total of 260 cases) in the five to 64 year group, and 20% (46 of a total of 228 cases) in the ≥65 year group (Table 2).

However, it should be noted that even with the greater disease coverage that PCV-13 would afford, there is still a considerable proportion (36% over all age groups) of remaining IPD in New Zealand that is due to serotypes not covered by any of the currently available pneumococcal conjugate vaccines (see the *Non-PCV-13 serotypes* row in Table 2).

Table 2. Number, proportion and rates of culture-positive invasive pneumococcal disease due to PCV-7, PCV-10, PCV-13 and non-PCV-13 serotypes in 2011, by age group

IPD due to:	<2 years		2-4 years		5 - 64 years		≥65 years		Total	
	No (% ¹)	Rate ²	No (%)	Rate	No (%)	Rate	No (%)	Rate	No (%)	Rate
PCV-7 serotypes	3 (11)	2.4	7 (41)	3.7	91 (35)	2.6	77 (34)	13.1	178 (34)	4.0
PCV-10 serotypes	7 (25)	5.6	10 (59)	5.3	132 (51)	3.8	80 (35)	13.6	229 (43)	5.2
PCV-13 serotypes	15 (54)	11.9	15 (88)	8.0	183 (70)	5.2	126 (55)	21.5	339 (64)	7.7
Non-PCV-13 serotypes	13 (46)	10.3	2 (12)	1.1	77 (30)	2.2	102 (45)	17.4	194 (36)	4.4
Total	28	22.2	17	9.6	260	7.4	228	38.8	533	12.1

1. Percentage of all cases within the age group

2. Rate per 100,000 population

The most prevalent non-PCV-10 serotypes causing IPD in 2011 were types 19A, 3 and 22F. The first two (19A and 3) are PCV-13 serotypes and accounted for 21% (63 cases) and 13% (39), respectively, of the IPD cases due to a non-PCV-10 serotype in 2011. Both these serotypes are discussed in more detail in the next sections. Serotype 22F was the fifth most prevalent type in 2011 and accounted for 12% (38) of the IPD cases due to a non-PCV-10 serotype in 2011 - this serotype is not included in any of the currently available PCV vaccines.

3.1 Serotype 19A

Serotype 19A has been reported in several countries, including the United States, England, Wales, and Australia, to be the non-PCV-7 serotype that has increased the most, or one of the key serotypes involved in serotype replacement following the introduction of PCV-7 (2-4).

The serotype 19F conjugated polysaccharide in PCV-10 appears to induce antibody responses against serotype 19A, [Synflorix Data Sheet; Sep 2010 version 4.0] and possibly cross-protection against 19A disease, whereas the 19F conjugated polysaccharide in PCV-7 does not (5).

Increases in type 19A disease have been of special concern, since this serotype is often associated with antibiotic resistance. There have been recent reports of increasing rates of resistance among invasive serotype 19A isolates, associated with shifts in the genetic structure of the isolates and the expansion of particularly resistant clonal complexes (6).

In 2011, serotype 19A was the most prevalent serotype overall, among cases of IPD, and also among cases aged <two years, two to four years and ≥65 years. However, the rates of 19A disease in the <two year and two to four year age groups have remained fairly stable since the introduction of PCV-7. In contrast to the situation in the younger age groups, there have been significant increases in the rates of 19A disease in the five to 64 year and ≥65 year age groups (Table 3 and Table 4).

Table 3. Increase in rates of culture-positive invasive pneumococcal disease due to serotype 19A between 2006/7 and 2011, by age group

Age group	Rate of IPD due to serotype 19A per 100, 000 population		Percentage change between time periods	Significance of change (p value) ²
	2006/2007 (immediate pre-PCV years) ¹	2011		
<2 years	5.1	6.4	+25	0.642
2 - 4 years	2.6	2.7	+4	1.000
5 - 64 years	0.3	0.7	+133	0.003
≥65 years	1.5	4.1	+173	<0.001
All ages	0.7	1.4	+100	<0.001

1. Average rate across the 2 years 2006 and 2007;

2. Based on Fisher's exact test

While the increases in the rate of 19A IPD in the population over >five years of age are significant, this trend may be ameliorated by the change from PCV-7 to PCV-10 for infant immunisation in late 2011, given the potential that PCV-10 provides some cross-protection against 19A disease.

Invasive serotype 19A isolates in this country are not especially associated with resistance and there have been no significant changes in resistance among this type over the last 10 years.

Table 4. Serotype 19A invasive pneumococcal disease case numbers, proportions and rates per 100,000 population, by age group, 2004–2011

Year	<2 years			2 - 4 years			5 – 64 years			≥65 years			All ages		
	# Cases ^a	% ^b	Rate ^c	# Cases ^a	% ^b	Rate ^c	# Cases ^a	% ^b	Rate ^c	# Cases ^a	% ^b	Rate ^c	# Cases ^a	% ^b	Rate
2004	8	6.3	7.0	2	6.1	1.2	5	2.6	0.2	8	4.2	1.7	23	4.2	0.6
2005	6	5.3	5.2	2	5.1	1.2	10	5.6	0.3	9	5.5	1.8	27	5.5	0.7
2006	5	4.2	4.3	5	16.1	2.9	13	6.4	0.4	4	2.4	-	27	5.2	0.6
2007	7	6.0	5.8	4	10.0	2.3	7	3.3	0.2	12	6.5	2.3	30	5.4	0.7
2008	5	6.4	4.0	2	5.9	1.1	22	7.6	0.6	11	4.8	2.0	40	6.3	0.9
2009	8	14.5	6.3	4	10.5	2.2	16	4.7	0.5	9	3.9	1.6	37	5.6	0.9
2010	7	19.4	5.5	3	11.1	1.6	23	9.8	0.7	22	10.1	3.9	55	10.7	1.3
2011	8	28.6	6.4	5	29.4	2.7	26	10.0	0.7	24	10.5	4.1	63	11.8	1.4

a. Number of cases due to serotype 19A.

b. Percentage of cases within the age group due to serotype 19A.

c. Rate per 100 000 population for IPD due to serotype 19A; rate not calculated where there are <5 cases.

3.2 Serotype 3

In 2011, serotype 3 was the third most common serotype among all IPD cases, after serotypes 19A and 4, and equal with serotype 19F. As noted above, after 19A, serotype 3 was the second most common non-PCV-10 type in 2011. However, unlike the situation with serotype 19A, none of the serotype 3 IPD cases in 2011 (and very few in previous years) were in cases <five years old. Also, in contrast to trends with type 19A disease, the rates of IPD due to serotype 3 have not increased since the introduction of PCV-7 infant immunisation (Table 5).

Table 5. Serotype 3 invasive pneumococcal disease case numbers, proportions and rates per 100,000 population, by age group, 2004–2011

Year	<2 years			2 - 4 years			5 – 64 years			≥65 years			All ages		
	# Cases ^a	% ^b	Rate ^c	# Cases ^a	% ^b	Rate ^c	# Cases ^a	% ^b	Rate ^c	# Cases ^a	% ^b	Rate ^c	# Cases ^a	% ^b	Rate ^c
2004	1	0.8	-	1	3.0	-	15	7.8	0.5	16	8.4	3.3	33	6.1	0.8
2005	0	-	-	0	-	-	10	5.6	0.3	10	6.1	2.0	20	4.1	0.5
2006	0	-	-	0	-	-	9	4.5	0.4	13	7.7	2.5	22	4.2	0.5
2007	2	1.7	-	0	-	-	8	3.8	0.2	12	6.5	2.3	22	4.0	0.5
2008	0	-	-	0	-	-	16	5.5	0.5	12	5.3	2.2	28	4.4	0.7
2009	3	5.5	-	0	-	-	12	3.5	0.3	11	4.8	2.0	26	3.9	0.6
2010	2	5.6	-	2	7.4	-	9	3.8	0.3	8	3.7	1.4	21	4.1	0.5
2011	0	-	-	0	-	-	22	8.5	0.6	17	7.5	2.9	39	7.3	0.9

a. Number of cases due to serotype 3.

b. Percentage of cases within the age group due to serotype 3.

c. Rate per 100 000 population for IPD due to serotype 3; rate not calculated where there are <5 cases.

3.3 Otitis media in NZ

In NZ, OM is the most common illness requiring medical attention in the under three year olds. A recent NZ study, conducted between May and October 2011, described middle-ear and nasopharyngeal samples from 325 children aged under three years, which were collected at three major NZ centres during procedures for ventilation tube insertion. Nasopharyngeal samples were age-matched to 138 children with no history of ear disease. Most of the study cohort had been vaccinated with PCV-7 (97%). Twenty-four percent of middle-ear specimens were culture positive for *H. influenzae*, and less than 10% of the samples were culture positive for *S. pneumoniae* and *Moraxella catarhalis*. The most common organisms present in the nasopharyngeal samples in both groups were *H. influenzae* and *M. catarhalis*; *H. influenzae* in 62% of cases and 43% of the comparison group, for *M. catarhalis* 58% and 49%; *S. pneumoniae* 43% and 29%, respectively. Serotyping of cultured *S. pneumoniae*, from either nasopharyngeal or middle-ear samples, demonstrated that 19F, 19A and 11A serotypes were the most common. The study concluded that in established ear diseases requiring surgical intervention, *H. influenzae* is a dominant pathogen in both the nasopharynx and the middle-ear (7).

3.4 Summary of NZ epidemiology

The introduction of PCV-7 has been associated with large reductions in IPD caused by the vaccine types. Conversely, there have been increases in rates of IPD due to non-PCV-7 types in all age groups, except two to four year olds, with the largest increases noted in the older age groups. The most prevalent non-PCV-10 serotypes, causing IPD in 2011, were types 19A, 3 and 22F. The first two (19A and 3) are PCV-13 serotypes and accounted for 21% (63) and 13% (39) of the IPD cases, respectively, due to a non-PCV-10 serotype in 2011.

Although rates of serotype 19A are high, they have remained stable throughout the period 2004-2011 in the under-five age group. Serotype 3 is rare among children under five years of age.

PCV-10 has now been in use since late September 2011. As of early 2013, no data is available to measure the impact of PCV-10 on disease caused by the three additional serotypes (1, 5 and 7F) it covers.

Based on 2011 IPD data, and not taking into account any potential cross-protection between serogroups, 29% more IPD cases in the under two year age group would be covered by PCV-13 serotypes than are covered by PCV-10 serotypes. The extra coverage afforded by PCV-13 in the other age groups would be 29% in the two to four year group, and 20% in both the five to 64 year and ≥ 65 year age groups.

4. Safety

4.1 Objective

The objective of this section is to review the most recent safety data for currently licensed pneumococcal vaccines. The focus is on PCV-10 and PCV-13 with some consideration for any recent updates to PPV-23. Only Adverse Events Following Immunisation (AEFI) considered subsequent to the pivotal clinical efficacy trials are reviewed here.

4.2 Outcomes

Outcomes of vaccine safety include adverse events following immunisation (AEFI) and serious adverse events (SAE). Excluded is reactogenicity (injection site reactions and minor systemic reactions) as this is considered thoroughly in the pivotal licensure studies (8).

4.3 Review

4.3.1 Safety of PCV-10

4.3.1.1 Infants and toddlers

The safety of PCV-10 was initially evaluated in five pivotal studies conducted between 2005 and 2008, in which, it was co-administered with a variety of DTaP-based and meningococcal vaccines. These studies included 4004 participants receiving either PCV-7 or PCV-10 for whom safety data was available. PCV-10 was demonstrated to have a safety profile similar to PCV-7 when used in both primary courses and as a booster with other paediatric vaccines (8).

Subsequently, there have been a number of studies evaluating PCV-10 in a variety of populations co-administered with other infant vaccines with no safety concerns detected (9-15).

4.3.1.2 Preterm infants

A study of 286 Greek and Spanish infants born at 27-30 weeks, 31-36 weeks and at term were given PCV-10 concomitantly with routine primary vaccination and as a booster. Fever and other solicited events were similar across all three groups and consistent with findings from other studies in term infants. Local reactions were lower in the pre-term infants (16).

4.3.1.3 Adults

There is no safety data available on the use of PCV-10 in adults.

4.3.2 Safety of PCV-13

In the pivotal trials for PCV-13, safety data for over 4700 infants receiving at least one dose and 354 older infants and young children were analysed and no clinically relevant differences were identified relative to PCV-7 (17). Post-licensure safety of PCV-13 has been assessed against PCV-7 for which there is global surveillance of over 195 million doses with no concerns identified.

4.3.2.1 Infants and toddlers

A review of the results from several global studies the safety profile of PCV-13 in infants and young children concluded that the safety profile of PCV-13 is similar to that of PCV-7 (18). Global results of studies that reported on the safety profile of PCV-13 were described in a meta-analysis of 13 clinical trials in nine countries. The conclusions of this analysis, which included data for 2760 infants and young children, found a safety profile similar to that of PCV-7 (19, 20).

There were no vaccine related SAE reported among 121 toddlers primed with PCV-7 receiving PCV-13 as a booster dose (21).

In 284 children, aged two-five years previously vaccinated with PCV-7 and receiving a PCV-13 booster, the local and systemic events were generally mild and self-limiting with unsolicited events consistent with common childhood illnesses (22).

4.3.2.2 Concomitant use

In a Canadian double-blind, randomised trial assessing the compatibility of PCV-13 and PCV-7 given concomitantly with DTaP-polio-Hib and meningococcal C vaccines at two, four, six and 12 months, there was no difference in safety (or reactogenicity) in infants receiving either the PCV-13 (n=300) or PCV-7 (n=303) vaccines with their other childhood vaccines (11).

In Spain, 449 infants and toddlers were randomised to receive either PCV-13 or PCV-7 with Meningococcal C conjugate TT and DTaP-HBV-IPV/Hib at two, four and six months and DTaP-IPV+Hib at 15 months. Safety outcomes were similar between the groups and no new safety signals were detected (23).

PCV-13 has been associated with increased risk of fever over 39°C and febrile convulsions when co-administered with inactivated influenza vaccine in infants and young children. After the

febrile convulsions were associated with the 2010 inactivated influenza vaccine administered in the Southern Hemisphere, near real time surveillance was conducted in the US using the Vaccine Safety Datalink Project. Concomitant administration of PCV-13 with inactivated influenza vaccine doubled the incidence risk ratio from 2.4 and 2.5, respectively, to 5.9 when given together in this age group. The CSL manufactured trivalent influenza vaccines (TIV) that were associated with febrile events in the Southern Hemisphere were not recommended for this age group in the US. The study does not note which brands of influenza vaccines were used (24).

A Canadian study, using active surveillance of influenza vaccine in infants and children under five years of age, found a higher rate of fever in recipients who received PCV-13 as a concomitant vaccine, but not with other vaccines (25).

4.3.3 Safety of conjugate vaccines in other age groups

4.3.3.1 Preterm infants

The safety of PCV-7 was evaluated in 40 preterm Polish infants receiving three doses at two, four, six and 16 months of age. Infants were grouped pre-30 weeks gestation and 30-34 weeks gestation. There was one case of a short apnoea in an infant born at 28 weeks weighing 980g (26).

4.3.3.2 Adults

Safety of PCV-13 was assessed in around 6000 adults over 50 years of age and found to be consistent with the profile of PPV-23 in this age group (27, 28).

In a trial, 1116 adults aged 50-59 years were randomised to influenza vaccine and PCV-13, concomitantly, or a placebo; after a month, they were crossed over. No vaccine related serious adverse events occurred (29).

PCV-13 has been evaluated when co-administered with trivalent influenza vaccine in adults aged over 65 years. Systemic reactions were more common (chills, rash and myalgia) after administration of both vaccines, but were low in severity. No serious events were vaccine related (30).

4.3.4 Safety of PPV-23

A 2012 review of data on currently registered PPV-23 formulations, that included safety outcomes, found injection site reactions were reported more commonly after PPV-23 revaccination compared with primary vaccination. These usually resolved within five days. There is considerable safety data for repeated doses of PPV-23 with no issues raised (31). However, in Australia in 2011, a cluster of severe local reactions was reported to the Therapeutic Goods Administration (TGA). Outcomes of a review of these cases and the batch of vaccine concluded that this cluster was consistent with the known increased local reactions, from subsequent doses of this vaccine, and the increased number of people having a repeat dose following the inclusion of PPV-23 on the schedule in 2005 with revaccination recommended every five years (32).

The most recent addition to PPV-23 safety profile data is a randomised double-blind placebo controlled study in Australia, in which, PPV-23 was administered concomitantly with zoster vaccine to participants aged over 60 years. No adverse events were considered to be related to vaccination, and no statistically significant difference was observed in reactogenicity between concomitant and nonconcomitant administration (33).

4.4 Summary vaccine safety

No safety concerns have been raised for either PCV-10 or PCV-13.

PCV-10 has a safety profile similar to PCV-7 and it has been demonstrated to be safe administered concomitantly with routine vaccines in infants and toddlers. It has also been demonstrated to be safe in preterm infants born after 27 weeks. There were no safety studies of PCV-10 that included adults.

PCV-13 has been shown to have a safety profile similar to PCV-7 for infants, children and adults. A higher risk for febrile events has been associated with PCV-13 when co-administered with inactivated influenza vaccine in infants and children less than five years of age. However, the risk of severe febrile events following the co-administration of these vaccines is still very low. No concerns have been identified with co-administration with any other childhood or adult vaccines.

For PPV-23, there are decades of safety data with no concerns identified. Local reactions are more common following subsequent doses.

Overall, pneumococcal vaccines have demonstrated an excellent safety profile in all groups studied.

5. Immunogenicity, efficacy, effectiveness and vaccine impact

5.1 Objective

The objective of this section is to review the most recent performance data for currently licensed pneumococcal vaccines. The focus is on PCV-10 and PCV-13 with some consideration for any recent updates to PPV-23. Consideration is given to relevant immunogenicity data, efficacy and effectiveness studies that contribute to the current understanding of the effectiveness of pneumococcal vaccines and evidence for the non-inferiority of alternative schedules and their impact in populations.

5.2 Outcomes

The outcomes considered for this review are:

- Invasive pneumococcal disease
- Pneumococcal pneumonia
- Otitis media.
- Immunogenicity and nasopharyngeal carriage
- Community immunity (herd immunity)
- Anti-microbial utilisation
- Duration of protection

5.3 Review

The *S. pneumoniae* polysaccharide capsule influences carriage prevalence, pathogenicity and case fatality, hence, different capsular serotypes are associated with different patterns of carriage and pathogenicity (34). The overall impact of vaccination on disease outcomes will be partially influenced by the relative virulence of the replacing serotypes.

5.3.1 Immunogenicity and carriage

Pneumococcal disease is preceded by nasopharyngeal colonisation by the bacteria, which is not only a prerequisite for disease, but also provides for horizontal spread. Reduction in vaccine-type pneumococci is sometimes associated with an increase in carriage of non-vaccine serotypes. The mechanisms are not yet fully understood, but may involve ecological

niches and/or unmasking of non-vaccine serotypes (35, 36). Nasopharyngeal carriage density decreases with increasing age and carriage is lower after vaccination. Younger children also have higher prevalence of carriage (37).

The pattern of predominant IPD-associated serotypes varies with age groups, geographically and over time. The occurrence of serotype replacement with the use of the PCV-7 has been well documented (38). Serotypes naturally fluctuate over time and replacement has not occurred everywhere where PCV-7 has been introduced. However, there is clearly an effect from the use of PCV-7 (38). While, in most cases, the decline in IPD from vaccine types has been greater than the rise from non-vaccine strain types, there has been one study in native Alaskan children indicating IPD incidence increased following PCV-7 use, due to a rise in disease caused by non-PCV-7 serotypes (39). In Europe, the serotypes 1, 3, 5, 6A, and 19A are of particular concern (40, 41). Serotypes 19A and 3 are associated with higher rates of IPD mortality in older children and adults (38). Serotype 1 is an important pathogen for pneumonia and empyema (40). In particular, 19A is now one of the most common causes of IPD in young children in developed countries and accounts for up to half of all IPD cases (38, 41, 42). Despite the broader protection offered by PCV-10 and PCV-13, there is still potential for further replacement. PCV-13 contains pneumococcal capsular polysaccharides corresponding to the serotypes currently causing over 70% of IPD worldwide; higher valency PCVs are not likely to be developed due to the associated high costs (43).

5.3.1.1 PCV-10 and carriage

In Panama, the Clinical Otitis Media and Pneumonia Study (COMPAS) evaluated nasopharyngeal carriage in *S. pneumoniae* and *H. influenzae* and other bacterial pathogens in a subset of 2000 trial participants. There was a trend towards a lower colonisation rate of any serotype of *S. pneumoniae* in the PCV-10 group compared with control (DTaP-IPV/Hib). The vaccine effectiveness against vaccine serotype carriage was 26% and against non-typeable *H. influenzae* (NTHi) 24% and 28% at one and three months post booster, respectively. There was no evidence in this study of serotype replacement by other pathogens (44).

A population-based study, among a random selection of 1291 children in Goiania, Brazil (1.2 million inhabitants) aged seven to 18 months, evaluated the impact of PCV-10 vaccination on community-acquired pneumonia (CAP) and nasopharyngeal carriage (NPC) six to nine months after the introduction of the vaccine. The effectiveness of PCV-10 on pneumococcal NPC, for children who had received at least one dose of vaccine or were fully vaccinated, was 26% (95% CI 0-50%) and 36% (95% CI 12-53%), respectively, once adjusted by age, day-care attendance and socioeconomic variables. Effectiveness against vaccine types was 39% (95% CI 17% – 56%). Effectiveness against CAP in fully vaccinated children was 40% (95% CI 1.4%-63%). An impact of the vaccine was seen soon after introduction into the routine schedule (45).

The carriage data from the Finnish Invasive Pneumococcal disease (FinIP) study has been analysed and was provided originally in confidence by the manufacturer for this report and is now published (46).

The FinIP study, consists of phase III and IV double-blind, cluster randomised trials to assess both the direct and indirect effects of PCV-10 (NCT00839254). The main study included over 47,000 children with a nested study (Study 053) of over 6000 children with AOM. Randomisation was 2:2:1:1 to receive PCV-10 3+1, PCV-10 2+1, HBV/HAV 3+1 or HBV/HAV 2+1. Blood samples were taken at six, 11, 12 and 22 months of age. Nasopharyngeal samples were taken pre immunisation at three, 11, 15 and 22 months of age. The key findings were:

- Both 3+1 and 2+1 schedules resulted in overall reduction in carriage due to reductions in two vaccine serotypes and lack of serotype replacement.
- Vaccine efficacy against serotype 19A for a 3+1 schedule, across all visits from six – 12 weeks of age to 18-22 months, was 47.4% (95% CI 18.4 – 66.7, $p=0.003$). This only became significant by the 18-22 month visit.
- Vaccine efficacy against nasopharyngeal carriage of vaccine serotypes was 19-56% in the 3+1 group.

There was no evidence of effect on NTHi. No replacement by *M. catarrhalis* or *S. aureus* was observed for either 3+1 or 2+1 schedules (unpublished data).

5.3.1.2 PCV-13 and carriage

In Israel, a double-blind trial randomised 733 infants to receive either PCV-7 or PCV-13 at two, four, six and 12 months, in whom nasopharyngeal pneumococcal carriage was assessed. PCV-13 was less immunogenic for the common serotypes, but more immunogenic for the additional six serotypes. PCV-13 was associated with reduced nasopharyngeal colonisation for the six serotypes not included in PCV-7. Reductions were particularly significant for types 1, 6A, 6C, 7F and 19A. PCV-13 was as effective, and for 19A more effective, than PCV-7 in preventing PCV-7 serotype NP colonisation (47, 48).

Data for the first year of PCV-13 use in the US, indicated significant decreases in nasopharyngeal carriage of PCV-13 serotypes in PCV-13 vaccinated infants compared with PCV-7 vaccinees ($p<0.01$). NPC carriage of *S. pneumoniae* was assessed from samples from infants taken during health visits, at six, nine, 12, 15 and 18 months of age, at the time of an AOM episode and one month later (49). Surveillance of nasopharyngeal carriage among children under 60 months of age in Massachusetts found that, following PCV-13 introduction, there was lower carriage of the six additional PCV-13 serotypes among immunised children in the first winter following its introduction (50).

A 10-year surveillance network on nasopharyngeal carriage was commenced in 2001 in France. PCV-13 was introduced in June 2010 for children under two years of age. Over nine years, there was a regular increase in the proportions of people carrying serotypes 19A, 6C and 7F following the implementation of PCV-7. Following introduction of PCV-13, a rapid decrease in these serotypes was observed in children vaccinated with PCV-13. These three serotypes continued to increase in non PCV-13 vaccinated children (51).

5.3.1.2.1 Cross reactivity of 6B and 19F with 6B and 19A

PCV serotypes 6B and 19F are able to elicit antibodies that cross-react with the non-vaccine related serotypes 6A and 19A. The capacity for cross-reactivity was assessed by using immunogenicity data from PCV-10 and PCV-7 comparative trials. The seropositivity rates against 6A were the same for both vaccines, with opsonophagocytic activity (OPA) titres of ≥ 8 post boost occurring in 95 to 100% of PCV-7 recipients and 85 to

96% of PCV-10 recipients. Seropositivity rates against 19A were 84 to 94% for ELISA and 49 to 69 for OPA in PCV-10 recipients, and 63 to 77% and 24 to 28%, respectively, in PCV-7 recipients. It appears that both vaccines elicit cross-reactive antibodies to 6A and 19A. PCV-10 elicits more functional antibodies against serotypes 19A than does PCV-7 (52).

5.3.2 Serotype replacement – International experience

The large impact of PCV on pneumococcal disease caused by vaccine types has been off-set to varying degrees by increases in disease caused by non-vaccine types. To date, most information on serotype replacement with non-PCV types is for non-PCV-7 types. As yet, there is little data on non-PCV-13 types following the use of PCV-13.

In England and Wales, serotype replacement, most notably by the non-PCV-7 types 7F, 19A and 22F, has been recorded among IPD cases in both age groups eligible for vaccination and older age groups (2). In contrast, other settings serotype replacement has only or predominantly occurred among IPD in older age groups, for example, in the Netherlands and British Columbia (53, 54), with serotypes 1,3,7F,19A and 22F commonly implicated. Consistent with the situation in the Netherlands and British Columbia, an Israeli study of vaccine-eligible children reported no significant change in IPD due to non-PCV-7 types among these children (55).

5.3.3 Serotype replacement in NZ

[Refer to NZ epidemiology section 3]

5.3.4 Invasive pneumococcal disease (IPD) and pneumococcal pneumonia

The reported incidence of IPD in children under two years of aged in European Countries, before and after the introduction of PCV-7, has been summarised. The reduction in incidence of IPD ranges from 30% to 75% and is generally, but not solely, related to vaccine uptake (56).

Pooled analysis of data from 11 randomised controlled trials (RCT) from Africa, US, Philippines and Finland, which included 113,044 children receiving PCV-7 or placebo, found efficacy against IPD associated with vaccine serotypes was 80% (95% CI 58% – 90%, $p<0.0001$) and efficacy against all serotypes was 58% (95% CI 29%– 75%, $p=0.001$). The pooled data found efficacy against World Health Organisation (WHO) X-ray defined pneumonia was 27% (95% CI

15% – 36%, $p<0.0001$) and 6% efficacy against clinical pneumonia (95% CI 2% – 9%, $p=0.0006$). Efficacy against all-cause mortality was 11% (95% CI -1 – 21%, $p=0.08$) (57).

5.3.4.1 PCV-10 and IPD

PCV-10 has been licenced on the basis of immunogenicity, non-inferiority and safety studies. Until 2012 there was no published effectiveness data for IPD. PCV-10 replaced PCV-7 in Quebec in 2009. The introduction has been associated with a decreasing incidence of IPD in exposed children with no break-through cases in children who had received at least two doses PCV-10 as a primary course or a single dose as a booster. Further published data are needed to support this emerging data (5).

The emerging results from efficacy and effectiveness studies have been presented at conferences and are summarised below.

5.3.4.1.1 PCV-10 in Latin America

The COMPAS study is being conducted in Latin America to assess the efficacy of PCV-10. There are 23,738 children in the intention-to-treat cohort for the endpoint of bacterial community-acquired pneumonia (B-CAP), defined as radiologically confirmed CAP with either alveolar consolidation/pleural effusion on chest X-ray or non-alveolar infiltrates and C-reactive protein $\geq 40\mu\text{g/mL}$. The vaccine efficacy against the first episode of CAP was 22% ($p=0.002$) in the per protocol cohort, confirming protective efficacy against lower respiratory tract infections (58).

5.3.4.1.2 PCV-10 in Finland

The FinIP (Finland) study aims to assess the vaccine effectiveness against IPD of PCV-10 in infants in a 3+1 or 2+1 schedule. The study is a nationwide phase III/IV cluster-randomised, double blind trial. The enrolled population are 47,369 children less than 19 months of age. Vaccine effectiveness was 100% against culture confirmed vaccine type IPD in a 3+1 schedule (95%CI 83%-100%). Effectiveness was 92% in a 2+1 schedule (95%CI 58%-100%); there was one case of IPD in the vaccinated group and 12 cases in the control group. The one case in the vaccinated group occurred 12 days after the first dose. Effectiveness against vaccine-type IPD after the primary series was 100% (95%CI 91%-100%). Effectiveness against any IPD was 93% (95% CI 75%-99%). In children enrolled older than seven months, there were five vaccine-type IPD cases and two non-vaccine type IPD, all occurring in the control clusters. PCV-10 demonstrated high clinical effectiveness for both the 3+1 and 2+1 schedules

as well as catch up schedules. As the local vaccine coverage varied from as low as 10% to 70% (mean 40%) it is likely that the impact on effectiveness is a primarily a direct effect (59). Finland first introduced PCV in a 2 +1 schedule from September 2010 for infants born on June 1 2010 or later without catch-up vaccinations (60).

Also in Finland, data from 2004-2008 were used as a baseline and were compared with 2011 data following the implementation of the national programme. Years 2009 and 2010 were excluded because of the FinIP trial (above). A significant reduction in IPD incidence among children 6-11 months of age was observed within this year of implementation. There were no significant changes in the unvaccinated population. On-going surveillance will determine indirect effects and changes in serotype distribution (61).

5.3.4.1.3 PCV-10 in Brazil

An interrupted time-series analysis was conducted in Brazil, using hospitalisation data during 2005 – 2011 and ICD-10 codes for pneumonia as the primary discharge diagnosis. Brazil had no previous PCV (PCV-7) programme. Rates were stratified by age. Early results indicated that there has been a significant decrease in pneumonia hospitalisation rates since the introduction of PCV-10 in 2010, particularly in children under two years of age; rate reduction in children under two years was 31% ($p=0.004$). This reduction was not observed in other age groups (62).

The effectiveness of one or more doses of PCV-10 was assessed in Brazilian children eligible to have received PCV vaccination using a case-control method. There were 135 cases of IPD, of which, 82% were caused by PCV-10 serotypes. The overall effectiveness of at least one dose of PCV-10 was 71% against all serotype disease (95% CI 48% - 83%) and 85% against disease caused by vaccine-serotypes (95% CI 64% - 94%) (63).

Incidence and mortality of pneumococcal meningitis in the state of Sao Paulo remained stable, from 2001 to 2009, prior to the introduction of PCV-10 in 2010. Incidence in under two year olds for 2001 – 2009 was 7.1 /100,000 inhabitants. The incidence for January to August 2011 was 3.7/100,000 inhabitants ($p=0.01$) (64).

5.3.4.1.4 PCV-10 in Kenya

Kenya had no PCV-7 immunisation programme. The Pneumococcal Conjugate Vaccine Impact Study (PCVIS) is evaluating the impact of routine PCV vaccination on IPD in the Kilifi district in Kenya, population 260,000, with little HIV or seasonal malaria. This region has a population based passive

morbidity surveillance system linking hospital and laboratory data to a vital registration system maintained by four-monthly household visits. Immunisation events are linked to a population register. PCV-10 was available to children aged six weeks to 12 months of age, in a three-dose schedule given four weeks apart, and a catch-up programme for children aged one to four years with two doses eight weeks apart. There are limitations to this early data, including baseline fluctuations in IPD incidence. However, the introduction of a primary course of three doses of PCV-10 through infant vaccination and a catch-up programme for children aged one - four has been associated with a 72% reduction in vaccine-type IPD (65).

5.3.4.2 PCV-13 and IPD

In a 2010-2011 trial, Alaskan Native children aged less than five years were offered PCV-13 scheduled according to age and prior history of PCV-7 vaccination. Following the introduction of PCV-13, IPD caused by PCV-13 serotypes declined significantly. No cases of IPD caused by PCV-13 serotypes occurred among children who had received at least one dose of vaccine over 3680 person follow-up years. Seven cases occurred among children who had not received the vaccine over 5007 person follow-up years. There were 52 IPD cases in under five year olds in the 2005–2008 period before the study and nine cases after study commencement (399/100,000/y vs 107/100,000/y; $p<0.001$) (66).

Data is emerging for the effectiveness of PCV-13. In the UK, data to date suggest that IPD in children under two years of age, caused by the serotypes unique to PCV-13, has halved since the introduction (67). In Germany, where both PCV-10 and PCV-13 have been introduced, early reports suggest that IPD associated with serotypes 1, 3 and 7F has reduced (68).

In the US, the impact of introducing PCV-13 was evaluated using the six serotypes included in PCV-13, but not PCV-7. Among children under five years of age, a 65% reduction in the rate of IPD these six serotypes was observed in the first quarter 2011 (one year after implementation). By the second quarter 2011, reductions were observed in adults over 65 years of age. By the fourth quarter of 2011, the rates of these six serotypes had declined by nearly 90% in children under five years of age and by 45-64 % across all adult age groups. Serotypes 19A and 7F contributed primarily to these reductions (69).

The HERACLES study in Madrid (population 6 million) has assessed changes in the incidence rate of IPD in

hospitalised children less than 15 years of age before and after the introduction of PCV-13. Between May 2007 and April 2010 there were 499 IPD cases. From May 2010 to April 2011 there were 115 cases. This impact was mainly seen in children under two years of age (70).

Mathematical modelling has been conducted in England and Wales to determine the likely short term effects of PCV-13 on disease caused by different serotypes, against a background of serotype replacement observed following PCV-7 introduction, and the longer term effects on the incidence of IPD. The model evaluated potential outcomes for two policy options: replacing PCV-7 with PCV-13 or discontinuing PCV vaccination. The modelling suggested that ceasing PCV vaccination would result in an increase in IPD, while replacing PCV-7 with PCV-13 would result in an overall decrease. The magnitude of the reduction was dependent on the level of competition induced by the additional PCV-13 serotypes. A reduction in overall IPD was predicted in all scenarios (71).

In the UK, PCV-13 replaced PCV-7 in April 2010. From May 1995 - November 2010, an interrupted time-series analysis, for admissions of 313 children aged up to 14 years, found an increase in the mean monthly rates of empyema from 1.1 cases per million in 1996 to 5.2 million in 2009, followed by a reduction in 2010 to 3.2 per million. Although, it is too soon to assume a causal relationship, paediatric empyema is primarily associated with pneumococcal disease, particularly serotype 1, in the UK (72).

5.3.5 PCV-13 in adults

Effectiveness data for PCV-13 in adults is lacking due to the complexities in undertaking the studies. The superior immune response to conjugate vaccines, and the performance in children, suggest PCV-13 will also perform well in adults. Studies are underway, including CAPiTA, which is a randomised controlled trial that has enrolled over 85,000 PPV naïve patients in the Netherlands since 2008; results are expected from 2013.

In a randomised, double-blind trial PCV-13 was compared with PPV-23 in 835 older adults. Immunogenicity was also compared with an additional group of 404 adults aged 50-59 years receiving PPV-13. In adults aged 60 to 64, GMTs at one month post vaccination were significantly higher in the PCV-13 group than the PPV-23 group for 8/12 common serotypes and were comparable for the remaining four serotypes. OPA GMTs in the 50-59 age group were higher than for the 60 to 64 age group for nine serotypes and comparable for the other four. OPA

titres in both age groups declined from one month to one year but remained above baseline (73). In a similar study in adults over 70 years of age, OPA GMTs were also higher in the PCV-13 vaccinated group. Boosting with PCV-13 stimulated higher titres in the group primed with PCV-13 than the group primed with PPV-23, indicating that a prior dose of PPV-23, but not PCV-13, attenuates the response to a subsequent dose of PCV-13 (74).

Adults, aged over 65 years who had received PCV-13 then PPV-23, were given PCV-13 at one year intervals. OPA GMTs for 12/13 serotypes were lower after the series that included PPV-23 than after the initial PCV-13 administration. Administration of an initial dose of PCV-13 did not prevent the attenuated immune response to the subsequent dose of PCV-13 when given after a dose of PPV-23 in the vaccine sequence PCV-13/PPV-23/PCV-13 (75). In adults aged 60 to 64 years, the initial administration of PCV-13 followed by PPV-23 resulted in noninferior OPA responses for all serotypes and superior for some serotypes. However, the administration of PPV-23 resulted in an attenuated response to subsequent administration of PCV-13. Hence, in persons naïve to PPV-23, PCV-13 should be given first (76).

In adults aged 60 to 64, who had received either PCV-13 or PPV-23 in an earlier study, received either PCV-13 or PPV-23 three to four years later. Diminished responses were observed in the PPV-23/PPV-23 group compared to a single dose of PPV-23. In 50 to 59 year olds, who received PCV-13/PCV-13, significantly higher GMTs were seen after the second dose for 6/13 serotypes. Administration of PCV-13 increases the OPA responses to a subsequent dose of PCV-13 or PPV-23 given three to four years later in adults over 50 years of age, and administration of PPV-23 is associated with reduced responses to subsequent PPV-23 doses (77).

PCV-13 was approved for use in adults aged 50 years and older by the US FDA in October 2011. The approval was based on the supporting immunogenicity data that indicated superior immune responses and that the product was likely to provide clinical benefit compared with PPV-23 (for which there is little evidence to indicate protection against nonbacteraemic pneumococcal pneumonia). As of June 2011, ACIP had identified two important gaps in evidence required to support routine use of PCV-13 in adults:

1. Lack of clinical efficacy data against pneumococcal pneumonia in adults
2. The impact of routine PCV-13 vaccination in children on the incidence of disease caused by PCV-13 serotypes in adults is not yet known (27).

5.3.5.1 Dosing intervals

In terms of the effect of dosing intervals on the immune responses to sequential vaccination with PCV-13 and PPV-23 in adults, aged 60 to 64 years previously naïve to PPV-23, PCV-13 enhances the responses to subsequent PPV-23 given at one year and PPV-23 or PCV-13 given three to four years later for most serotypes. Responses to a second dose of PPV-23 given three to four years after an initial dose of PPV-23 are diminished (78).

5.3.6 Efficacy and effectiveness of PPV-23

Although it is generally accepted that PPV-23 is effective at preventing IPD in immunocompetent adults, a meta-analysis published in 2009 concluded that, in trials of high quality, there is no evidence of vaccine protection against IPD and that PPV may not be protective against either IPD or pneumonia (79). A subsequent case-control study published in 2010, in patients over 60 years of age in Spain, concluded a significant protective effect against IPD in elderly immunocompetent patients (80). However, a 2012 review of the most recent data in the elderly concluded possible low protection but study heterogeneity still prevents definitive conclusions (81).

5.3.7 Otitis media

There is limited data on the epidemiology of otitis media in NZ. Refer to 3.3 for a summary on a recent unpublished study which found *H. influenzae* a predominant pathogen in established ear disease requiring surgery.

A meta-analysis assessed recent studies on the global etiology AOM. The study found that *S. pneumoniae* and *H. influenzae* were globally consistently the primary OM pathogens and usually clinically indistinguishable. *S. pneumoniae* was more frequent in PCV unvaccinated children. However, *H. influenzae* was more frequently the causative pathogen in AOM episodes in children vaccinated with PCV-7, supporting a shift in the epidemiology. Recurrent episodes were more likely to yield *H. influenzae* than non-recurrent episodes (82).

The 2010 Cochrane Review found PCV-7 conjugated with CRM₁₉₇ as the carrier protein administered in infancy was associated with a 6% (95% CI -4 - 16%) to 7% (95% CI 4 - 9%) reduction in AOM episodes. However since the introduction of PCV-7 into the US population in 2000, there has been a reduction of over 40% in ambulatory visits and antibiotic prescriptions related to AOM. The incidence of frequent OM has

reduced in birth cohorts from Tennessee and upstate New York. In contrast, results from Boston show declines in uncomplicated AOM, treatment failure and relapse occurred in the preceding period 1996-2000 suggesting a more modest role for PCV-7 (83).

A 2012 systematic review on the impact of PCV on OM found the efficacy of PCV-7 on all-cause AOM visits to be 0% to 9%, in randomised trials, and 17% to 23% in non-randomised trials. Observational studies assessing physician visits for AOM found that visits were declining prior to the introduction of PCV as well as continuing to decline following introduction indicating the influence of other factors (84).

5.3.7.1 PCV-10 and otitis media

PCV-10, from GlaxoSmithKline also known as PHiD-CV10, is expected to reduce the burden of middle ear disease due to non-typeable *H. influenzae*, because it contains protein D. PCV-11, the predecessor to PCV-10, showed clinical efficacy against otitis media caused by *H. influenzae*, however further clinical data is needed to be clear about the efficacy against disease caused by non-typeable *H. influenzae* (40). A 2010 Cochrane review on pneumococcal vaccines for preventing OM found PCV-11 conjugated to *H. influenzae* protein D was associated with a 34% (21 - 44%) reduction in overall AOM episodes (83).

A phase III/IV study has been completed underway in Europe (FinIP Study) aiming to demonstrate the overall effectiveness of PCV-10 against diseases caused by *S. pneumoniae* or *H. influenzae* in 91,000 children (40, 46).

Emerging results from the FinIP trial indicate that the effectiveness in the per protocol cohort in reducing the number of subjects reports at least one AOM episode is 16% (95% CI -8%-35%) in the 3+1 schedule. Effectiveness in the 2+1 schedule was estimated at 4.9% (95% CI -26%-28%). Clearly more data is required before conclusions can be drawn (85).

5.3.7.2 PCV-13 and otitis media

Lower OM rates and myringotomy rates have been reported in many studies following the introduction of PCV-7 (40). OM rates are also expected to be lower with the use of PCV-13.

Data from the US, for the first year following introduction of PCV-13 found among PCV-13 vaccinated AOM cases 1 /15 had *S. pneumoniae* (ST11) compared with 15/23 PCV-7 vaccinated AOM cases (p=0.001). Otopathogen distribution of AOM in PCV-13 vaccinees indicated a trend towards nontypeable *H. influenzae* (NTHi) (p=0.08) (49).

The Finnish Otitis Media study (FinOM) analysed the data for PCV-7 and found evidence of replacement diseases, occurring soon after the first vaccine dose with vaccine and vaccine-related pneumococcal AOM, replaced to some degree by other pneumococci and NTHi AOM. There was no significant impact of the vaccine on overall AOM episodes. There was a greater impact of the vaccine on subjects experiencing less than two AOM episodes suggesting a subgroup of AOM-prone children. It is not known if the vaccine-associated replacement is primarily occurring in these children (86). This PCV-7 data is assumed to stand for the same types common to both PCV-7 and PCV-13 vaccines.

5.3.7.3 Comparability of PCV-10 and PCV-13

There are no head-to-head studies of PCV-10 and PCV-13 for OM.

5.3.8 Effectiveness against antimicrobial utilisation

Immunisation has the potential to reduce the use of antimicrobial agents. A 2012 review, extending from 1948 to 2012, systematically identified and evaluated the literature associated with immunisation programs and reductions in antibiotic use. Few studies were found, although there was evidence that pneumococcal vaccine may reduce antibiotic use associated with OM (87). A reduction in carriage of PCV-13 serotypes among children with AOM has been reported in France since the vaccine's introduction in 2010 (88).

Given the experience with serotype replacement observed following the introduction of PCV-7, it is expected that a similar pattern will occur following PCV-13. This may be of clinical significance should the replacement involve serotypes that have high invasive potential (35).

In the FinIP trial (see above), the impact of PCV-10 on outpatient antimicrobial prescriptions commonly used against respiratory infections was assessed in children who had received at least one dose of PCV-10 before seven months of age. In 26,411 infants less than seven months of age at enrolment, there were over 81,000 outpatient antimicrobial prescriptions reported. The vaccine effectiveness estimate was 10% (95% CI 2%-16%) for both 3+1 and 2+1 schedules. These preliminary results suggest that there potential for a significant absolute reduction in antimicrobial prescriptions in children. Higher effectiveness was observed with increasing rank (number) of prescriptions per child (89, 90).

5.3.9 Vaccine performance in high risk groups

High-risk groups, identified as indications for pneumococcal vaccination in children, have been summarised by the ACIP.

Table 6. Underlying medical conditions considered indications for pneumococcal vaccination in children. Adapted from ACIP recommendations 2010 (91)

Risk Group	Condition
Immuno-competent children	Chronic heart disease – particularly cyanotic heart disease and cardiac failure
	Chronic lung disease – including asthma if treated with high-dose oral corticosteroid therapy
	Diabetes mellitus
	Cerebrospinal fluid leaks
	Cochlear implants
Children with functional or anatomical asplenia	Sickle cell disease and other haemoglobinopathies
	Congenital or acquired asplenia, or splenic dysfunction
Children with immuno-compromising conditions	HIV infection
	Chronic renal failure and nephrotic syndrome
	Diseases associated with treatment with immunosuppressive drugs or radiation therapy - including malignant neoplasms, leukaemia's, lymphoma and Hodgkin disease; or solid organ transplantation
	Congenital immunodeficiency – including B or T cell deficiency, complement deficiencies particularly C1, C2, C3 and C4; and phagocytic disorders (excluding granulomatous disease)

5.3.9.1 Immunosuppressed

Many patients, for whom pneumococcal vaccination is recommended due to risk factors, are taking immunosuppressive agents including corticosteroids, azathioprine, methotrexate, cyclosporine, monoclonal antibodies, 6-meraptopurine and others. A 2012 systematic review of prospective controlled studies assessing the pre and post vaccination titres among both children and adults receiving a variety of immunosuppressive therapies found five studies of PPV-23 in adults with rheumatic diseases and IBD and summarised the results.

- Similar responses seen among those treated with anti-TNF therapy alone
- Some studies reported diminished responses among those treated with methotrexate as monotherapy.
- Most studies showed diminished responses across a variety of immunosuppressive regimens. Heterogeneity precluded conclusions about specific drugs
- Rheumatic disease patients had more normal responses to vaccines than did IBD patients on similar treatments, although IBD dosage may be higher (92).

Schedules for pneumococcal vaccination in high risk groups are presented in 10.2.1.

5.3.9.2 Recurrent infections

In children with recurrent infections, there is likely to be heterogeneity among the groups in terms of immunocompetence and PPV history prior to the studies, making conclusions about the use of PPV-23 in these groups difficult (93).

5.3.9.3 HIV patients

A 2010 Systematic review of the effectiveness of PPV-23 in HIV infected people concluded that the current evidence provides moderate support of PPV-23 in HIV infected adults and that more data are needed on the performance of conjugate vaccines in this group (94).

A trial of one versus two doses of PCV-7 in HIV infected adults on combination anti-retroviral therapy found significant antibody responses and a better serological response to at least one serotype following two doses rather than one dose (95).

5.3.9.4 Cardiac patients

In children aged two to 18 who had undergone cardiac transplant primed with PCV-7 and receiving PPV-23 6-8 weeks later, there were no increases in IgG for the two non PCV-7 serotypes measured, although, healthy controls had significant rises. In children aged 3 years of age primed with PCV-7 and receiving PPV-23 eight to 12 weeks later, there were significant rises. Differences in the timing of immune suppression regimens may explain the discrepancy (93).

5.3.9.5 Sickle cell disease

Two studies that included children and young adults aged 15 months to 27 years with sickle cell disease indicated that children with sickle cell disease are able to mount antibody responses to PPV (93).

5.3.9.6 Cystic fibrosis

Pneumococcal vaccination may offer some protection against cystic fibrosis, however most recent literature search shows there are no published trials to draw conclusions on the efficacy of routine pneumococcal immunisation in people with cystic fibrosis (96).

5.3.9.7 Chronic suppurative lung disease/bronchiectasis

A recent Cochrane review of pneumococcal vaccines in children and adults with chronic suppurative disease concluded that there is current, but limited evidence, to support the use of PPV-23 as routine management in adults with bronchiectasis, and circumstantial evidence to support PPV-23 in children. There is no evidence on how often the vaccine should be given (97).

5.3.9.8 Renal disease

Serospecific IgG responses can be elicited in children with renal disease, including nephritic syndrome or dialysis treatment, who are immunocompetent at the time of vaccination.

5.3.9.9 Pregnancy

Maternal immunisation with PPV-23 results in effective transfer of IgG to the fetus with a median half-life of around 35 days post birth. The IgA measured in breast milk is significantly higher (98).

Pneumococcal vaccination during pregnancy may prevent pneumococcal disease during the first months of an infant's life before the primary course is completed. The Cochrane Pregnancy and Childbirth Group's Trials Register was searched and from this five trials contributed data. To date, there is no direct evidence that pneumococcal vaccination during pregnancy reduces the risk of neonatal infection (RR 0.66, 95%CI 0.20-2.17), although there may be a reduction in pneumococcal colonisation by 16 months of age (99).

Pneumococcal vaccine is considered safe in pregnancy and it is recommended for pregnant women in special groups in some countries including the US and Australia (100).

5.3.9.10 Preterm infants

Very low birth weight infants ($\leq 1000\text{g}$) have similar antibody responses to most PCV-7 serotypes (101). Timely boosters are recommended.

5.3.10 Duration of protection

The duration of protection offered by pneumococcal vaccines can be difficult to assess as this outcome relies on the timing of breakthrough disease in vaccinees. The significant reduction of vaccine serotypes that occurs following implementation of conjugate vaccines, coupled with the effect of herd immunity contribute to this difficulty. As serum antibody, in particular functional antibody, is known to play an important role in conferring protection against pneumococcal disease, most information that contributes to estimates of duration of protection is immunological data.

5.3.10.1 Duration of immunity conferred by conjugate vaccines

There is generally no data on the duration of immunity for the conjugate vaccines. An analysis of the timing of serotype 1 and 5 breakthrough cases was carried out using trial data for PCV-10 and PCV-13, used as a 3+0 schedule as per WHO recommendations, and concluded that the cases may have been as a consequence of the absence of a booster in the second year of life. Serotype 1 and 5 are less immunogenic than the other serotypes for both licenced vaccines. Overall, there is limited data on the longevity of immunity in the absence of a booster dose. However, this data was based on the 3+0 schedule with no booster in populations from the Gambia and South Africa and may have limited relevance to the NZ population (102).

5.3.10.2 Duration of immunity conferred by PPV-23

A 2012 review of current PPV-23 formations conducted by Merck, for which long term data are available, found that most studies reported that IgG and functional antibody levels in adults vaccinated with PPV-23 persist above the concentrations measured in unvaccinated adults for at least five to 10 years. Exceptions involve populations with a range of underlying conditions including non-ambulatory adults. Revaccination with PPV-23 every five to 10 years after a previous dose results in an increase in both IgG and functional antibody levels. People with lower circulating antibody prior to revaccination have a higher increase in antibody. This review concluded that revaccination appeared to sustain antibody levels in elderly populations and that clinical protection is likely to be achieved (31).

Supporting the review above, a recent trial designed to provide data on antibody persistence over 10 years after a first or second PPV-23 vaccination in 143 ambulatory older adults was published. It found that, ten years after a first or second dose, the mean IgG concentrations were higher than in unvaccinated controls for 7/8 serotypes tested. Second and third doses induced similar post vaccination levels. GMCs declined after the first dose, but remained above revaccinated levels for ten years for all vaccine serotypes, except serotype 3. Ten years post vaccination, the group who received a second dose had higher IgG GMCs than the first dose group, but these were not significant. Ten years after subjects received a first or second PPV-23 dose, mean IgG levels declined slightly from the levels observed at five years post vaccination, but for most serotypes, they still remained higher than pre-vaccination levels in vaccine-naïve subjects (103).

5.4 Summary of effectiveness

The implementation of routine use of pneumococcal conjugate vaccines is consistently followed by rapid and dramatic reductions in disease caused by the vaccine serotypes in vaccinated cohorts; subsequent decreases are seen across the population demonstrating a strong indirect effect. In many countries, at least some of the decrease in disease due to vaccine types has been off-set by an increase in disease caused by non-vaccine types. Such serotype replacement has the potential to erode the benefits of vaccination.

Data to date suggests that PCV-10 has a moderate impact on nasopharyngeal colonisation and carriage and lack of serotype replacement. Clinical trials and the introduction of PCV-10 into routine schedules in other countries have both been associated with very high efficacy and effectiveness in both 3+1 and 2+1 schedules against IPD caused by vaccine serotypes and clinical pneumonia. There is no data to support the use of PCV-10 in adults at this time. PCV-10 elicits superior cross-reactive antibodies against serotypes 6A and 19A compared with PCV-7 and also reduces 19A carriage. The ability of these antibodies to protect against disease is not yet known. The FinIP data does not indicate an effect on NTHi carriage.

PCV-13 has been demonstrated to be highly immunogenic and efficacious in children against IPD, and immunogenic in adults over 50 years, including adults over 70 years of age. It is at least as immunogenic as PCV-7 in children and PPV-23 in adults. The vaccine has performed well in clinical trials and early data indicate a reduction in disease caused by PCV-13 serotypes following its introduction. As of early 2013, there is no data on clinical efficacy. More data is required to support its use in other adult groups as well as the use of booster doses. However, priming adults with PCV-13 prior to any doses of PPV-23 vaccine seem well supported. The effectiveness of a childhood programme on the ability to reduce adult disease remains unclear.

PCV-7 has been shown to have some small effect against AOM. PCV-11 (the precursor to PCV-10) demonstrated good effectiveness against AOM, but further studies are awaited determine the effectiveness of PCV-10. PCV-10 effectiveness appears better against AOM in a 3+1 schedule than a 2+1 schedule. There is no robust data to date on the effectiveness of PCV-13 against AOM. There is the potential for PCV vaccines, particularly PCV-10, to reduce antibiotic usage in AOM.

The most recent analysis of the protective effect of PPV-23 in immunocompetent adults indicates that PPV-23 is probably protective against IPD in immunocompetent older adults. Effectiveness in more fragile elderly is currently unsupported. However, immunogenicity data indicate that the elderly mount immune responses to first and subsequent doses that are likely to confer protection. Diminished responses are seen in repeat doses compared with a single dose. The use of a conjugate vaccine in these age groups may improve effectiveness, but the results of studies are pending. Data suggests that immune responses are blunted if PPV-23 is used prior to PCV vaccines; however, the use of PPV-13 prior to PPV-23 or in a PCV-13/PPV-23/PCV-13 schedule gives effective immune responses.

There is very little evidence that immunosuppressed children in at risk groups mount responses to PPV-23. Immunosuppressed individuals do respond to PCV vaccines, although, responses are reduced with considerable heterogeneity.

There is no direct evidence that vaccinating in pregnancy will reduce neonatal infection. However, mothers vaccinated during pregnancy with PPV-23 transfer significant antibody to the fetus.

Duration of protection is unclear for conjugates; immunogenicity of PPV-23 in immunocompetent adults lasts for five to 10 years.

6. Age-specific issues

6.1 Objective

This section reviews the differences that need to be considered for various age groups. Literature for age-related morbidity and mortality is included. Issues around the use of available vaccines in age groups other than infants and young children are also considered.

6.2 Review

6.2.1 Burden of disease by age

Pneumococcal infections are most common in children under one year of age; the 2010 rates for IPD in the US population were at 34.2/100,000 dropping dramatically by the age of two to 3.1/100,000. Risk increases after the age of 18 years, peaking at 36.4/100,000 in the over 65 year old age group. In New Zealand, the 2011 rates were similar (see Figure 3).

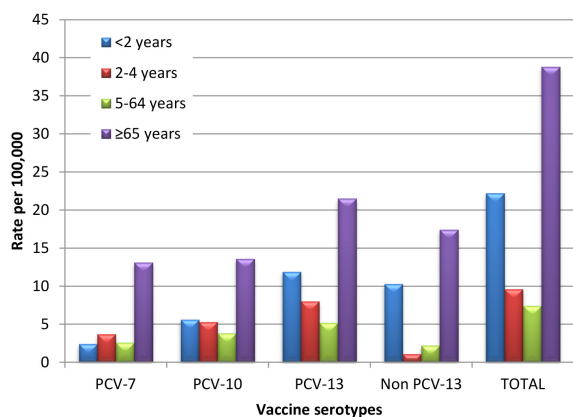


Figure 3. Rates of culture-positive IPD in NZ by age group and vaccine-related serotype (ESR)

While rates of IPD caused by the PCV-7 serotypes are now very low, overall increases in serotype 19A have been significant. Numbers and rates of 19A IPD have remained relatively stable in the under-five age group. However rates of 19A disease have increased in the five to 64 year age group and the ≥65 age group (see Figure 4). Serotype 3 contributes to the non-PCV-10 cases, but primarily only in older age groups. The cases of serotype 3 disease in the under-five age group appear sporadic, having occurred in only four of the eight years between 2004 and 2011.

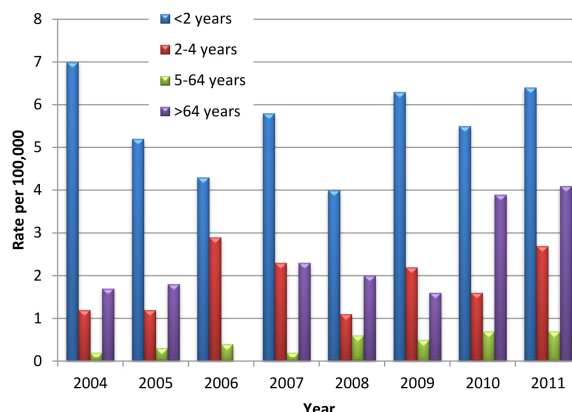


Figure 4. Age specific IPD caused by serotype 19A from 2004 – 2011¹

6.2.2 Vaccine issues for different age groups

Most data around vaccination has been obtained in infants and young children, and is discussed elsewhere in this report. Data supporting use of PCV in adults is emerging and is the focus of this section.

6.2.2.1 Infants under two years of age

In infants under two years of age conjugated vaccines are the only option for use. A variety of scheduling options are possible (see section 8)

6.2.2.2 Older children and adults under 50 years of age

Overall older children and adults generate a superior response when vaccinated with a conjugate vaccine compared with polysaccharide vaccines (PPV), regardless of previous PPV vaccination history (104). Regulatory agencies in Europe and the US are moving to licence PCV-13 in adults, this needs to be considered when choosing pneumococcal vaccination in this population (80). Two issues around the use of the PCV in adults have been highlighted: firstly, immunologically, PPV-23 primed adults may require a higher antigen content compared with children, possibly a double dose, adding significantly to cost (105). Secondly, it has been shown that repeated doses of PCV-7 do not demonstrate a booster effect in adults who received an initial dose of PPV-23, indicating that the hyporesponsiveness induced by the PPV-23 cannot be overcome (106). Priming with a conjugate vaccine appears essential prior to administration of PPV.

There is no evidence to support the routine use of PPV-23 to prevent all-cause pneumonia or mortality in adults (107).

¹ Rate not show in <5 cases

6.2.2.3 Adults aged over 50 years

Two phase three trials have been assessing the performance of PCV-13 in adults over 50 years of age. Participants have been randomised to receive either PCV-13 or PPV-23. The immune response (OPA) was evaluated and a second dose of one of the vaccines was administered a year later. In pneumococcal vaccine naïve 60 to 64 year olds, the response to a single dose of PCV-13 was at least as good as PPV-23 for all serotypes. In adults aged 50 to 59 years, the response to PCV-13 was superior to the older age group for most of the serotypes indicating age is a contributing factor in the immune response. In these studies the single dose of 2-4µg polysaccharide in the conjugate vaccine induced a better response than the 25µg of free polysaccharide in the PPV-23 vaccine (104).

One year following the initial dose of PPV-23 or PCV-13, antibody levels had waned in all groups. The second dose of PCV-13 resulted in an anamnestic response at least as high as the initial response. In those participants who received PPV-23 as a booster, the response was significantly higher for 7/13 serotypes demonstrating that the PCV-13 had successfully primed the immune system for a booster response to later vaccination with either vaccine. Two doses of PPV-23 resulted in a response significantly lower for 8/12 serotypes common to both vaccines. Overall, the PCV-13/PCV-13 groups had higher responses for all common serotypes compared with PPV-23/PPV-23 groups (104).

Modelling in the US was conducted to estimate the potential public health and economic impact of using the PCV-13 vaccine in adults over the age of 50 years. Assuming that the effectiveness of this vaccine is comparable to the PCV-7 vaccine in children, the model predicted that the use of PCV-13 instead of PPV-23 would result in a greater overall reduction in disease burden among older adults in that country (108).

6.2.2.4 Elderly adults over 65 years

The superior immune response to conjugate vaccines compared with polysaccharide vaccine in adults, including the elderly, predicts they are more likely to offer the best protection. There is little evidence that PPV is effective in the over 65 age group. Limited efficacy data in adult populations are a barrier to decision making on the use of these vaccines. However, based on the immunogenicity data for PCV-7, in principal, the use of PCV-13 as a primary dose in any vaccination regimen for the elderly seems supported (106). The PCV-13 vaccine has already been indicated for adults aged 50 years and older (80).

6.3 Summary of age-specific issues

The burden of pneumococcal disease in NZ is now caused primarily by non-conjugate vaccine serotypes. Of the vaccine specific serotypes associated with disease that are not included in PCV-10, 19A is the most common, but has remained stable in infants and children over the past eight years despite increasing among older age groups. Serotype 3 is generally not associated with disease in children under five years of age.

With regard to the use of conjugate vaccines, the age-specific issues reside primarily with the adult population. Efficacy data are still lacking in these groups, however, there is good immunogenicity data that supports either priming both older adults and high-risk groups with PCV-13 prior to using PPV-23, or the use of PCV-13 alone. There is little evidence for use of PPV-23 in elderly over 60 years of age. Efficacy data for the use of PCV-13 in adults is expected over the coming years.

7. Vaccine options

7.1 Objective

The objectives for this section are to consider the different vaccine options available to NZ in terms of available vaccines and schedules. Consideration is given to the replacing serotypes in NZ and their pathogenicity, and the implications for herd (community) immunity.

7.2 Review

In England, an evaluation of the impact of different serotypes on quality adjusted life years (QALY) loss was conducted. The main IPD burden, as expressed as QALY, occurred among five to 64 year olds in whom the higher number of life years lost outweighed the higher mortality rate in the over 65 year olds due to a lower life expectancy. The different pathogenicity between serotypes in this study was found to be marked, stable and consistent with nine other studies from various countries. The study concluded that PCV-13 is likely to protect against a greater burden of disease in England than PCV-10, particularly mortality, due to its coverage of serotypes 3, 6A and 19A. However, other factors need to be taken into account when considering vaccine options, such as the burden of non-invasive disease, particularly pneumonia and OM including OM disease due to non-typeable *H. influenzae*. In contrast the three additional serotypes in PCV-10 (1, 5 and 7F) have low carriage prevalence in England, whereas, the extra serotypes in PCV-13 have higher prevalence in terms of carriage (34).

7.2.1 Implications for herd immunity

Recent publications have added to the already strong evidence for the indirect effects of infant PCV immunisation on pneumococcal disease due to vaccine serotypes in the non-vaccinated population, especially the ≥ 65 year age group. These recent publications include data showing reductions in the rates of IPD due to PCV-7 serotypes in non-vaccinated groups in the US, England and Wales, The Netherlands, Norway and Denmark (2, 3, 53, 109, 110). While most of the data available is for the indirect effect on IPD, there is also evidence of an all-age effect on non-bacteraemic pneumonia (111).

7.2.2 New Zealand epidemiology and implications for vaccines and vaccination

The indirect effects of adding PCV-7 to the national childhood immunisation schedule in 2008 were evident by 2011, by which time, rates of IPD due to PCV-7 serotypes had decreased significantly ($p < 0.05$) in all age groups, not just the vaccine-eligible groups (Table 7).

Although, this indirect effect has resulted in significantly reduced rates of IPD due to PCV-7 serotypes in the five to 64 and ≥ 65 year age groups, there have been no corresponding significant decreases seen in the rate of all IPD (i.e., due to any serotype) in either of these age groups. This is due to the fact that PCV-7 serotypes constituted a smaller proportion of the disease in these age groups than those groups directly targeted for PCV vaccination, and also due to significant serotype replacement in the older age groups since the introduction of routine infant immunisation.

Table 7. Decrease in rates of culture-positive invasive pneumococcal disease due to PCV-7 serotypes between 2006/2007 and 2011, by age group

Age group	Rate of IPD due to PCV-7 serotypes per 100 000 population		Percentage change between time periods	Significance of change (P value) ²
	2006/2007 (immediate pre-PCV years) ¹	2011		
<2 years	83.1	2.4	-97	<0.001
2-4 years	15.5	3.7	-76	<0.001
5-64 years	3.6	2.6	-28	0.011
≥ 65 years	22.2	13.1	-41	<0.001
All ages	8.6	4.0	-53	<0.001

1. Average rate across the 2 years 2006 and 2007

2. Based on Fisher's exact test

7.2.2.1.1 ≥65 year age group

The positive herd immunity effect in the ≥65 year age group raises the question of whether there is a need to continue to recommend vaccination of ≥65 year olds in settings where infant immunisation coverage is high. However, the currently recommended vaccine for this age group (PPV-23) gives a wider coverage of the serotypes causing disease in this age group than either of the currently available PCV vaccines. For example, in 2011, 80.4% of the IPD in the ≥65 year age group was due to serotypes included in PPV-23, compared with 35.1% due to PCV-10 types and 55.3% due to PCV-13 types. Furthermore, as commented above, overall IPD rates have not dropped in this age group with the use of PCV-7 in the infant schedule. The use of PCV-10 or PCV-13 in the infant schedule could lead to a greater reduction in this group.

The herd immunity effect of PCV in the ≥65 year olds is particularly pertinent to any proposal to replace PPV-23 with PCV-13 (the only PCV vaccine approved for use in adults) as the recommended vaccine for this age group. The herd immunity conferred by pneumococcal conjugate vaccines may effectively render redundant adult immunisation with vaccines with the same serotype coverage as the vaccine used in the infant immunisation programme. Consequently, any indirect benefits of using PCV-13 for the vaccination of the ≥65 year age group may be quite limited if PCV-13 was used for routine infant immunisation. However, if PCV-10 continues to be used for infant immunisation in NZ, the benefit of extended serotype coverage with PCV-13 of types 3, 6A and 19A will not be seen. In particular, coverage of serotype 19A disease is important as IPD due to this serotype has increased significantly in the five-64 year and ≥65 year age groups since the introduction of PCV to the infant immunisation schedule.

7.3 Summary for vaccine options

While the current implementation strategy for NZ is the reduction in burden of IPD, a significant shift in the burden of OM as a result of the use of PCV-10 over PCV-13 would be important to include in future cost-benefit analysis.

Extrapolation from the current data suggests PCV-10 is expected to reduce IPD in under two year olds by a further 14% (n=4) over PCV-7. If PCV-13 was introduced, it could reduce IPD by a further 29% (n=8) over PCV-10. In the two to four year olds, PCV-10 is likely to reduce IPD by a further 18% (n=3) over PCV-7 and PCV-13 by a further 29% (n=5) over PCV-10. PCV-13 would further reduce IPD in all older age groups over PCV-10 by approximately 19-20%.

The effectiveness of PPV-23 in older adults remains unclear. The potential for herd immunity effects in reducing the disease burden, particularly in older adults, from the use of PCV-13 in the childhood schedule may effect considerations for when and how to use PCV-13 in the elderly and high risk populations. Conversely, there may be a place for a routine single dose of PPV-23 in the elderly.

These estimates do not take into account any potential cross-protection between serogroups, such as between 19F and 19A and between 6B and 6A). Also, this data does not take into account reductions in non-invasive pneumococcal disease, in particular non-bacteraemic pneumonia, but also otitis media.

Even with the greater disease coverage that PCV-13 would afford, there is still a considerable proportion (36% over all age groups) of remaining IPD in New Zealand that is due to serotypes not covered by any of the currently available pneumococcal conjugate vaccines.

8. Options for scheduling

8.1 Objective

This section reviews the evidence for different options for placement of PCV-13 and PCV-10 on the childhood immunisation schedule and options for adult vaccination.

8.2 Outcomes

IPD and OM are the outcomes for which different schedules are compared.

8.3 Review

8.3.1 Schedules for primary course PCV: 2+1 versus 3+1 and 3+0

Many countries are using a primary course of three doses followed by a booster dose in the second year of life (3+1), while other countries have adopted a two dose primary course with a booster (2+1). For example, PCV-7 given as a 2+1 was safely and effectively introduced in Denmark in 2007, in Israel in 2009 and in Norway in 2006 (55, 109, 110). A systematic literature review published in 2012 concludes that clinical data is now available demonstrating that PCV-7 can be safely and effectively administered in a 2+1 dosing regimen (112). While studies have noted that a primary course of three doses does seem to better protect against PCV serotypes and carriage than two doses in the first year of life, after a booster most of these differences disappear (113).

Immunogenicity data, following two primary doses of PCV-13, 'tentatively' indicates that this vaccine can be administered safely and effectively using this regimen and the authors of the systematic review recommend the use of a 2+1 schedule due to the cost and convenience gains (114). However, the article does caution that some inferior data has emerged with regards to the immunogenicity to certain pneumococcal serotypes, hence if a 2+ 1 regimen is used, prospective continued surveillance for IPD disease should take place (112). An earlier systematic review of studies up to March 2010 concluded that there were small differences between schedules, which tended to favour 3+1 schedules for serotypes 6B and 23F, in particular. Between-study heterogeneity was high and clinically relevant outcomes were not identified. Both schedules result in high levels of

seropositivity, and the clinical relevance of differences in immunological outcomes between schedules is not known (115). The FinIP data supports a 2+1 regimen for PCV-10 with 92% efficacy (60). A three-dose primary schedule of PCV-10 administered at two, four and six months of age elicits effective priming which has been confirmed by robust boosted observed at 15-18 months of age (116).

A 2012 review of PCV-13 concluded that the 2+1 series to be immunologically equivalent to the 3+1. The USA has adopted a 3+1 and the UK a 2+1 schedule. The WHO have recommended an Expanded Programme on Immunization (EPI) schedule of 3+0 at six, 10 and 14 weeks for PCV which has been adopted by Global Alliance for Vaccines and Immunisation (GAVI) (28).

8.3.2 3+1 vs. 2+1 against otitis media

In one population study in the US, among a 2002 birth cohort of over 38,000 highly insured children, there was no difference between a two-dose and a three-dose primary schedule of PCV-7 in the incidence of AOM up to four years of age (117).

Early results from the FinOM trial in Finland indicated a trend toward protective effect of PCV-10 against \geq AOM in infants of around 16% in a 3+1 schedule and 5% in a 2+1 schedule. The confidence intervals are wide and cross zero for all groups (85) (see 5.3.7.1).

8.3.3 Schedules for adults

Based on immunogenicity trials, PCV-13 can be administered to adults over 50 years regardless of their PPV history. Reduced IgG responses to PCV-13 are observed when it is given following PPV-23 compared to PCV-13 alone. PCV-13 followed by PPV-23 augments the immunogenicity of PPV-23. The need for a booster dose of PCV-13 has not been determined (28).

8.3.4 Alternative options for adults and indigenous populations

The use of PCV vaccination in adults over 65 years of age is expected to have an immunological advantage over PPV-23, as PCV induces a broader immune response and does not lead to depletion of memory cells and antibody hyporesponsiveness (118).

Phase III trials of PCV-13 in adults are underway in a number of settings. PCV-13 appears comparable to PPV-23 in the 50 to 64 year age range.

Immunogenicity, including functional antibody responses elicited by PCV-13 in the 50 to 64 year age group, are higher for the majority of serotypes in PCV-13 than those induced by PPV-23. Safety and tolerability are comparable (43).

An open-labelled randomised study comparing vaccine schedules of either two doses of PCV-7 followed by PPV-23; PCV-7/ PPV-23/ PCV-7; or PPV-23 followed by two doses of PCV-7 in 348 adults aged 50 to 70 years showed that priming with two doses of PCV-7 produced significantly higher antibody concentrations for three of the seven serotypes compared to a single dose of PPV-23. However, prior vaccination with PPV-23 attenuated the antibody response to subsequent PCV-7, which was not restored by additional doses of PCV-7. The authors concluded that vaccination schedules combining PCV-7 and PPV-23 do not provide improved immunogenicity over the use of a single dose of PPV-23 for most of the serotypes contained in PCV-7 (106).

In the 1990s, pneumonia hospitalisation rates in Western Australia were 13 times higher in indigenous children than non-indigenous people. Since the introduction of a primary course of three doses of PCV-7 and a booster of PPV-23 at 18 months in 2001, a reduction of 9% per annum has been seen in pneumonia hospitalisations in Australian indigenous children for all-cause pneumonia and a reduction in disparity to non-indigenous by a third. While this is only an observational study, the introduction of PCV-7 is likely to be the major factor in this reduction in disparity gap (119).

8.3.5 Duration of protection

Duration of protection offered by these vaccines is difficult to measure due to the impact of herd immunity which follows implementation. It is the issue of serotype replacement which is likely to influence decisions around vaccine and scheduling options the most.

8.3.6 Summary of schedule options

For the routine infant immunisation schedule the use of PCV-13, either in a 3+1 or a 2+1 schedule, is supported by the literature. The FinIP data supports using PCV-10 in a 2+1 schedule. Some evidence suggests a 2+1 schedule may have less impact on AOM than a 3+1. For adults, a schedule that uses PCV-13 alone or as a priming dose prior to the use of PPV-23 is consistently supported. There is little data to support timing of booster doses for conjugate vaccines. The use of PPV-23 does create potential for hyporesponsiveness for repeat doses. The immunogenicity data for PPV-13 in older adults suggests antibody persistence for five to 10 years.

9. Implementation issues

9.1 Objective

The objective of this section is to review the most recent data for currently licenced pneumococcal vaccines with respect to potential implementation issues in the NZ context. This includes the effect of vaccines on serotype replacement, types and timing of schedules for a universal childhood schedule, co-administration, specific vulnerable population groups and adult schedules. The focus is on use of conjugate vaccines in the universal childhood programme. For the vulnerable groups and adult populations, there is consideration for any recent updates to use of conjugates, polysaccharides and mixed schedules.

As the childhood schedule already includes universal PCV vaccination and a high-risk programme, other implementation issues, such as workforce and increased service delivery, are not covered in this review.

9.2 Review

9.2.1 Co-infection and influenza vaccination

Co-infection with influenza A has been associated with increased IPD. For example, in the recent H1N1 pandemic, pneumococcus was the most common co-infecting agent isolated from patients with fatal H1N1 infection (38). There has been international discussion around the use of influenza vaccination administered concomitantly with pneumococcal vaccine to further reduce IPD. One adult study of co-vaccination did not show any additional protection against pneumococcal pneumonia, but co-vaccination did reduce the risk of pneumococcal bacteraemia, compared to pneumococcal vaccination alone (120). An RCT on paediatric concomitant influenza/pneumococcal vaccination did not show a difference in risk reduction for influenza infection and otitis media compared with using influenza vaccine alone, however, it did not evaluate IPD as an outcome (121). Mehr and Woods commented in a 2012 review article that further studies of concomitant vaccination are required, but note that the benefit of co-vaccination may be limited given the range of other respiratory viruses also likely to be associated with IPD risk (38).

9.2.2 Conjugate and polysaccharide vaccine use

9.2.2.1 Hyporesponsiveness

As of early 2013, there is no evidence to suggest that conjugate vaccines are associated with hyporesponsiveness (93).

It appears that the most likely mechanism for hyporesponsiveness is depletion of the type-specific B-memory cell pool in older children and adults, and B-cell fatigue/unresponsiveness due to early binding/deactivation of B-cells by polysaccharide antigens in young children (93).

Administration of PPV prior to PCV has the potential to attenuate responses to subsequent doses of PCV (38). The clinical relevance of this phenomenon, which is serotype specific, is controversial (93). Hence, the current international recommendation is to use PPV-23 for children from 18 months of age who are at greatest risk of IPD once the primary series with a PCV has been completed (38).

Interpretation of studies of multiple doses of PPV-23 in adults is difficult due to the increasing age of participants and associated immunosenescence (93). However, immunogenicity data from immunocompetent older adults supports antibody persistence of five to 10 years (103).

9.2.2.2. Polysaccharide vaccine use in children

Four issues for the use of PPV-23 (and other polysaccharide vaccines) in children have been identified:

- The efficacy and effectiveness of PPV in children is unclear
- There is variable immunogenicity between serotypes in young children and more so for high-risk groups
- There is increasing evidence for hyporesponsiveness following a dose of PPV-23 to subsequent doses of PPV or PCV
- PCV followed by PPV in children results in a reduced memory response.

There is evidence for immunogenicity of PPV-23 in children aged three months to 24 months; this depends on the population and the serotype. Generally, serotypes 2, 3, 4, 5, 7F, 8, 9N, 9V, 11A, 18C, 22F and 33F are immunogenic in most immunocompetent infants (93).

9.2.2.3 Outstanding questions for PPV-23 use in high-risk groups

The 2012 Borrow, Heath and Siegrist review on the use of PPV vaccine summarised a number of research questions remaining, including:

- Does receipt of multiple doses of PPV-23 place recipients at higher risk for IPD?
- Do longer intervals between doses reduce risk of hyporesponsiveness?
- What is the best schedule for revaccination of high-risk people in terms of vaccine type and dose interval?
- What is the optimal schedule for high-risk children?
- What is the optimal schedule for high-risk older children, adolescents and adults?
- What is the optimal schedule for high-risk immunocompromised (93)?

9.2.3 Co-administration

PCV-7 can be safely co-administered with a combined meningococcal serogroup C and *H. influenzae* type b conjugate vaccine, and with MMR vaccine at 12 months of age (122)

PCV-10 is safe and immunogenic when co-administered with other paediatric vaccines and as a booster dose with MMRV in children 12-18 months (40, 123).

PCV-13 can be co-administered to infants and children with routine DTaP-Hib-polio-hepB, meningococcal C, MMR and varicella vaccines with no safety issues or immune interference. Co-administration with trivalent influenza vaccine resulted in lower influenza IgG GMC, but not for PCV-13 serotypes with the exception of 19F. The concomitant use with influenza vaccine is considered satisfactory from both a safety and immunogenicity perspective (28).

9.3 Summary for implementation issues

Both PCV-10 and PCV-13 can be co-administered with a wide range of other vaccines. Primary courses for infants are suited to the NZ schedule at six weeks, three months and/or five months with a booster in the second year of life. Further studies are needed to support the concomitant use of PCV with influenza vaccines.

Questions remain around the use of both conjugate and polysaccharide vaccines in adults and high risk groups.

10. International policy and practice

10.1 Objective

Summarise some of the international experience on the use of pneumococcal vaccines and the position statements and policies from countries with comparable populations to NZ.

10.2 Review

10.2.1 United States

The US Advisory Committee on Immunization Practice (ACIP) previously recommended use of PPV-23 for persons living in high-risk environments, including Alaskan natives and some American Indians aged two to 64 years, where rates of IPD were high. This recommendation was removed in 2008, except for those aged 50 to 64 years, in recognition of the fact that much of the excess disease burden occurs among those with an existing medical condition, as well as, the concerns around hyporesponsiveness when using multiple PPV-23 doses (124). As of June 2012, ACIP was recommending a single dose of PPV-23 for all persons aged 65 years and over (27).

For adults aged 19 to 64 years of age, ACIP recommend PPV-23 for those with immunocompromising conditions, functional or anatomical asplenia, immunocompetent but with chronic conditions, including alcoholism, diabetes mellitus, chronic lung disease, smokers and those with cochlear implants or cerebrospinal leaks (27).

In June 2012, ACIP recommended routine use of PCV-13 for adults aged 19 years and over with immunocompromising and other high-risk conditions. These conditions, administration and revaccination advice are summarised in Table 8. Adults with immunocompromising conditions eligible for pneumococcal vaccine should be vaccinated with PCV-13 during their next pneumococcal vaccination opportunity (125). The recommendations on schedules are summarised in Table 8.

Adults aged over 19 years with immunocompromising conditions, functional or anatomic asplenia, CSF leaks, or cochlear implants, and who have not previously received PCV-13 or PPV-23, should receive a dose of PCV-13 first, followed by a dose of PPV-23 at least 8 weeks later (126). Persons who have previously received at least one dose of PPV-23 should receive a PCV-13 at least one year after the last PPV-23. For those who require PPV-23, at least eight weeks should lapse after PCV-13 and at least five years after the most recent dose of PPV-23 (125). (Table 8 next page)

Table 8. High risk indications for administration of PCV-13 and PPV-23 vaccines as per ACIP, US, 2012 (125)

Risk Group	Condition	PCV-13	PPV-23	PPV-23
		Recommended	Recommended	Revaccination after 5 years
Immunocompetent persons	Chronic heart disease		✓	
	Chronic lung disease		✓	
	Diabetes mellitus		✓	
	Cerebrospinal fluid leaks	✓	✓	
	Cochlear implants	✓	✓	
	Alcoholism	✓	✓	
	Chronic liver disease, cirrhosis	✓	✓	
	Cigarette smoking	✓	✓	
Persons with functional or anatomical asplenia	Sickle cell disease and other haemoglobinopathies	✓	✓	✓
	Congenital or acquired asplenia, or splenic dysfunction	✓	✓	✓
Immuno-compromised persons	Congenital or acquire immunodeficiency	✓	✓	✓
	HIV infection	✓	✓	✓
	Chronic renal failure	✓	✓	✓
	Nephrotic syndrome	✓	✓	✓
	Leukaemia	✓	✓	✓
	Lymphoma	✓	✓	✓
	Hodgkin disease	✓	✓	✓
	Generalised malignancy	✓	✓	✓
	Iatrogenic immunosuppression	✓	✓	✓
	Solid organ transplant	✓	✓	✓
Multiple myeloma	✓	✓	✓	

10.2.2 United Kingdom

The UK joint committee on Vaccines and Immunisation (JCVI) suggested in Feb 2009 that PCV vaccination could be of benefit to adults over the age of 65 and certain other adult populations (including individuals with HIV, chronic renal disease and bone marrow transplants, but that more evidence was required (43). Subsequently, in 2011, the JCVI advised that the PPV-23 programme was no longer effective in preventing pneumococcal disease in adults >65 and should be ceased: furthermore, based on a review of unpublished data from Pfizer, there was no conclusive evidence that PCV-13 would be more effective in older adults (127).

As of early 2013, the Health Protection Agency recommends all older adults over the age of 65 years receive a single dose of PPV-23.

At-risk children aged two -five who have not received PCV should receive single dose of PCV. Children over the age of five years should receive one dose of PPV-23 at least two months after the final dose of PCV. The recommendations are further summarised in the Department of Health's Green Book (128).

10.2.3. Australia

In 2011, PCV-13 was introduced for all children at two, four and six months of age (3+0) in Australia. Recently, Australia has moved to a fourth dose of PCV-13 to Aboriginal and Torres Strait Islander children. This programme replaced PPV-23 given as the fourth dose.

At-risk children over 12 months are recommended to have PCV-13 at 18-24 months. At-risk children four years and over are to receive PPV-23.

Revaccination of adults with PPV-23 is now only recommended for those who have a predisposing condition and indigenous people; further doses are not recommended for those who are immunocompetent. This is based on the incidence of severe local reactions associated with revaccination with the vaccine (see section 4.3.4) (129).

10.3 Summary of international policy and practice

There are a range of schedules in use internationally for PCV vaccination, including 3+1, 2+1 and 3+0, which have all been implemented. Generally, there is a move internationally to replace first doses of PPV-23 with a primary dose of PCV-13.

11. Summary of evidence on the use of pneumococcal vaccines

11.1 NZ epidemiology

The introduction of PCV-7 has been associated with large reductions in IPD caused by the vaccine types. There have been some increases in rates of IPD due to non-PCV-7 vaccine types, in all age groups except two to four year olds, and the largest increases have been noted in the older age groups. The rates of serotype 19A are high, but they have remained stable throughout the period 2004-2011 in the under-five age group. Serotype 3 is rare among children under five years of age.

There is insufficient data to be able to assess the impact of the implementation of PCV-10 on disease reduction caused by the additional three strains (1, 5 and 7F).

11.2 Safety

Three issues for safety have been identified in this review. Firstly, the co-administration of TIV and PCV-13 has been associated with an increased risk for febrile convulsions in infants and young children. Secondly, the use of PPC-23 prior to a conjugate vaccine or in repeat doses has the potential to lead to hyporesponsiveness. There is a concern that vaccine induced hyporesponsiveness may place individuals at higher risk of IPD, however as of early 2013, there is no current evidence for this. Thirdly, the severe local reactions associated with wide use of PPV-23 in subsequent doses.

11.3 Direct and indirect effects of PCV vaccines

11.3.1 Direct effects

Based on summarised data, all PCV vaccines appear to be immunogenic and protective against the serotypes included in the vaccines. Both the levels of immunogenicity and impact on disease do vary with different serotypes. It is expected that these vaccines will be protective against pneumonia, but the extent of effectiveness is still unclear. A clearer picture of the level of protection against OM will emerge with further studies; some degree of effectiveness is expected.

Although, PCV-10 has a theoretical advantage by being conjugated with NTHi, there are no head to head studies to know if any one vaccine is more effective than another.

Based on NZ epidemiology, it is expected that PCV-13 could lead to a further reduction in IPD in the order of nearly 30% in children under two years, although the absolute numbers are low (around 15 cases per year). By extrapolation, an increased reduction in pneumonia is also likely but there is no data to confirm this. Immunogenicity data suggest that PCV-10 may have some cross protection to 19A, although there is no evidence to date.

Even with the greater serotype coverage than PCV-13 would afford, there is still a considerable proportion (36% over all age groups) of remaining IPD in New Zealand that is due to serotypes not covered by any of the currently available pneumococcal conjugate vaccines.

The evidence for the effectiveness of PPV-23 in preventing IPD and pneumonia is both weak and mixed. There is no evidence that PPV-23 offers protection in the elderly, although it does appear immunogenic.

11.3.2 Indirect effects

PCV vaccines clearly have strong indirect impact on the reductions of IPD. PCV-13 may have more potential than PCV-10 to reduce disease among the older groups based on the extra serotype coverage, potentially, by as much as 20%. This may prevent up to 110 cases per annum. However, as mentioned above, PCV-10 does have the potential for cross protection with 19A which could reduce this number.

11.3.3 Serotype replacement

It is clear that serotype replacement occurs following implementation of PCV vaccination programmes. However, there are excellent reductions in IPD have been noted internationally with the exception of one Alaskan study. Ongoing monitoring of serotypes will continue to be important.

11.4 Age specific issues

Generally, the age specific issues for pneumococcal vaccination reside with the older age groups rather than the infants. There are still questions about the efficacy of conjugate vaccines in adults, although the immunogenicity data that supports priming older adults and high risk groups with PCV-13 prior to using PPV-23 provides evidence of superior performance in these groups. Efficacy data for the use of PCV-13 in adults is anticipated.

11.5 Vaccine options

One of the considerations for the continued use of PCV-10 is the potential for the reduction in burden of OM, which will be important to include in future cost-benefit analysis.

It is expected that data will show that there has been reductions in disease in under two year olds caused by the additional three serotypes in PCV-10. Further impact on IPD might be expected from the introduction of PCV-13 which may be particularly evident in the elderly.

The potential impact of cross protection and the reductions in non-IPD pneumococcal disease, such as non-bacteraemic pneumonia and otitis media, have not been assessed as yet.

11.6 Schedule options

Within the NZ context, either a 2+1 or a 3+1 option should be effective. While a 3+0 option is also feasible, this is more useful in the context of the EPI programme in developing countries, where doses in the second year of life are programmatically harder to achieve.

There is limited data to support a range of schedule options for high-risk populations as identified in Table 6. To date, the best evidence supports the use of PCV-13 followed by PPV-23. The issue of hyporesponsiveness is a major obstacle to making recommendations for the continued use of PPV-23 and no evidence to support repeat doses. Also, the fact that PPV-23 also appears to induce hyporesponsiveness to conjugate vaccination suggests caution in the repeated use of this vaccine.

The optimal schedule for adults remains unclear. PPV is generally advocated for high-risk groups, but does not have convincing data for its effectiveness. Most recent studies would suggest PCV followed by PPV are likely to be the most effective strategies – providing coverage of the additional 10 serotypes in PPV-23 is still desired.

Dosing intervals for repeat vaccinations are still unclear, although some evidence suggests that, in the case of PPV-23, spacing of five to 10 years may be appropriate.

11.7 International policy and practice

Internationally, there have been slightly different approaches to the use of pneumococcal vaccines. Overall, there is a move towards wide use of PCV-13 in place of first doses of PPV-23. The place and role of PPV-23 in high risk populations and for the elderly remains mixed.

11.8 Quick table of evidence

Table 9. Outcomes and level of evidence

Outcome	PCV-7	PCV-10	PCV-13	PPV-23
Reduction in carriage of vaccine types	Yes – high level of evidence	Yes – high level of evidence	Yes – high level of evidence	No
Reduction in IPD	Yes – high level of evidence	Yes-high level of evidence	Yes-high level of evidence	Possible
Reduction in OM	Yes – moderate level of evidence for some effect	Possible – awaiting further data	Possible – weak evidence	No
Reduction in pneumonia	Yes – high level of evidence	Yes-high level of evidence for CAP in children	Results for adults expected 2013	No evidence
Induction of immunological memory	Yes – high level of evidence	Yes – high level of evidence	Yes – high level of evidence	No
Safety	Concerns with concomitant delivery with TIV vaccines leading to higher fever and febrile convulsions	No safety concerns identified	Concerns with concomitant delivery with TIV vaccines leading to higher fever and febrile convulsions	Severe local reactions after >1 dose Hyporesponsiveness
Evidence for 2+1 schedule	Yes – high level of evidence	Yes – high level of evidence	Yes – high level of evidence	n/a

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