



The Immunisation Advisory Centre

Antigen Literature Review for the New Zealand National Immunisation Schedule, 2016: Pneumococcal disease – in high-risk groups

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Executive summary

Pneumococcal infections are frequently opportunistic and wide ranging, from otitis media or sinusitis to pneumonia and invasive disease, including septicaemia and meningitis, particularly for individuals with impaired immune responses due to comorbidity and therapy.

Invasive pneumococcal disease (IPD) is a severe condition caused by the bacterium *Streptococcus pneumoniae*. It is defined by the Communicable Disease Control manual as detection of *S. pneumoniae* infection in normally sterile sites, such as the meninges, cerebrospinal fluid, blood, pleural fluid and joints.

There is strong and consistent evidence that immunisation with pneumococcal conjugate vaccines (PCVs) significantly reduces rates of IPD and community-acquired pneumonia (CAP). In New Zealand, rates of pneumococcal disease have fallen considerably since the introduction of the vaccines, and disparities between ethnic groups and regions, particularly for Māori and Pacific people in areas of high socioeconomic deprivation, remain but are reducing.

New Zealand's approach to IPD / CAP control consists of immunisation and passive surveillance. These measures are of high quality and are in line with international practice and World Health Organization (WHO) recommendations.

To reduce rates of IPD further, multiple avenues at the policy and societal level, and focus on primary prevention vaccination, are required. It is therefore necessary to identify who is most susceptible to infection to direct these strategies.

Age and comorbidities are important factors for increasing the risk of IPD and CAP. Infection with the most invasive serotypes are more commonly seen in younger people with few comorbidities, whereas the low invasive types are more opportunistic, infecting those with multiple comorbidities and older age.

This literature review was undertaken across scientific articles and systematic reviews published between January 2013 and October 2016 to examine this rapidly expanding topic. The aim was to identify who is at highest risk from IPD and to evaluate the role of pneumococcal vaccination of adults and children in these high-risk groups in reducing disease with currently available conjugate and polysaccharide vaccines.

From the literature, two classifications of risk are identified: namely, high-risk conditions for which there is a significant risk from pneumococcal infection and IPD, and 'at-risk' conditions, which on their own may not significantly increase risk, but when combined together or with life-style risk factors can increase an individual's likelihood of developing IPD. This is described as 'risk stacking' – infants, the elderly or younger adults with more than one comorbidity are at greatest risk from IPD. It appears that the risk of life-threatening pneumococcal infections in children and adults with two or more comorbidities is as high as in those with a recognised high-risk condition. The risk of IPD for adults aged 50 to 64 years with a single non-immunocompromising medical condition was found to be twice that of the general population.

Patients with comorbidities affecting the respiratory system and the immune system are at particularly high risk of IPD and death. Chronic respiratory disease, particularly chronic obstructive pulmonary disease (COPD), cystic fibrosis and lung cancer, is associated with impaired respiratory immunity and increased infection risk. Compromised immunity is a significant risk factor in opportunistic infections like pneumococcus. Other high risk groups include:

- Solid organ and haematopoietic stem cell transplant (HSCT) recipients
- Human immunodeficiency virus (HIV) infection
- Malignancies
- Immune-mediated inflammatory diseases (IMiDs; autoimmune diseases)
- Immunotherapy and chemotherapy recipients
- Functional and anatomic asplenia
- Chronic liver failure
- Chronic kidney disease
- Previous pneumonia and IPD episodes

Some life-style factors, such as air pollution, smoking and alcoholism, can increase the risk of severe disease, especially in those with chronic diseases who are already predisposed to increased risk of infection, for example, asthma, dementia, mental illness and diabetes. Socioeconomic deprivation, particularly unemployment and low income as well as homelessness and overcrowding, was strongly associated with increased risk of IPD in adults in a region of the United Kingdom (UK).

Individuals with compromised sterile sites, such as those with cochlear implant and cerebral spinal leakage, portals for intravenous medications and mechanical ventilation, are at high risk of invasive disease.

There is less data around groups at-risk of community-acquired pneumonia not resulting from invasive disease as, in many countries, only IPD is notifiable.

New Zealand epidemiology

As seen elsewhere, a significant decrease (95.6%) in IPD was observed following the introduction of pneumococcal conjugate vaccines (PCV-7 and then PCV-10) to the universal immunisation schedule in children under 5 years of age in New Zealand. Since the introduction of PCV-13 in to the schedule in 2014, there has been a decrease in IPD associated with serotypes 19F and 3 in infants. These vaccines have also had an indirect effect in older non-target groups for vaccine-serotype IPD.

For the 12 months from June 2015 to June 2016, the highest incidence rates remain in adults aged 65 years or older (30.8 cases per 100,000 population) and infants under 2 years of age (16.0 cases per 100,000).

Chronic illness was the most common risk factor for IPD in cases aged 5 years or older. For infants, smoking in the household was a significant risk factor. The rates of IPD were 3.2 and 4.5 times higher for people with Pacific and Māori ethnicity, respectively, than European and Other.

Pneumococcal disease in the elderly

Elderly adults with waning immunity and increasing comorbidities are at high risk of pneumococcal disease. Infections in older patients with multiple comorbidities are more likely to be of less-invasive opportunistic serotypes.

'Risk stacking' is highly relevant in older adults as comorbidities increase. For example, the high incidence of cardiovascular disease, chronic liver disease, diabetes and lung disease, in particular, in those aged over 65 years adds to the IPD risk in older people. Almost half of the IPD cases in the over 65-year age group reported in the UK had at least one risk factor, the most common being cardiovascular disease.

Pneumococcal disease in children

Compromised immunity is the most significant risk factor in children for opportunistic infections like pneumococcus. While the high-risk groups in children are similar to the high-

risk groups in adults and include organ and bone marrow transplant recipients, HIV infection, haematological malignancies, immunotherapies and asplenia, children with primary immune deficiencies are unable or inadequately respond to immunisation as infants, and are also at risk of recurrent pneumococcal infections.

Children with comorbidities affecting the respiratory system, which can impair respiratory immunity, and those directly affecting the immune system are particularly at high risk of IPD and death. Children with congenital heart disease and renal disease are also at high risk from pneumococcal infection.

Meningitis is a risk for children who have received cochlear implants, intracranial shunts or have cerebrospinal fluid leakage and are at high risk of pneumococcal infection entering the normally sterile nervous system.

Some life-style factors, such as air pollution and smoke exposure can increase the risk of severe disease, especially in children who are already predisposed to increased risk of infection, such as those with chronic diseases like diabetes and asthma.

Frequent hospitalisation may be as strong a risk factor for IPD in children as specific underlying chronic disease.

Safety of pneumococcal vaccines

Pneumococcal vaccines have been shown to be generally well tolerated and safe in clinical trials and post-licensure surveillance. Most common reactions are mild to moderate injection site pain and mild systemic reactions such as fever, fatigue and muscle pain. No serious adverse events have been identified following pneumococcal vaccination of adults, children or associated with underlying disease and immunocompromise.

Immunogenicity

Few studies have investigated the immunogenicity of PCV-13 in adult populations or in children with increased risk of IPD. Data around the long-term persistence of immunity is also lacking in older children and adults.

Most studies found that PCV-13 was immunogenic in 23-valent pneumococcal polysaccharide vaccine (PPV-23) naïve and experienced adults with increased risk of IPD, including the elderly and the immunocompromised.

There is no serological correlate of protection and anti-pneumococcal antibody titres may not be an informative measure of protection. The functional ability of these antibodies to opsonise pneumococcal bacteria has greater significance in providing protection. Prior exposure to pneumococcal polysaccharides (through vaccine or disease) may contribute to a decreased effectiveness of PPV-23 in older people as a result of a decline in IgM memory B cells.

The optimal timing between doses of PPV-23 was determined to be at least 5 years in adults and children with increased risk of IPD. There was no evidence that a different timing would be required for children. Due to the risk of pneumococcal antigen-specific hyporesponsiveness following repeat doses of PPV-23, the recommendations are a maximum of three life-time doses and for PCV-13 to given at least one year after any doses of PPV-23.

Delaying immunisations to improve immunogenicity in those at high risk of pneumococcal infections may not be advantageous when opportunities to vaccinate could be missed. PPV-23 provides extra coverage for those most at risk from IPD; lower antibody concentrations and functional antibody titres need to be balanced with clinical risk.

Vaccine Effectiveness

Although there is limited data, PCV-13 appears to be effective in preventing vaccine-type community-acquired pneumonia and IPD in adults over the age of 65 years. There is very little literature around the impact PCV-13 vaccination of high-risk groups on the incidence of IPD. Much of the research has investigated the indirect effects of vaccination of infants rather than direct effects of vaccination of older children or adults.

Vaccine effectiveness in adults

Most of the recent studies that have investigated immunogenicity and efficacy or effectiveness of the pneumococcal conjugate vaccines PCV-7 and PCV-13 have reviewed their use together with the PPV-23 in adults. The CAPiTA study is the most comprehensive study of PCV-13 to date in those aged 65 years or older. It found PCV-13 to have 45% efficacy against pneumococcal CAP and 75% efficacy against IPD in the elderly compared with placebo.

When given alone, PPV-23 can provide protection against IPD, reduce hospital stays and reduce cardiovascular outcomes in the elderly. PPV-23 has been demonstrated to be around 50% effective in preventing IPD in adults aged 50 years or older. The protection afforded by PPV-23 in the prevention of pneumococcal pneumonia was seen to wane within 5 years.

PCV-13 followed by PPV-23 vaccination is effective, but there are issues with non-responsiveness to PPV-23 in some individuals. When used after PCV-13 vaccination, PPV-23 may provide broader, but short-lived, protection against IPD caused by the additional pneumococcal vaccine serotypes in high-risk individuals.

Vaccine effectiveness in high-risk children

High-risk groups of children and adolescents benefit from broader serotype protection provided by PCV-13 when oropharyngeal carriage is considered as a risk for pneumococcal disease.

No recent literature was identified investigating the effectiveness of PCV vaccines in preventing IPD in children with high-risk conditions, specifically.

Dosing schedules

To date there have been very few studies investigating options for administration of PCV vaccines in older high-risk groups other than those evaluating the efficacy of infant schedules. The 2012 pneumococcal antigen review found in adults that PCV-13 alone, or as priming dose prior to PPV-23 was consistently supported by literature. No recent data change that position and the questions around the use of both conjugate and polysaccharide vaccines in older adults and high risk groups remain unanswered.

Recommendations around the number and interval between PPV-23 doses vary from one lifetime booster to a maximum of three doses per adult lifetime for those with high IPD risk.

Since 2012, the Centers for Disease Control and Prevention (CDC) have recommended that high-risk individuals over the age of 2 years receive one dose of PCV-13 then PPV-23 at least 8 weeks later.

International recommendations

Internationally, there is a wide variation in the use of pneumococcal vaccines in older adults and at-risk groups. Some countries only recommend PPV-23 not conjugate pneumococcal vaccines, or vice versa.

International recommendations tend to agree broadly with who is at high risk of IPD. Many countries identify those older than 60-65 years of age as being at increased risk of IPD and recommend PCV-13 and/or PPV-23 vaccination. Some countries, including the US, identify individuals with alcoholism and tobacco smokers as being at risk from IPD and recommend pneumococcal vaccination for these groups. Canada recognises drug users and homeless adults as being at increased risk. However, where pneumococcal vaccination is recommended, it is not necessarily funded for some or all of these conditions.

In Australia and Canada, indigenous people are identified as being at increased risk of IPD and recommend extra PCV boosters in childhood and for adults from the age of 50 rather than 65 years as for non-indigenous individuals.

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Abbreviations

ACIP	Advisory Committee on Immunization Practices
AE	Adverse events
AEFI	Adverse Events Following Immunisation
AOM	Acute otitis media
ART or HAART	Antiretroviral treatment / highly active antiretroviral treatment
CAP	Community-acquired pneumonia
CAPiTA	Community-acquired pneumonia immunization trial in adults
CDC	Centers for Disease Control and Prevention
CFR	Case-fatality rate
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CSF	Cerebrospinal fluid
ESR	Institute for Environmental and Scientific Research
GMC or GMT	Geometric mean concentration or titre
GMFR	Geometric mean-fold rise
HR	Hazard ratio
HIV	Human immunodeficiency virus
HSCT	Haematopoietic stem cell transplant
IBD	Inflammatory bowel disease
IC or non-IC	Immunocompromising or non-immunocompromising
IMiD	Immune-mediated inflammatory disease
IPD	Invasive pneumococcal disease

NPP	Non-bacteraemic pneumococcal pneumonia
NP	Nasopharyngeal
NZ	New Zealand
OM	Otitis media
OP	Oropharyngeal
OPA	Opsonophagocytic activity
OR	Odds ratio
PCV	Pneumococcal conjugate vaccine
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
PCV-7	7-valent pneumococcal conjugate vaccine with serotypes 4, 6B, 9V, 14, 18C, 19F and 23F
PPS	Pneumococcal polysaccharide
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 control trial
RR	Relative risk
SAE	Serious adverse event
TIV	Trivalent inactivated influenza vaccine
UK	United Kingdom
US	United States of America
WHO	World Health Organization

1 Background

Streptococcus pneumoniae is a gram positive bacterium. The outer polysaccharide capsule has over 90 distinct compositions, which are defined by different serotypes. This capsule interferes with complement opsonisation and phagocytosis, and is one of the primary factors responsible for the virulence of this bacterium.¹ Each serotype has different virulence, which varies in different regions of the world. Clinical disease caused by *S. pneumoniae* ranges from mild disease, including sinusitis and otitis media, through to non-bacteraemic pneumococcal pneumonia (NPP) and community-acquired pneumonia (CAP) to severe invasive disease, including bacteraemic pneumonia, meningitis and bacteraemia. Pneumococcal disease begins with asymptomatic colonisation of the nasopharynx and asymptomatic carriage is common. Rates of colonisation are higher in low income countries (85%) compared with high income countries (27%), and young children and infants are likely to be the main reservoir. When *S. pneumoniae* enters normally sterile fluids causing disease, such as cerebrospinal fluid (CSF), blood, pleural fluid and joints, it is termed invasive pneumococcal disease (IPD).^{2, 3}

Pneumococcal disease affects all age groups, with the greatest burden in the very young, particularly unvaccinated Māori and Pacific infants in New Zealand (NZ), the elderly and immunocompromised. The World Health Organization (WHO) estimated that, in 2008, 476,000 out of 8.8 million deaths among children younger than 5 years were caused by pneumococcal infections. These infections are the most common cause of CAP requiring hospitalisation in adults in Europe and the United States of America (US). A large proportion of the IPD and pneumococcal meningitis cases occur in children under the age of 2 years; mortality is highest in the youngest infants. As well as age-related incidence, socioeconomic settings with poor nutrition, high air pollution and tobacco smoking, poor hygiene and lack of exclusive breast feeding are associated with increased incidence and poorer outcomes.

1.1 The vaccines

There are two types of pneumococcal vaccines; both utilise the antigenicity of the serotypes defined by the outer polysaccharide capsule, a major virulence factor of *S. pneumoniae*. These vaccines have good safety data in both children and adults.

1.1.1 Polysaccharide vaccine

The older 23-valent pneumococcal polysaccharide vaccine, PPV-23, has been recommended in the US for more than a decade for high-risk groups and all adults over 64 years of age. While some impact on IPD rates has been observed, there has been little influence on NPP and mucosal disease, such as otitis media, caused by the serotypes in this vaccine. In NZ, PPV-23 has been funded for high-risk groups over the age of 2 years only.

PPV-23 consists of a mixture of 23 purified capsular polysaccharides from *S. pneumoniae*, as shown in Table 1. The immune response to polysaccharide vaccines is B cell driven with little T cell help. This T cell-independent response produces low-affinity antibody and poor quality, short-lasting immunological memory as a result of inefficient antibody switching. Infants under the age of 2 years are immunologically immature and unable to respond to this vaccine. Furthermore, repeated doses of this vaccine results in an attenuation of the immune response against pneumococcal vaccine serotypes, termed hyporesponsiveness.

1.1.2 Polysaccharide conjugate vaccines

To obviate the poor immunogenicity of polysaccharide antigens, pneumococcal conjugate vaccines are constructed by attaching polysaccharide antigens of the different serotypes onto highly immunogenic carrier protein molecules. The pneumococcal conjugate vaccines PCV-7 and PCV-13 use a non-toxic recombinant variant of diphtheria toxin called CRM₁₉₇. In PCV-10, the polysaccharides are conjugated to either CRM₁₉₇, tetanus toxoid carrier protein or protein D of non-typeable *Haemophilus influenzae* for the different serotypes. These proteins induce vigorous T-helper cell-dependent immune responses against the vaccine serotypes with the resultant B cell switching to high-affinity antibody production to induce good quality, sustained immunological memory. Unlike PPV-23, these conjugate vaccines can be used to immunise infants and children under 2 years of age as part of the routine childhood immunisation schedule.

In June 2008, the 7-valent pneumococcal conjugate vaccine (Prevenar[®]) was added to the NZ national immunisation schedule. It was replaced by the 10-valent PCV (Synflorix[®]) in July 2011, which in turn was replaced by PCV-13 (Prevenar[®] 13) in July 2014. From July 2017, infants will routinely be immunised with PCV-10; PCV-13 and PPV-23 will remain available, and funded, for children and adults with specific conditions that put them at high risk of IPD. A summary of the serotypes contained within these vaccines is shown in Table 1.

Table 1: The pneumococcal serotypes included in the various vaccines

PCV-7, Prevenar [®] 13 Conjugate vaccine				4		6B				9V			14		18C	19F		23F						
PCV-10, Synflorix [®] Conjugate vaccine		1		4	5	6B	7F			9V			14		18C	19F		23F						
PCV-13, Prevenar-13 [®] Conjugate vaccine		1	3	4	5	6A	6B	7F		9V			14		18C	19A	19F		23F					
PPV-23, Pneumovax-23 Polysaccharide vaccine		1	2	3	4	5	6B	7F	8	9N	9V	10A	11A	12F	14	15B	17F	18C	19A	19F	20	22F	23F	33F

Consistent with the rest of the world, since the introduction of PCV-7 to the childhood immunisation schedule, there has been a dramatic decline in rates of IPD in NZ in the vaccine-eligible age groups and in unvaccinated age groups, due to the indirect herd immunity effect from decreased nasopharyngeal carriage. Worldwide, the impact of the non-invasive pneumococcal disease in children has been clearly observed with reduction in NPP hospital admissions.

Cross-protection against IPD has been detected between serotypes 6B and 19A, which are included in the PCV-7 and PCV-10 vaccines, and serotypes 6A and 19F, respectively, providing additional protection to serotypes not contained within these vaccines.

The focus of this review is to identify who is at highest risk from IPD and to evaluate the role of pneumococcal vaccination of adults and children in these high-risk groups in reducing disease with conjugate and polysaccharide vaccines. Literature published between January 2013 and October 2016 will be evaluated.

The role of the different serotypes in disease virulence and incidence of serotype replacement are outside the scope of this review and will not be considered in depth. Infant pneumococcal immunisations are not considered as part of this review since the focus is on children and adults with increased risk from pneumococcal infections. However, in response to changes to the NZ national immunisation schedule in 2017, a separate review will be conducted to review literature on the safety and effectiveness of PCV-10 in the childhood immunisation schedule and the impact this has had on pneumococcal disease.

2 Methodology for review

2.1 Literature search strategy

The points below form the focus of the literature search. Particular emphasis in this part of the pneumococcal antigen literature review is around the use of pneumococcal vaccines in the high-risk groups, the identification of who is at risk of pneumococcal disease and vaccination strategies. The objectives for this review have been informed by the general specifications for the New Zealand (NZ) academic antigen review 2016 and those specifically specified for the review of pneumococcal vaccines in high-risk groups.

1. Incidence of pneumococcal disease and identification of high-risk adult and child groups
2. Safety
3. Immunogenicity in different groups
 - 1) Conjugate vaccines
 - 2) Polysaccharide vaccines
 - 3) Use of both vaccines
4. Effectiveness in disease control in different groups
 - 1) Against community-acquired pneumonia
 - 2) Against invasive pneumococcal disease
5. Differences that need to be considered for each age group
6. Different options for scheduling
7. Current international research and evidence around use of vaccines as above.

This is neither a systematic review nor a critique of the literature. The choice of articles reviewed is based on the purposeful selection of recent reviews and studies that may best inform policy discussions around the use of pneumococcal vaccines in high-risk individuals.

Medline

MeSH terms: "Pneumococcal vaccines AND conjugate"

Limit to Humans, English, 2013 – current, removed duplicates = 781

Cochrane Library search terms and strategy

Search term: title, abstract, keywords: "Pneumococcal vaccine"

Limit to Cochrane Reviews, Other Reviews, 2013-present = 7 (including protocols)

Scopus search terms and strategy

Search term: "Pneumococcal vaccine" Published 2013 – present

All documents excluding physical and social sciences = 2933

Limit to: English, medicine, article review, article in press, conference paper, human, humans, vaccination = 2268

Also: "Pneumococcal disease AND Risk", limited to 2013-2016, article or review, medicine, English = 227

2.1.1 Grey literature

No grey literature was considered in this review.

2.1.2 Additional searches

Where questions arose, additional searches were undertaken to identify further available data. Where articles were missing they were accessed and added to the library. All duplicates were removed from the final library.

2.1.3 Final Endnote library 974 articles

Where systematic reviews and/or meta-analysis were available the preceding literature has been excluded from the review. This final library included articles related to the childhood immunisation schedule and use of PCV-10 in infants rather than being specifically related high-risk groups, and therefore were not considered in this review.

2.2 Participants/populations

The focus of this review was on groups of adults and children (over 2 years of age) who are at high risk of invasive pneumococcal disease and community-acquired pneumonia for whom pneumococcal vaccination is recommended.

High-risk persons identified from the literature include those with:

- Age over 65 years
- Immune deficiency: asplenia or dysfunction of the spleen, HIV infection, congenital immunodeficiencies
- Immunosuppression: chemotherapy, systemic steroids and certain disease modifying agents (e.g. disease-modifying anti-rheumatic drugs; DMARDs)
- Sickle cell disease and other haemoglobinopathies
- Haematopoietic stem cell transplant (HSCT) recipients
- Chronic respiratory illness, including bronchiectasis, cystic fibrosis, COPD, other respiratory diseases, severe asthma
- Chronic heart disease
- Chronic kidney disease including nephrotic syndrome, chronic renal failure and renal transplant
- Chronic liver disease including cirrhosis, biliary atresia, hepatitis
- Neurological disorders that impair oral secretion clearance, such as cerebral palsy
- Haematological malignancies, including leukaemia and lymphoma
- Solid organ transplant recipients
- Diabetes mellitus
- Cochlear implant recipients
- Indigenous ethnicity
- Cerebrospinal fluid leaks
- Inflammatory bowel disease
- Alcoholism
- Tobacco smoking
- Multiple comorbidities
- Homelessness and overcrowded housing
- Severe psychiatric disorders, dementia and Parkinson's disease
- Occupational exposure to inhaled metal fumes, such as welding
- Previous pneumonia episodes

2.3 Interventions

2.3.1 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 carrier protein (CRM₁₉₇). Each dose contains aluminium phosphate adjuvant and 4.3mg of sodium chloride as a buffer with water for injection.

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

PCV-13 (Prevenar[®] 13; Pfizer) 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 non-toxic diphtheria CRM₁₉₇ (CRM) 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 aluminium as aluminium phosphate adjuvant and no thimerosal preservative. With the addition of six further serotypes, PCV-13 replaced Wyeth Pharmaceutical's (subsidiary of Pfizer) 7-valent PCV (PCV-7, Prevenar[®]) which contained serotypes 4, 6B, 9V, 14, 18C, 19F and 23F.

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

PPV-23 (Pneumovax 23, Merck, Sharpe and Dohme) 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 25 µg of each polysaccharide in isotonic saline solution with 0.25% phenol as a preservative.

These are the vaccines currently available in New Zealand. Some of the literature reviewed considers PCV-7. Studies have shown non-inferiority between the current PCV-13 and PCV-7 for the serotypes in common and are discussed in this review.

2.4 Study designs

Included in this review are meta-analyses, systematic reviews, other literature reviews, randomised control trials, case-control studies, and observational studies using database matching.

3 Epidemiology of pneumococcal disease in New Zealand

3.1 Notified invasive pneumococcal disease

Invasive pneumococcal disease (IPD) has been a notifiable disease in New Zealand since October 2008. According to the most recent Institute of Environmental Science and Research (ESR) annual IPD report, during 2014 there were 489 cases of IPD notified (10.8 cases per 100,000 population) and *S. pneumoniae* was isolated from an invasive site in 96.5% of these cases. The rates of IPD in Māori and Pacific ethnic groups were 3.2 and 4.5 times higher, respectively, than the rate for European and Other ethnicity. Of the 34 cases

in infants (younger than 2 years of age), 16 were Māori and 6 were Pacific ethnicity. IPD case-fatality rate (CFR) was 4.9% and the rate of pneumococcal meningitis was 0.8 per 100,000 across all ages. Those younger than 1 year had the highest rate of meningitis (11.9 per 100,000).⁴

3.1.1 Exposure to risk factors

The most common risk factor for IPD during 2014 among all cases was chronic illness (47.3% of cases). For infants <2 years of age, smoking in the household was the most common risk factor (information for this risk factor was recorded in 9/34 cases). For those aged ≥5 years, chronic illness was the most common risk factor recorded, which included CSF leak, intracranial shunts, diabetes, cardiac disease, pulmonary disease, chronic liver disease, renal impairment and alcohol-related disease. In some cases, more than one risk factor was recorded. Further details are shown in Table 2.⁴

Table 2: Exposure risk factors associated with cases of invasive pneumococcal disease during 2014 (source: ESR IPD surveillance annual report, 2014)

Risk factor	Cases ^a	Total reported ^b	Percentage ^c
Smoking in the household ^d	6	11	54.5
Chronic illness ^e	208	440	47.3
Premature birth ^f	3	10	30.0
Current smoker ^g	89	330	27.0
Immunocompromised ^h	74	439	16.9
Chronic lung disease / cystic fibrosis	60	443	13.5
Attends childcare ^d	2	15	13.3
Resident in long-term or chronic care facility ⁱ	35	435	8.0
Cochlear implants	1	419	0.2
Anatomical or functional asplenia	6	436	1.4
Congenital or chromosomal abnormality	5	424	1.2

a. Number of cases recorded 'yes' for each risk factor – some cases reported exposure to more than one risk factor
b. Number of cases for which information was recorded for each risk factor
c. Percentage of cases with the risk factor for which information was supplied
d. Cases <5 years only
e. Includes CSF leak, intracranial shunts, diabetes, cardiac, pulmonary, chronic liver diseases, renal impairment and alcohol-related disease
f. Cases <1 year only, born <37 weeks gestation
g. Cases aged ≥ 15 years only
h. Includes HIV/AIDS, lymphoma, organ transplant, multiple myeloma, nephrotic syndrome, chronic drug therapy, dysgammaglobulinaemia and sickle cell anaemia
i. Among cases aged ≥75 years, 24.0% (25/104 cases for whom information was supplied) were long-term care facilities

Although the epidemiology of IPD notifications is reasonably well described in NZ, and as mentioned, certain risk factors have been identified, there remains missing data around the incidence of pneumococcal disease and comorbidities. This may be because some

comorbidities are not currently categorised as being associated with increased risk of IPD or information on risk factors are not being recorded when cases are notified.

3.2 Serotype prevalence

The most prevalent pneumococcal serotypes detected in 2014 were 19A, 7F, 3 and 22F (resulting in 87 cases, 54 cases, 42 cases and 39 cases, respectively): these four serotypes accounted for 47% of all culture-positive cases across all age groups. Since 2011, serotype 19A (included in PCV-13) has been the most common among IPD cases, with significant increases in the 5-64 years and over 65-year age groups since PCV-7 was introduced. It was anticipated that the introduction of PCV-13 in July 2014 would provide direct and indirect protection from these three most common types.

The rates of IPD due to 7F have decreased since the switch from PCV-7 to PCV-10 in late 2011, and this now appears to be having an indirect effect on type 7F disease in older age groups. A notable change in the serotype prevalence in IPD was observed in 2014 for serotype 3 (a PCV-13 serotype). The total number of cases with this type increased from 23 in 2013 to 42 in 2014, particularly in the <65 year age group.⁴

As reported in the 2016 April-June quarterly IPD surveillance report, published in August 2016, 121 IPD cases were notified during the second quarter of 2016. The IPD notification for the preceding 12 months (June 2015-June 2016) was 10.2 per 100,000 with 468 cases (a similar rate to 2014-2015). The age distribution of cases is presented in Table 3. Similar to 2014, the four most prevalent serotypes during 2015-2016 were 19A, 7F, 22F and 3. However, notable decreases were observed in IPD due to types 19A and 3 (PCV-13 serotypes) in infants aged <2 years. An increase, from 5 cases to 22 cases, was observed for IPD due to serotype 33F (non-PCV serotype) for both the <2 year and ≥5 year age groups.⁵

Age group	Apr-Jun 2016	12 months ending Jun 2016		12 months ending Jun 2015	
	Cases	Cases	Rate ^a	Cases	Rate ^a
<2 years	9	19	16.0	25	20.9
2-4 years	5	15	8.0	19	10.0
5-64 years	64	226	6.3	216	6.1
≥65 years	43	208	30.8	197	30.3
Total	121	468	10.2	457	10.1

^a Rate is expressed as cases per 100,000 population

Table 3 Number of cases and rates of invasive pneumococcal disease by age group in New Zealand (source: ESR)

3.3 Impact of routine pneumococcal vaccination

In children under 5 years of age, there was a 95.6% decrease in IPD due to PCV-10 serotypes between 2006/7 and 2014 (from 44.2 to 1.9 per 100,000 population) and the overall rate of IPD due to any serotype decreased by 66.7% in this age group, from 53.5 to 17.8 per 100,000.

Indirect effects have also been observed following the introduction of routine PCV vaccination of infants. Significant reductions of 60.0% and 69.9% were observed in PCV-10 serotype IPD notifications in those aged 5-64 years and over 65 years, respectively,

between 2006 and 2014. Although, unlike for the <5 year-olds, no corresponding decline was seen for overall IPD and non-PCV-10 serotypes in these age groups.⁴

During June 2015-June 2016, an increase in the prevalence of serotype 33F (non-PCV serotype) from 5 IPD cases to 22 cases was observed for both the <2 year and ≥5 year age groups.⁵ This may be suggestive of serotype replacement in response to PCV-13 immunisation.

The indirect effects of infant PCV vaccinations on IPD in adults has been demonstrated in other countries. A systematic review of literature published in English from 1994-2011 found declines in vaccine serotype IPD follow the introduction of PCV-7 in children aged >5 years and adults. At the time of the review data for PCV-10 and PCV-13 were not available.⁶

3.4 Summary

Since the introduction of PCV-13 to the NZ childhood immunisation schedule in 2014, there has been a decrease in IPD associated with serotypes 19F and 3 in infants. A significant decrease (95.6%) in IPD was observed following the introduction of PCV-7 and then PCV-10 to the childhood immunisation schedule in children <5 years of age. These vaccines have also had an indirect effect on older age groups for vaccine-serotype IPD.

During the year from June 2015 to June 2016, the highest rates of IPD remained in adults aged ≥65 years (30.8 cases per 100,000 population) and infants <2 years (16.0 cases per 100,000).

Chronic illness was the most common risk factor for IPD in cases ≥5 years of age. For infants, smoking in the household was a significant risk factor. In addition, the rates of IPD were 3.2 and 4.5 times higher for Pacific and Māori ethnicity, respectively, than European and Other.

4 Pneumococcal disease in adults

4.1 Background

IPD is characterised by infection of normally sterile body sites through the failure of defences or because these sites have been exposed to infection via surgery or insertion of medical devices. It is less likely to occur in healthy adults with robust immunity, however as seen in the elderly and in infants, individuals with impaired immunity are at increased risk of the disease. Certain underlying medical conditions are known to increase risk of IPD, in particular conditions resulting in immunocompromise.

Several studies and literature reviews have been conducted to better identify who is at greatest risk from IPD. In this section, the predisposing risk factors for IPD and CAP are reviewed for adults aged between 18-64 years.

4.2 Community-acquired pneumonia

IPD notification data can underestimate the impact of pneumococcal disease in a population because the majority of cases of CAP are non-invasive, also known as non-bacteraemic pneumococcal pneumonia (NPP). The most recent UK data showed that PCV-13 serotypes account for 12.6% of all CAP and 41% of pneumococcal CAP.⁷

A systematic review was conducted to evaluate the burden of vaccine-type adult pneumococcal disease in the UK. The incidence of IPD across all adult age groups in England and Wales during 2013/14 was 6.85/100,000 population. The incidence of pneumococcal CAP, including non-invasive disease, was 20.6/100,000 in hospitalised adults. There was limited data on serotype distribution in high risk groups and no data on vaccine-type CAP managed in the community.⁷

4.2.1 Comorbidity and predisposing factors in adults

A literature review found that several comorbid conditions increased the risk of CAP in adults in Europe, as given in Table 4. The overall incidence of CAP ranged from 1.07 to 1.2 per 1000 person-years and increased with age to 14 per 1000 person-years over the age of 65 years. Incidence was higher in men than women. A range of lifestyle factors, including smoking, alcohol abuse, being underweight, poor dental hygiene and having regular contact with children also increased the risk of CAP. The risk of CAP was increased two to fourfold when comorbid conditions were present, these included chronic respiratory disease (up to 68% of patients) and cardiovascular disease (47%), diabetes, cerebrovascular disease, Parkinson's disease, epilepsy, dementia, dysphagia, HIV or chronic renal or liver diseases. In patients with COPD, chronic renal failure or cirrhosis, the frequency of comorbidities was generally higher compared with those without these conditions. The review included studies of pneumonia of any aetiology, however, since *S. pneumoniae* is the most frequently isolated pathogen in patients with CAP in Europe and estimated to cause 30-50% of CAP cases requiring hospitalisation in adults, these findings are likely to reflect those at risk of pneumococcal CAP.⁸

Table 4: Frequency of comorbid conditions in adults with community-acquired pneumonia (Source: Torres et al 2013, Thorax open access)

Comorbid condition	Number of cohorts with data*	Patients with condition (%)
Previous pneumonia	10	3.2–33.8
Chronic respiratory disease	25	9.7–68
COPD	21	9.4–62
Asthma	9	3–50.0
Chronic heart disease	23	10–47.2
Heart failure	27	1.0–46
Diabetes mellitus	48	4.9–33.0
Cerebrovascular disease/ stroke	26	3.2–33
Dementia	12	1.1–33.6
Cancer	33	4.3–18.0
Chronic liver disease	36	0.3–20
Chronic renal disease	39	0.5–26.7

*For studies that only reported data separately for each cohort, all cohorts were included; for studies that reported data for the overall study population, the summary data were used.
COPD, chronic obstructive pulmonary disease.

A population-based cohort study of 27,204 individuals aged ≥60 years, conducted in Spain, found that nursing home residents and those with underlying chronic pulmonary disease or immunocompromise were at highest risk of pneumococcal pneumonia. In a multivariate analysis, a statistically significant increased risk of pneumococcal pneumonia hospitalisation (bacteraemic and non-bacteraemic) was associated with age (hazard ratio [HR] 1.05; 95% confidence interval [95% CI] 1.03-1.07), nursing home residence (4.59; 2.32-9.11), chronic pulmonary disease (4.09, 2.78-6.02), history of pneumonia within 5 years (3.58; 1.97-6.53), history of stroke (2.5; 1.56-4.03), immunosuppressive medication (1.87; 1.06-3.32), smoking (1.69, 1.03-2.76), diabetes (1.66, 1.15-2.41) and chronic heart disease (1.53; 1.01-2.33). Overall, the case-fatality rate (CFR) was 10.4% (12.5% bacteraemic and 10.1% non-bacteraemic cases, p=0.885), with maximum CFR seen in 30% of nursing home residents, 20% with chronic liver disease, 18.2% with a history of stroke and 13.3% receiving immunosuppressive therapy.⁹

4.2.1.1 Chronic kidney disease

A systematic review conducted by McDonald et al. investigated chronic kidney disease (CKD) as a risk factor for CAP in high income countries. The review found that pre-dialysis CKD is associated with an increased risk of severe infection, however, it was unable to determine whether CKD increases the susceptibility to infection or whether this association is modified by age.¹⁰

4.3 Invasive pneumococcal disease

4.3.1 Comorbidity and predisposing factors in adults

Predisposing factors were examined in an epidemiological study of 2977 cases diagnosed with IPD and associated case-fatality rates (CFR) in Västra-Götaland region of Sweden during 1996 to 2009 (mean population 1.5 million). The mean IPD incidence was 15.1/100,000 people per year across all age groups, as expected the highest incidences were among those aged over ≥ 65 years (45/100,000) and infants aged 0-23 months (23/100,000). During this period, 19 adults aged 18-64 died of IPD and there were 485 cases (incidence rate 6/100,000 and 17/100,000 population per year for those age 18-50 years and 51-64 years, respectively). When looking at the relative risks for patients with specific comorbidities, the estimated annual IPD incidence varied widely between specific groups. The highest incidence was seen in those with myeloma, followed by chronic lymphoid leukaemia, haemodialysis, lung cancer, HIV, systemic lupus erythematosus, asplenia, rheumatoid arthritis, COPD and diabetes mellitus. The risk of death within 30 days of hospitalisation for IPD was 3.4 times higher in patients with comorbidities than those without. Solid tumours, notably lung cancer, were associated with a high relative risk of death, followed by haemodialysis, cardiovascular disease and haematological malignancy, particularly myeloma.¹¹

The systematic review by Chalmers et al reported data for high- risk comorbidities; including asplenia, chronic respiratory, heart, renal and liver diseases, diabetes, immunosuppression, cochlear implants and CSF leaks. Prior to the introduction of PCV-13 in the UK, a study conducted by van Hoek et al in 2008/2009 observed that the pattern of IPD incidence was similar for young adults aged 16-64 years with at least one risk factor as for those age ≥ 65 years. From a baseline incidence of 5.2/100,000 in those with no risk factors, the incidence rose to 39/100,000 for those with at least one risk factor and the highest incidences were seen in those with chronic liver disease (172/100,000) and chronic respiratory disease (91/100,000).⁷

4.3.1.1 Immunocompromise

The Chalmers et al systematic review, which evaluated the burden of vaccine-type adult pneumococcal disease in the UK, highlighted a study by van Hoek et al that identified immunocompromise (including by disease, such as HIV, leukaemia and asplenia) as the single greatest risk factor for IPD in the UK population during 2009. In adults aged 16-64 years the incidence of IPD was 88 per 100,000 for those who were immunocompromised (odds ratio of 17.1 compared with adults without immunocompromise). The review also identified HIV infection as a notable risk factor for IPD: incidence rate of 316 per 100,000 in adults aged 16–64 years (odds ratio of 61.2 compared with patients without HIV).^{7, 12}

4.3.1.2 Inflammatory bowel disease

A Danish cohort study, based on database data from 1977-2013, of 74,156 patients with inflammatory bowel disease (IBD) showed that IBD increased the risk of IPD, especially within the first 6 months of diagnosis. Of the IBD patients, 277 (0.37%) were diagnosed

with IPD compared with 3,984 (0.27%) matched controls. Patients with Crohn's disease had a two-fold higher risk and those with ulcerative colitis had 1.5-fold higher risk of IPD than the controls (HR 1.99; 95% CI 1.59-2.49 and HR 1.46; 1.25-1.69, respectively). The risk of IPD was greater in the ulcerative colitis patients who had received azathioprine but not in those with Crohn's disease. Exposure to 5-ASA/sulfasalazine, corticosteroids and tumour necrosis factor-alpha (TNF- α) antagonists did not affect the risk of IPD in IBD patients. The study also found that the risk of IPD was increased prior to IBD diagnosis, the risk was most pronounced within 6 months of diagnosis and remained elevated with time.¹³

4.3.1.3 Asthma

A Canadian systematic review of literature published between January 1990 and February 2013 investigated the risk of IPD in children and adults with asthma. The review found consistent evidence of a positive association between asthma and the risk of IPD. The magnitude of this effect was heterogeneous; adjusted odds ratio ranged from 6.7 in adults >18 years to 1.7 in individuals aged 2-49 years with low risk asthma. The review concluded that the positive association between asthma and IPD supports the addition of asthma as a high-risk condition for pneumococcal vaccination programmes, however, PPV-23 vaccine effectiveness in this population is undetermined.¹⁴

These findings differ from the epidemiological study conducted in Sweden, where asthma in the absence of COPD was not associated with increased risk. Patients with asthma had a significantly lower CFR (RR = 0.27) compared with all IPD patients without asthma, even when sex, age and comorbidities were considered.¹¹

4.3.1.4 Lifestyle risk factors

Evidence for smoking and alcohol intake as risk factor for IPD was systematically reviewed by Cruickshank et al. in 2014. Five out of six studies reported that smoking increased risk for IPD with an odds ratio of 4.1 (ranging from 2.4-7.3) and bacteraemic pneumococcal pneumonia (OR 2.2 [1.7-3.0]). Four out of six studies reported that high alcohol intake increased risk for IPD with an odds ratio range from 2.9 (1.5-5.4) to 11.4 (5.4-21.9). Note that there is an overlap between these studies in what was considered high and moderate alcohol intake. Only one study suggested protective effect for moderate alcohol use (OR 0.7; 0.5-1.0). The review concluded that although the risk of IPD may be increased by smoking and alcohol misuse, the magnitude of this risk is unclear.¹⁵ Both smoking and alcoholism are considered risk factors on the US and Australian pneumococcal vaccination programmes, but not in the UK, Europe or NZ.

4.3.1.5 Socioeconomic deprivation

A population-based study in the UK assessed the incidence of IPD and socioeconomic deprivation in the North-East of England (a region with poorer health and shorter life expectancy than elsewhere in the UK). Between 2006 and 2011, there were 1,351 cases of IPD reported and 57 were aged <65 years. IPD incidence was found to increase linearly with increasing deprivation from 7.0 to 13.6 per 100,000 population, and was strongly associated with adult IPD (aged 16-64 years and \geq 65 years) but not children (<16 years). This IPD incidence was strongly associated with all individual domains of deprivation, except 'barriers to housing and services'; this domain was subdivided into 'wider barriers' which consisted of household overcrowding and homelessness for which there was a positive association with IPD, but it was outweighed by a negative association with 'geographical barriers' which included road distance to a general practice, shops and schools. Employment and income deprivation were the most strongly associated risk factors. The study recommended targeted pneumococcal vaccination for adults living in socially deprived areas.¹⁶

4.3.1.6 Mental illness

A data-linkage study in the UK used two hospital-admission databases to investigate the risk of pneumococcal disease in people hospitalised with severe mental illness compared with a cohort of hospitalised people without recorded mental illness. In the English National Dataset (1999-2011), the relative risk (RR) of pneumococcal disease in people hospitalised with schizophrenia, bipolar disorder, depression or anxiety was 2.3 (95% CI 2.2-2.4), 2.3 (2.2-2.3), 2.1 (2.0-2.1) and 2.2 (2.1-2.2), respectively. The risk appeared to be associated with the psychiatric disorder, rather than being hospitalised, as it remained elevated for years after hospital discharge. This study was unable to determine how health risk or lifestyle factors were linked to the increased risk in this group, but speculated that smoking, drug and alcohol abuse, poverty and homelessness are likely to influence risk in this population. When restricted to those aged <60 years in England, the RRs were 2.8, 2.6, 2.9 and 2.8, respectively, for schizophrenia, bipolar disorder, depression and anxiety. The same data-linking methodology was used to compare these data with diseases known to increase the risk of IPD: the risk of pneumococcal disease was around 4.0% for COPD and 2% for diabetes mellitus (across both datasets analysed).¹⁷

4.3.2 Incidence of vaccine serotype disease

Differences in CFRs were found between serotypes and age in patients with IPD in Europe. IPD notifications were collected from 26 European countries and reported to The European Surveillance System. During 2010, there were a total of 21,565 reported cases. Serotypes were determined in 46.1% of cases, although both outcomes and serotypes (as PCV-7, PCV-13 specific and non-PCV serotypes) were recorded for only 2,921 cases; death occurred in 264 of these cases (9%). Just over half of these were men (56.8%), 38.2% of cases were adults aged ≥65 years and 19.7% were in children aged <5 years.

The serotypes most associated with deaths were serotype 4 (PCV type, RR = 2.03, $p=0.038$), PCV-13-specific type 1 (RR=0.025, $p<0.001$) and type 5 (RR=0.15, [<0.001]) and non-PCV type 11A (RR=1.97, $p0.001$) and type 35B (RR= 4.98, $p<0.001$). Meningitis was present in 391 cases, of which 329 (84%) were non-fatal and 62 (16%) were fatal – with a significantly higher CFR than the non-meningitis cases (91% non-fatal, 8% fatal).¹⁸

4.3.3 Risk of sepsis associated with serotype invasiveness

A retrospective study in Sweden evaluated the capacity of different *S. pneumoniae* serotypes to cause septic shock based on 513 patients with IPD during the pre-vaccine era 2006-2008. Serotypes, comorbidity and sepsis severity were assessed. Serotypes were grouped according to their invasive potential compared with serotype 14 as a reference: high (types 1, 5 and 7), intermediate (types 4, 9, 14 and 18) and low (types 3, 6, 8, 15, 19, 23 and 33). The study found that patients with serotype 3 had significantly higher incidence of septic shock (25%; odds ratio 6.33), higher mortality (30%; OR 2.86) and more comorbidities (83%; OR 3.82) than serotype 14. No difference in sepsis severity was seen between the three groups. Patients with low invasive serotypes were older and had more underlying comorbidities (median age 72 years, 79% comorbidity). Highly invasive serotypes were associated with younger patients with fewer comorbidities (median age 62 years, 48% comorbidity). The authors concluded that these findings support a hypothesis that high invasive serotypes cause IPD in younger patients with fewer comorbidities whereas the low invasive serotypes, such as serotype 3 and 19F, are more opportunistic infecting older patients with defined comorbidities.¹⁹

4.4 Multiple comorbidities – risk stacking

A US-based study investigated the risk of IPD in adults with underlying medical conditions during 2008-2014 within members of Kaiser Permanente Northern California. The risk of IPD for adults aged 50 to <65 years with a single non-immunocompromising (non-IC) medical condition was twice that of the general population. For those with non-IC conditions, the risk of IPD was greatest for adults with chronic liver disease (RR 2.1; 95% CI 1.5-2.8) and those with COPD (RR 2.1, 95% CI 1.8-2.5). The risk of IPD increased with more medical conditions: for one condition - adjusted RR 2.2 (95% CI 1.9-2.5); two conditions – RR = 2.9 (2.5-3.5) and three conditions – RR=5.2 (4.4-6.1). For those with an immunocompromising condition the adjusted RR was 6.8 (6.1-7.7) – this was described as ‘stacking comorbidities’. For this study, there were not sufficient cases of some conditions, such as cochlear implants, to calculate the risk. A total of 1549 IPD cases were detected over the study period across 15,102,047 person-years.²⁰

A US-based retrospective cohort study investigated data from three large health claims repositories between 2006-2010 to compare rates of pneumococcal disease in ‘at-risk’ immunocompetent adults with chronic medical conditions and ‘high-risk’ immunocompromised adults with healthy adults without these conditions. The study identified rheumatoid arthritis, systemic lupus erythematosus, Crohn’s disease, and neuromuscular or seizure disorders as conditions associated with additional risk of pneumococcal disease. Risk stacking was also observed for all-cause pneumonia: rate ratios among persons aged 18-49 years increased from 2.5 (95% CI 2.5-3.5) for one at-risk condition, to 6.2 (95% CI 6.1-6.3) with two conditions and the risk ratio for three or more at-risk conditions was 15.6 (95% CI 15.3-16.0). In the high-risk group overall, the risk ratio for the 18-49 year group was 6.1 and for those with asplenia the risk was 18.2. Findings were similar for pneumococcal pneumonia and IPD with pneumococcus is the most common pathogen associated with pneumonia in the US.²¹

A further study was conducted looking at the incidence of at-risk conditions and risk stacking, using data from the US-based retrospective study comparing rates of pneumococcal disease in ‘at-risk’ immunocompetent adults with chronic medical conditions and ‘high-risk’ immunocompromised adults. It found that 19% of adults aged ≥18 years had at least one at-risk condition in the absence of a high-risk condition; 5% of the adult population had a high-risk condition. The prevalence of both at-risk and high-risk conditions increased with age, as did the proportion with two or more at-risk conditions. Diabetes and heart disease was a common combination for all adults. Asthma and diabetes were important for the 18-49 year old age group and chronic lung disease and heart disease was an important contributor for those aged ≥65 years. As noted previously, the pneumococcal disease incidence rates for adults with two or more at-risk conditions were as high or higher than those who had known high-risk conditions.²²

In the Swedish epidemiology study, across all the IPD cases 1,994 (67%) patients had one or more comorbidity, 983 of patients did not have any comorbidity. Only 67 had received pneumococcal vaccination (mostly PPV-23). The most common comorbidities were cardiovascular and respiratory disease, followed by malignancy and diabetes – likely to be reflective of the high incidence of these conditions in the ≥65 year age group. The rate of CFR was 12.9% among patients with comorbidities and 3.8% among those without.¹¹

4.5 Summary of pneumococcal disease risk in adults

Pneumococcal infections are frequently opportunistic, particularly for adults with impaired immunity due to comorbidity. Age and comorbidities are important factors for increasing the risk of IPD and CAP. Infection with the most invasive serotypes are more commonly seen in younger people with fewer comorbidities, whereas the low invasive types (including serotype 3, 19F and 31) are more opportunistic infecting those with multiple comorbidities and older age.

Patients with comorbidities affecting the respiratory system and the immune system are particularly at high risk of IPD and death. Chronic respiratory disease, particularly COPD and lung cancer, is associated with impaired respiratory immunity and increased infection risk. Older adults with a history of pneumonia episodes and those in residential nursing care are also at increased risk of pneumococcal pneumonia (both invasive and non-invasive infections).

Compromised immunity is a significant risk factor in opportunistic infections like pneumococcus. High risk groups include organ and bone marrow transplant recipients, HIV infection, haematological malignancies, immunosuppressive therapies and asplenia. Chronic liver failure was also found to be a significant risk factor of IPD. Inflammatory bowel disease also increased the risk of IPD.

Some life-style factors, such as air pollution, smoking and alcoholism, can increase the risk of severe disease especially in those who are already predisposed to increased risk of infection, such as those with chronic diseases like asthma, dementia and diabetes. Socioeconomic deprivation, particularly associated with employment and income as well as homelessness and overcrowding, was strongly associated with increased risk of IPD in adults as shown in the UK. These factors may also be compounded by mental illness and other health issues.

Individuals with compromised sterile sites, such as those with cochlear implant and cerebral spinal leakage, portals for intravenous medications and mechanical ventilation, are at high risk of invasive disease.

Two classifications of risk are identified in the literature: namely, 'high-risk' conditions for which there is significant risk of IPD and 'at-risk' conditions, which on their own may not significantly increase risk, but when combined together or with lifestyle risk factors can increase an individual's risk of IPD. This is described as 'risk stacking'. Infants, the elderly or young adults with more than one comorbidity are at greatest risk from IPD. It appears that the risk of pneumococcal infections in those with two or more comorbidities is as high as the risk for those with a recognised high-risk condition. For example, in the 18-49 year age group, the combination of asthma and diabetes was shown to be an important contributor as was chronic lung disease and heart disease in those age ≥ 65 years. The risk of IPD for adults aged 50 to < 65 years with a single non-immunocompromising medical condition was found to be twice that of the general population.

There is less data around groups at risk of community-acquired pneumonia not resulting from invasive disease since, in many countries, only IPD is notifiable (defined as infection of normally sterile organs).

5 Pneumococcal disease in the elderly

5.1 Background

As of 2016 in New Zealand, pneumococcal vaccination is not universally funded for older adults.

In this section, the predisposing factors that increase the risk of invasive pneumococcal disease and pneumococcal community-acquired pneumonia in the elderly will be reviewed to further identify who is at highest risk of IPD and may benefit from pneumococcal vaccination.

5.2 Pneumococcal pneumonia in the elderly

A study in Sicily found that the risk of pneumococcal pneumonia hospitalisations was strongly correlated with increasing age ($p < 0.001$), with a 15-fold increased risk from the age of 50-54 years to ≥ 80 years. Over 8 years, there were a total of 72,372 hospitalisations with at least one ICM-9 code suggesting all-cause pneumonia, of these 1,943 (2.7%) were specifically coded to pneumococcal pneumonia. Pneumococcal pneumonia is not notifiable in Italy and the study found a wide discrepancy between the ICD-9 diagnosis rate (13.4 per 100,000) and a model estimate hospitalisation rate of 113.3/100,000. According to the proposed model, 22.9% of pneumonia out of all-cause pneumonia hospitalisations was estimated to be associated with *S. pneumoniae* infection. A small fraction of adults ≥ 65 years or with underlying medical conditions were immunised with PPV-23 but uptake was very low. The study concluded that although pneumococcal pneumonia was diagnosed in all age groups, vaccinating those ≥ 65 years may be effective in preventing pneumococcal pneumonia hospitalisations.²³

5.3 Invasive pneumococcal disease in the elderly

In the US, as seen in New Zealand, the incidence of IPD is associated with age – the youngest and the oldest are most at risk. Active Bacterial Core Surveillance (ABC) data reported an overall IPD incidence rate of nine cases per 100,000 with one death per 100,000 across all age groups. The risk of death increases in the over 65 year-olds – case rate 19.1/100,000 with 2.4 deaths/100,000 up to a case rate of 42.6/100,000 with 8.0 deaths/100,000 in the over 85 year old age group.²⁴

Differences in CFRs were found between serotypes and age in patients with IPD in Europe. IPD notifications were collected from 26 European countries and reported to the European Surveillance System. During 2010, there were a total of 21,565 reported cases. Serotypes were determined in 46.1% cases, although both outcomes and serotypes (as PCV-7, PCV-13 specific and non-PCV serotypes) were recorded for only 2,921 cases; death occurred in 264 of these cases (9%). Just over half of these were men (56.8%) and 38.2% of cases were adults aged ≥ 65 years.¹⁸

The European study found that individuals of an older age had a significantly higher risk of death than children < 5 years of age (RR age 5-64 years = 3.55 and ≥ 65 years = 4.79). For adults ≥ 65 years the risk of death did not significantly differ among serotypes. It should be noted that this study did not investigate comorbidities, although there are reports that meningitis and co-occurring conditions have been shown to be significantly associated with death.¹⁸

5.4 Comorbidity and predisposing factors in the elderly

As described, age is a significant risk factor for IPD as immunity wanes. There is also an increase in comorbidities in the older age groups, in particular cardiovascular disease, respiratory disease, diabetes, chronic liver and kidney failure, neurological diseases such as dementia, and certain haematological malignancies.

5.4.1 United Kingdom

A systematic review was conducted to evaluate the burden of vaccine-type adult pneumococcal disease in the UK. The incidence of IPD across all adult age groups in England and Wales during 2013/14 was 6.85/100,000 population and 20.6/100,000 for those aged >65 years. Among adults aged >65 years, the incidence of PCV-13-serotype IPD reduced from 10.3/100,000 to 3.7 per 100,000 from 2008/10 and 2013/14, respectively. There was no significant reduction in non-PCV-13 serotypes. PCV-13 was introduced as part of the childhood immunisation schedule in 2010 in the UK but was not part of the adult immunisation programme, although PPV-23 was available for adults aged ≥ 65 years.⁷

From a 2009 survey, the review reported data for high-risk comorbidities; including asplenia, chronic respiratory, heart, renal and liver diseases, diabetes, immunosuppression, cochlear implants and CSF leaks. It identified that 44.8% of patients aged >65 years had at least one risk factor with chronic heart disease the most common. The incidence of IPD increased from 18 per 100,000 to 48/100,000 for those with at least one risk factor. For those with COPD or chronic liver disease, the risk was higher still at 91/100,000 and 129/100,000, respectively.

This review noted a study conducted by van Hoek et al. in 2008/2009 that identified immunosuppression as the single greatest risk factor for IPD in the UK population with an IPD incidence of 209 per 100,000 in immunosuppressed patients aged >65 years (odds ratio 11.7 compared with immunocompetent adults aged >65 years).⁷

5.4.2 United States

Using data from a US-based retrospective cohort study, a further study was conducted looking at the incidence of at-risk conditions and risk-stacking. The prevalence of both at-risk and high-risk conditions increased with age, as did the proportion with two or more at-risk conditions. Diabetes and heart disease was a common combination for all adults and chronic lung disease and heart disease was an important contributor for those age ≥ 65 years. As found in the previous study, the pneumococcal disease incidence rates for adults with two or more at-risk conditions were as high or higher than those who had known high-risk conditions.²²

5.4.3 Sweden

Predisposing factors were examined in an epidemiological study in the Västra Götaland region of Sweden. The highest incidence rate of IPD was among those age ≥ 65 years (45/100,000). The mean age for cases was 60.6 years and median age was 65 years. The most common comorbidities were cardiovascular and respiratory diseases, followed by malignancy and diabetes – likely to be reflective of the ≥ 65 year age group. Pneumonia, the most common manifestation of IPD, occurred in 79% of those ≥ 65 years, 5% had meningitis. Being male was an independent risk factor for death (after correcting for age and comorbidities) with the differences in CFR between the sexes being most pronounced between 50 and 70 years of age.¹¹

5.5 Summary of pneumococcal disease in the elderly

Elderly adults with waning immunity and increasing comorbidities are at high risk of pneumococcal disease. Infections in older patients with multiple comorbidities are more likely to be of the less invasive opportunistic serotypes (for example serotypes 3, 19F and 31).

Patients with comorbidities affecting the respiratory system and the immune system are at highest risk of IPD and death. Chronic respiratory disease, particularly COPD and lung cancer, is associated with impaired respiratory immunity and increased infection risk.

All these factors can be additive and are described in the literature as 'risk stacking'. For example, the high incidence of cardiovascular disease, chronic liver disease, diabetes and lung disease, in particular, in those over 65 years adds to the IPD risk in older people. Almost half of the IPD cases in the over 65 year age group reported in the UK had at least one risk factor, the most common being cardiovascular disease.

6 Pneumococcal disease in children

6.1 Background

The incidence of pneumococcal disease in children is greatest in those under 2 years of age. In the US, as seen in New Zealand, the youngest and oldest are at highest risk, where the incidence rate for IPD in infants age under 1 year was 15.9 per 100,000 with 0.5/100,000 deaths during 2014.²⁴ For this reason, pneumococcal vaccines are included in the national childhood immunisation schedule in the first year of life with a booster in the second year. Cases in older children are frequently associated with factors that increase the risk of invasive disease and will be reviewed here. The use of pneumococcal vaccines as part of the routine childhood immunisation schedule will not be reviewed. Unlike the adult populations, CAP is not distinguished from IPD or pneumococcal disease in the literature for children.

6.2 Risk factors for IPD in children

Literature published between January 2005 and July 2012 relating to the incidence and risk of IPD in at-risk children in Europe and North America was reviewed by Rose et al. In the US, the highest incidence of IPD was seen in children aged >5 years with HIV infection, which peaked at 4,167 per 100,000 person-years in 2000 (the year PCV-7 was introduced to <2 year olds and post highly active antiretroviral treatment [HAART] introduction). The highest risk of IPD was reported in children with haematological cancer or immunosuppression (specifically HIV infection). The lowest risk ratios (≤ 1.5) were reported for respiratory conditions, gastrointestinal disease, congenital immune deficiency, diabetes, cerebral palsy and hydrocephalus. One reviewed study reported that, where risk appears not to be significantly increased compared with controls, a higher number of IPD cases may be a reflection of the increased frailty and susceptibility these children have to disease in general. This leads to frequent hospital contacts and hospitalisation, which may in turn, be as strong a predictor of IPD as a stabilised specific underlying condition.

A decrease in the incidence of IPD in at-risk children was observed after the introduction of PCV-7 vaccine. However, the review reported that there were very few articles from Europe (written in English) investigating the incidence of IPD in children with underlying medical conditions and data were absent for several conditions commonly associated with increased IPD risk. One factor highlighted in an Italian study was that pneumococcal vaccination

coverage in high-risk children is relatively low compared with routine childhood vaccination with PCV. This study found that pneumococcal vaccination rates were below 25% for children with HIV infection, cystic fibrosis, liver transplantation or diabetes mellitus, which demonstrated a need to educate health professionals and families regarding the importance of vaccination in at-risk children.²⁵

A US-based study identified 1,052 cases of IPD in children aged <18 years in Massachusetts from 2002-2014. Of these, 223 (22.1%) had one or more comorbidity, including immunocompromise (32.7%) due to primary immunodeficiency or immunosuppressive therapy and chronic respiratory disease (22.4%). The mean age for IPD in children with at least one comorbidity was 54 months (range 19-101 months) compared with 23 months for those without any other conditions; more than 40% of IPD cases with comorbidity were aged >5 years. Patients with comorbidities were twice as likely to be hospitalised and more than three-times likely to die. The case-fatality rate for children with meningitis was six-fold higher than those with isolated bacteraemia (OR 6.1) after adjusting for comorbidity, age, gender, year of diagnosis and immunisation status. Among children with comorbidities during 2012-2014, 50% (6/12) had non-PCV-13 serotype infections that were included in PPV-23 and 50% had non-vaccine serotypes.²⁶

Recurrent IPD in children was seen in 10 patients out of a total of 593 IPD cases in Spain. Five out of seven patients with reinfection had underlying risk factors including three with CSF leak, one on chemotherapy and one had a toll-like receptor immune defect. No predisposing risk factors were identified in the remainder.²⁷

6.2.1 Asthma in children

A population-based cohort study examined the effect of asthma on childhood pneumococcal disease (PD) in Denmark prior to the introduction of PCV-7 vaccine. Among 88,655 children born between 1994 and 2007, there were 2,253 cases of childhood PD. The study found that asthma was an important risk factor for PD in children and that the effects of asthma are increased in children with other underlying comorbidities. Among children with asthma, 55% to 73% of PD cases (age 2-<5 years and ≥6 years, respectively) were accounted for by an interaction between asthma and comorbidity. The adjusted incidence ratio of the effect of asthma on childhood PD was 2.2 (95% CI 2.0-2.5).²⁸

6.2.2 Passive smoking exposure in children

A US-based study investigated whether passive tobacco smoke exposure increased the risk of IPD in children and found that similar proportions of cases and controls had definite or probable smoke exposure (25% vs 30%, odds ratio = 0.76). This case-control study identified 171 children aged 0-12 years with culture-confirmed IPD during 1994-2004 who were age and health-plan membership matched with two controls. Household cigarette smoke exposure was predicted based on family medical records within two years of IPD diagnosis. IPD cases were more likely to be racially non-white than controls (OR = 4.4) and IPD was associated with pulmonary diagnoses and antibiotic use (OR=2.2 and 1.6, respectively) within 3 months prior to the reference date.²⁹

In the European literature review, tobacco smoke exposure was shown to increase the risk of IPD, particularly for children with other risk factors.²⁵

6.2.3 Ethnic and socioeconomic disparities.

Racial disparities in IPD incidence in children have been observed in the US. Even when socioeconomic conditions were taken into consideration, the IPD rate in children aged <5 years with a black ethnicity remained higher than that for white children (RR 1.60; 95% CI 1.39-1.84). On introduction of the PCV-7 vaccination programme in 2000, socioeconomic

disparities were observed in disease incidence, however, the rate of IPD in poorest children declined between 2001 and 2009. Socioeconomics did not account for racial differences in incidence. Among black children, a significant decreasing linear trend indicated that IPD incidence decreased as poverty increased. Various reasons were proposed for this observation, which may relate to clinical reporting and access to health care, or fewer of the poorest black children attending childcare centres reducing their exposure to infection.³⁰

6.3 Summary of risk factors in children

Compromised immunity is a significant risk factor for opportunistic infections like pneumococcus in children. High-risk groups include organ and bone marrow transplant recipients, HIV infection, haematological malignancies, immunotherapies and asplenia. Children with undiagnosed primary immune deficiencies are unable or inadequately respond to vaccination, and are at risk of recurrent pneumococcal infections. Children with comorbidities affecting the respiratory system and the immune system are at particularly high risk of IPD and death. Chronic respiratory disease is associated with impaired respiratory immunity and increased infection risk.

Air pollution and smoke exposure can increase the risk of severe disease in children, especially in those who are already predisposed to increased risk of infection, such as those with chronic diseases like diabetes and asthma.

Frequent hospitalisation may be as strong a risk factor for IPD in children as specific underlying chronic disease.

One study found that the pneumococcal vaccination rate of children with high-risk conditions was much less than for the general population, and therefore, better education and awareness of the importance of PCV immunisation is required to better protect these children.

7 Safety

7.1 Background

Pneumococcal vaccines have excellent safety profiles. Post-licensure and global surveillance data for PCV-7 did not identify any safety concerns and pivotal trials for PCV-13, in over 4,700 infants and toddlers and 6,000 adults, found no clinically relevant difference between PCV-13 and PCV-7 safety. Since PCV-13 has been available globally, no safety concerns have been identified. Decades of safety data have not identified safety concerns for PPV-23.

The objective of this section is to review the most recent safety data for currently licensed pneumococcal vaccines used for high-risk programmes. It does not include administration as part of routine childhood immunisation schedules. Literature on safety of PCV-10 focuses on children and infants as part of the childhood schedule, not high-risk groups, therefore, it will be covered in a separate antigen literature review. The focus of this section is on PCV-13, with some consideration of any recent updates to PPV-23, when used in adults and children at high risk of pneumococcal disease and when these vaccines are used in combination. Only adverse events following immunisation (AEFI) considered subsequent to the pivotal clinical safety and efficacy trials are reviewed here.

7.2 Review of safety in immunocompetent recipients

7.2.1 Adults aged <65 years

In a US-based study, safety and tolerability of a single dose of PCV-13 were compared between two groups of PPV-23-naïve adults stratified by ages 18-49 and 60-64 years. Local injection site reactions, in particular pain, were more frequently reported in the younger age group. Severe pain occurred in 15.6% of participants aged 18-49 years and 1.7% of participants aged 60-64 years. Local reactions resolved within 3 days for both groups. At least one systemic event, including generalised muscle ache, headache and fatigue, was reported by 96% and 83% of adults aged 18-49 and 60-64 years, respectively. This was considered to reflect a more robust immune response in the younger age group. Systemic events were also more commonly reported by the younger age group, with the exception of fever. The frequency of adverse events (AE) within one month of vaccination was similar between each group. One serious adverse event (SAE) of migraine was considered to be vaccine related in a subject in the 18-49-year group. The study concluded that PCV-13 has an acceptable safety profile in all adults, regardless of age.³¹

The safety following revaccination with PCV-13 was investigated in 727 adults aged 50-59 years five years after initial vaccinations of PCV-13 and seasonal trivalent influenza (TIV) vaccine (given concurrently or 1 month apart). Following revaccination with PCV-13, at least one injection site reaction with pain was reported for most participants. The most common systemic events were generalised muscle ache, headache and fatigue. There were a few reports of fever <39°C. AEs within 1 month of vaccination were reported by 4.7% of recipients. Three out of the six AE considered to be vaccine-related were cases of injection site swelling. No SAE or deaths were considered vaccine related.³²

7.2.2 Adults aged over 65 years.

The CAPiTA (Community-Acquired Pneumonia Immunization Trial in Adults) study is a large randomised control trial (RCT) conducted in the Netherlands to investigate the impact of PCV-13 vaccination in reducing vaccine-serotype CAP during 2008-2013. The study randomised 85,000 vaccine-naïve adults aged ≥65 years to PCV-13 or placebo. Initial findings reported no safety concerns. Most local and systemic AEs were mild to moderate and no vaccine-related SAEs were reported. No significant differences between groups were found in the frequency of newly diagnosed chronic medical conditions, SAEs or deaths.³³

7.2.2.1 PCV-13 and PPV-23

An open-label study conducted in 105 Japanese nursing homes compared the immunogenicity and safety of PPV-23 and PCV-7 vaccines among people aged ≥80 years. The study confirmed that both vaccines were safe with comparable AE profiles and no SAEs were reported.³⁴

A double-blind RCT also conducted in Japan compared the immunogenicity and safety of PCV-13 with PPV-23 in 733 PPV-23-naïve adults aged >65 years. Both vaccines were judged to be safe and well tolerated. Mild to moderate local reactions were reported more frequently for PCV-13 than PPV-23, however, systemic adverse reactions were similar across both groups. No SAEs were reported.³⁵

Adults aged ≥70 years, who had previously received PPV-23, were randomised to receive either PCV-13 then PCV-13 (PCV-13 group) or PPV-23 then PCV-13 (PPV-23 group) a year apart. Of these, 795 participants, 36.9% in the PCV-13 group and 48.4% in the PPV-23 group had one or more underlying chronic disease (including cardiovascular, liver or respiratory disease, diabetes and renal disorders). Local reactions was significantly higher

for the PPV-23 group after the first vaccination. In this group, there were more reports of vomiting following subsequent vaccination with PCV-13 but for both groups the frequency was low (3.1% vs 0.4%). No vaccine-related SAEs were reported after the first vaccination at 1 and 6 months. One case of idiopathic thrombocytopenic purpura in an 81 year old man, occurring 132 days after the second vaccination, was considered to be related to the study vaccines PPV-23/PCV-13. No deaths were considered related to vaccination.³⁶

7.3 Review of safety in immunocompromised adults and children

7.3.1 HIV infection

A Brazilian RCT found no safety concerns for the use of PCV-7 or PPV-23 administered alone or in combination to HIV-infected adults.³⁷

No safety concerns were identified following immunisation with three doses of PCV-13 in 279 HIV-infected adults who had previously been vaccinated with at least one dose of PPV-23. Pain at the injection site was the most common local reaction (around 81% of recipients) and severe injection site or systemic AEs were uncommon. No deaths or vaccinated related SAEs were reported.³⁸

Similarly, in 301 PPV-23-naïve HIV-infected adults and children aged 6-17 years, only mild-moderate local reactions and systemic events were reported following each of three doses of PCV-13. No SAEs or deaths were considered by the investigator to be related to PCV-13.³⁹

7.3.2 Allogenic haematopoietic stem cell transplant

The immunogenicity and safety of PCV-13 followed by PPV-23 was investigated in an open-label study in allogenic haematopoietic stem cell transplant (HSCT) recipients aged ≥ 2 years – 71 years (54 paediatric [median age 10 years] and 162 adults [median age 47 years]). Approximately 3-6 months after HSCT, three doses of PCV-13 were given at 1 month intervals followed by a fourth dose 6 months later and a dose of PPV-23 was given a month after dose four. Local and systemic reactions occurred significantly more frequently after PCV-13 dose four than dose three (local swelling, redness, fever, fatigue and muscle pain). Infections were the most common AE reported and the frequency of AEs possibly related to PCV-13 were similar after dose four and dose one. Six SAEs were considered to be possibly related to vaccination but no causal association was established due to the complexity of the comorbidity conditions in these patients, including facial diplegia (14 days after dose one), injection site erythema and pyrexia (one day after dose two), one patient had two episodes of autoimmune haemolytic anaemia (18 and 116 days following dose three), one case of Guillain-Barré syndrome (29 days after PCV-13 dose four and 1 day after PPV-23) and one case of cellulitis (2 days after PPV-23). There was one case of bilateral pneumococcal pneumonia (36 days after PCV-13 dose three) that was thought to be due to a lack of vaccine efficacy in a severely immunocompromised patient, however the serotype was not determined. The conclusion was that the overall safety profile of the four-dose regimen was considered acceptable when considering the risk/benefit of vaccination.⁴⁰

7.4 Summary of vaccine safety

Pneumococcal vaccines have been shown to be generally well-tolerated and safe in clinical trials and post-licensure surveillance. Most common reactions are mild-moderate injection site pain and mild systemic reactions such as fever, fatigue and muscle pain. No serious

adverse events have been identified for adults, children or associated with underlying disease and immunocompromise.

Although six SAEs were identified in HSCT patients as possibly being associated with the administration of pneumococcal vaccines, no causal association could be established due to complex and multiple comorbidities in these patients.

8 Immunogenicity of pneumococcal vaccines

8.1 Background and scope

The immunogenicity of pneumococcal vaccines are assessed in two ways: measuring functional antibody and serotype-specific IgG antibody titres. Functional antibody titres are measured by opsonophagocytic assay (OPA titres), which measure the ability of the anti-pneumococcal antibodies to opsonise (label) and lead to the killing of pneumococcal bacteria by phagocytes. These antibodies therefore play an important role in protection against pneumococcal disease. The production of serotype-specific IgG antibodies (as determined IgG geometric mean concentration [GMC]) is driven by the activation of T cell immunity by conjugate vaccines and results in immune memory. Polysaccharide vaccines induce a T cell-independent response and are unable to generate long-lived cellular memory. No serological correlation of protection has been established for pneumococcal infection.

The objective of this section is to review the most recent immunogenicity data of currently licensed pneumococcal vaccines. The focus is on PCV-13 with some consideration for any recent updates to PPV-23 data, and the combined use of PCV-13 and PPV-23. Consideration is given to relevant immunogenicity data that contributes to the current understanding of alternative schedules and their effectiveness in preventing pneumococcal disease high-risk populations.

Immunogenicity of conjugate and polysaccharide vaccine (specifically PCV-13, where possible, and PPV-23) in terms of serotypes, functional antibodies and immunity against vaccine-specific pneumococcal serotypes will be reviewed. Age-related risk factors and immune responses to these vaccines are reviewed in adults, the elderly and children at-risk of invasive pneumococcal disease.

In clinical trials, the immunogenicity of PCV-13 has been shown to be non-inferior to PCV-7 for the seven serotypes in common, therefore, there is little new data to review. Data published since the last antigen literature review in 2012 mostly investigates the immune response to the six additional serotypes in PCV-13 administered in childhood immunisation schedules, and is therefore, not relevant to this review. Much of the current literature about the immunogenicity in immunocompromised individuals considers those with HIV infection and those with sickle cell disease in the US and South Africa, but these forms of immunocompromise are uncommon in New Zealand and will not be reviewed in depth.

8.2 Immunogenicity of PCV-13 in adults

The immunogenicity of PCV-13 was evaluated in the US in healthy adults aged 18-49 years, naïve to PPV-23 and compared with adults aged 60-64 years. For all 13 serotypes, OPA geometric mean titres (OPA GMTs) and IgG geometric mean concentrations (GMCs) were non-inferior when comparing the two age groups, and were significantly higher in the younger age group for all except serotype 3 for OPA and IgG GMCs for serotypes 3, 5, 7F,

9V and 18C. Overall, the highest immune responses were seen in the 18-29 year age subgroup.³¹

An open-label study in Mexico investigated the immunogenicity of PCV-13 in PPV-23-naïve adults aged at least 50 years. The study found that OPA GMTs at one month post-vaccination were similar between the 50-64-year age group and the ≥65-year age group, although they were lower pre-vaccination in the younger age group.⁴¹

PCV-13 stimulated a robust immune response against all vaccine serotypes in 134 Japanese adults aged 50-54 years in an open-label study. However, the study found that the immune responses to PCV-13 in adults aged 50-64 years were significantly lower at one month post-vaccination for six out of 13 vaccine serotypes than those reported in similar study populations in the US and the EU; only serotype 14 was higher. The OPA titres were lower for all vaccine serotypes and significantly lower for eight out of 13 serotypes in the 50-64 year age group than the ≥65 year age group in the same study. Although pre-vaccination diphtheria antitoxin levels were significantly lower pre and post-vaccination in the younger age group, no correlation between pre-vaccination diphtheria antitoxin and post-vaccination serotype-specific pneumococcal responses was shown.⁴²

8.2.1 Adults ≥ 65 years

An open-label study found that the OPA GMTs following PCV-13 vaccination in 134 Japanese adults aged ≥65 year were higher for all vaccine serotypes and significantly higher for seven out of 13 serotypes than those reported in a similar EU study for the same age group. All recipients produced robust immune responses to the 13 vaccine serotypes. No influencing factors were identified in the study population in a post hoc analysis.⁴²

8.2.2 Concomitant PCV-13 and influenza vaccination in adults

In two studies, conducted prior to 2013 in Europe, in adults aged ≥65 years and in the US in adults aged 50-59 years, PCV-13 was administered concurrently with trivalent inactivated influenza vaccine (TIV) or one month later (sequentially). The findings showed that, in general, PCV-13 given concurrently induced non-inferior antibody responses to sequential administration. The only exception was numerically lower antibody responses for influenza strain A/H3N2 and pneumococcal serotype 19F seen in those aged ≥65 years who received concurrent vaccines compared with sequential PCV-13 and TIV. The clinical significance of this was not determined.^{43 32}

In a follow-on study revaccination with PCV-13, five years after initial vaccination with PCV-13 and either TIV concomitantly or sequentially, induced OPA GMTs and IgG GMCs comparable with or higher than the levels observed at one month after the initial vaccination for most vaccine-serotypes. In the time between vaccinations, antibody levels declined but remained higher than the pre-vaccination baseline. The study revaccinated 727 participants out of the 1116 adults who were aged 50-59 years at the time of the initial vaccination.³²

Functional opsonising anti-pneumococcal antibodies were measured in an RCT in PPV-23-naïve adults aged ≥65 years who received PCV-13 and TIV concomitantly. In a previous study, the concentrations of serotype-specific IgG antibodies were found to be lower after PCV-13+TIV than PCV-13 alone. Post hoc analysis was conducted to evaluate the functional antibody titres (as measured by OPA). It found that, although the functional pneumococcal response were generally lower, the proportion of OPA responders after PCV-13+TIV vaccination was similar to that observed after PCV-13 alone. The authors recommend that concomitant administration be considered to avoid missing opportunities to vaccinate individuals who may fail to return for subsequent vaccination.⁴⁴

8.2.3 Adults with end-stage renal disease

The immunogenicity of PCV-13 was assessed in 17 patients aged >50 years with end-stage renal disease (ESRD) on dialysis. The overall response rate (defined as \geq two-fold increase in antibody concentration from baseline and ≥ 1 $\mu\text{g/ml}$ post-vaccination) to individual vaccine serotypes ranged from 23.5%-94.1% at 2 months and 23.5%-65% at 12 months. All patients showed a vaccine response to at least one serotype at both 2 and 12 months post-vaccination. However, there was a significant decline in antibody concentrations 12 months post-vaccination. The conclusion was that removal of antibody during dialysis and the effect ESRD has on the immunological memory may contribute to the reduction in antibody concentrations.⁴⁵

8.2.4 Summary of PCV-13

PCV-13 induces robust immune responses in high-risk and elderly adults. The antibody titres vary with serotype and between age groups, particularly for the ≥ 65 year age groups. However, the clinical significance of this variation was not determined.

Lower antibody titres were observed following concomitant PCV-13 and TIV vaccination than when the vaccines were administered a month apart, however, there was no difference in the proportion with functional antibody. The recommendation was not to delay PCV-13 and TIV vaccination as opportunities to vaccination can be missed.

Patients with end-stage renal disease have variable responsiveness to PCV-13 which is not generally maintained over the long term (one year). Although these patients retain immunological memory, variable degrees of haemodilution as a result of haemodialysis affect antibody levels.

8.3 Immunogenicity of PPV-23

8.3.1 Adults aged >65 years

A review of immune responses to PPV-23 in the elderly identified that anti-pneumococcal polysaccharide (PPS) antibody levels may not correlate with disease prevention and the preferred measure of pneumococcal vaccine immunogenicity in adults is by OPA. IgM antibodies are more efficient at fixing complement than IgG to generate opsonic responses (bacterial killing with complement). The review noted that age-related decline in IgM memory B cells was associated with reduced opsonic activity. In young adults IgM memory B cells (CD27⁺IgM⁺) are predominant post vaccination with PPV-23 and have been shown to be important in the response to polysaccharides. In the elderly, prior exposure to pneumococcal polysaccharides may contribute to the decreased effectiveness of PPV-23 since more IgM⁺ B cells are found in this age group than in younger adults prior to vaccination. Following vaccination, the IgM⁺ B cells found in the elderly recipients' blood switched to CD27⁺IgM⁻ memory cells. Therefore, in the absence of IgM⁺ memory cells, diminished anti-PPS IgM antibodies and opsonising activity may increase the risk of infection and decrease the effectiveness of polysaccharide vaccines in the elderly.⁴⁶

8.3.2 Adults with HIV infection

A double-blind RCT conducted in the US investigated the PPV-23 antibody responses in 107 patients with HIV infection immediately, or delayed by 6 months, after initiation of antiretroviral treatments (ART). The study found, in patients with ≥ 200 CD4 cells/ μl , that delaying PPV-23 vaccination for 6 months after the initiation of ART did not make a significant difference to serotype IgG or IgM antibody levels or OPA titres.⁴⁷

A similar study evaluated the antibody response to PPV-23 in adults newly diagnosed with HIV-infection with CD4 <200 cells/ μ l. No significant differences in functional IgM antibody titres or antibody concentrations were seen between 12 patients with low CD4 counts who were vaccinated immediately or 11 patients whose vaccination was delayed for 6-12 months for highly active antiretroviral treatment (HAART). Overall, the HIV-positive individuals had low PPV-specific antibody concentrations post-vaccination, but the OPA titres were increased at least two-fold post-vaccination to a level thought to be protective. For all groups, PPS-specific B cells were evenly distributed between IgM memory and switched memory B cells. However, as anticipated due to a recognised early B cell dysfunction following HIV-infection, the numbers of IgM memory B cells were significantly lower in HIV infected subjects than in 22 HIV-negative PPV-23 vaccinated controls. The authors concluded that PPV-23 vaccination should not be delayed in newly diagnosed patients with HIV-infection and <200 CD4 cells/ μ l.⁴⁸

8.3.3 Revaccination with PPV-23

A systematic review of literature published up to June 2013 was conducted to determine the optimal dose and timing of PPV-23 revaccination in adults. This review did not investigate the role of PPV-23 revaccination in those who were initially immunised with conjugate vaccines (PCV). From the included studies, the review found that revaccination with PPV-23 induced an antibody response at least as high as that following a single priming dose in adults for the majority of serotypes tested. The optimal interval between doses in high-risk adults was found to be at least 5 years. Based on antibody responses, not effectiveness against IPD, the review concluded that an adequate immune response was demonstrated following revaccination with PPV-23, given on average 5 years after the previous dose. However, it was noted that there is a lack of data on the use of multiple PPV-23 booster doses in both adult and paediatric populations.⁴⁹

8.3.4 Summary of PPV-23

The loss of IgM memory B cells and ability to produce IgM antibodies following PPV-23 immunisation may decrease the effectiveness of this vaccine in the elderly.

There was little or no advantage in delaying PPV-23 vaccination of adults infected with HIV on antiretroviral therapy.

Adequate antibody responses were induced by revaccination with PPV-23 in high-risk adults and the optimum interval for a single revaccination was found to be at least five years. However, clinical effectiveness was not assessed. Although there is a concern that multiple doses of PPV-23 would result in immunological hyporesponsiveness to vaccine serotypes, there is insufficient data to provide evidence of a clinical effect.

8.4 Immunogenicity of PCV-13 and PPV-23 when used sequentially

PCV-7 vaccine was the predecessor to PCV-13. Some of the studies reviewed report immunogenicity findings for long-term follow-up and revaccination with PPV-23 following initial vaccination with PCV-7. For the serotypes in common between PCV-7 and PCV-13, non-inferiority in immunogenicity and efficacy was established during pre-licensure trials in healthy recipients. As such, findings for the PCV-7 studies can be anticipated to be similar for PCV-13.

8.4.1 Adults aged younger than 65 years

Two head-to-head RCTs compared functional OPA antibody responses of PCV-13 with PPV-23 in 831 PPV-23-naïve adults aged 60-64 years. The studies found that OPA responses for PCV-13 were non-inferior to those who received PPV-23 for the 12 serotypes in common. OPA GMTs were significantly higher in PCV-13 than PPV-23 recipients for the majority of the serotypes in common and for serotype 6A. OPA response non-inferiority was shown for PCV-13 between recipients aged 50-59 years and 60-64 years. Revaccination with either PCV-13 or PPV-23 at around 4 years after the initial PCV-13 vaccination resulted in anti-pneumococcal recall responses, whereas those who received initial and subsequent PPV-23 vaccination did not respond. Another phase III study in 720 PPV-23-naïve adults aged 60-64 years showed that initial PCV-13 administration augmented the functional OPA response to subsequent PPV-23 administrations. Conversely, initial PPV-23 vaccination diminished OPA responses to subsequent PCV-13 for all serotypes. Participants were randomised to receive either PCV-13 then PCV-13, PCV-13 then PPV-23 or PPV-23 then PCV-13 after 12 months. Both studies included patients with stable pre-existing chronic conditions (not including significant immune impairment).⁵⁰⁻⁵²

8.4.2 Adults aged over 65 years

An RCT vaccinated 936 adults aged over 70 years, who had received PPV-23 at least 5 years prior to the study, with PCV-13 or PPV-23. OPA titres were significantly greater at 1 month after vaccination in the PCV-13 group than the PPV-23 group for 10 out of 12 serotypes and to serotype 6A (in PCV-13 only). Responses were non-inferior for the other two common serotypes. One year after enrolment, all participants received a follow-on dose of PCV-13. One month after the follow-on vaccination, responses to PCV-13 serotypes were statistically lower in the PPV-23 group, but not in the PCV-13 group. PCV-13 responses were similar in age subgroups 70-74 and 75-79 years, but slightly lower in those aged ≥ 80 years. The study concluded that PCV-13 may be better than PPV-23 to re-establish, maintain and generate anti-pneumococcal recall responses in PPV-23-pre-immunised older adults.³⁶

A Japanese RCT compared functional antibody responses to PCV-13 with PPV-23 in PPV-23-naïve adults aged ≥ 65 years. Statistically greater OPA responses were elicited in the PCV-13 group (n=366) than the PPV-23 recipients (n=367) one month after vaccination for nine out of 12 of the common serotypes (and for 6A, unique to PCV-13). For serotype 3, OPA GMTs were lower for PCV-13 than PPV-23 and were similar for both vaccines for serotypes 1 and 14.³⁵

8.4.3 HIV infection

In an US-based open-label study, the immunogenicity of three doses of PCV-13 was assessed in adults with HIV infection (CD4 ≥ 200 cells/ μ l) who had previously been vaccinated with PPV-23 at least 1 year prior to the study. A total of 329 participants (mean age 47.3 years) received \geq one dose of PCV-13 (of these, 300 had received two doses and 279 received three doses of PCV-13, 6 months apart). The mean interval since PPV-23 vaccination was 3.7 years (standard deviation 2.57 years). No correlation between vaccine-serotype specific IgG concentrations or OPA titres and the time interval since PPV-23 vaccination (after one or \geq two doses) was found. The authors concluded that the study supported the use of PCV-13 in HIV-infected adults with prior experience of PPV-23. The study also found limited impact on immunogenicity of additional doses of PCV-13 when given at six-monthly intervals.³⁸

Statistically significant increases in IgG GMCs and OPA GMTs were seen for all serotypes following one dose of PCV-13 in 151 pneumococcal vaccine naïve adults (mean age 41.2 years) with HIV-infection (CD4 counts ≥ 200 cells/ μ l). Only modest increases in antibody

titres were observed following doses two and three of PCV-13 and one dose of PPV-23 given at one monthly intervals. The phase III open-label study was conducted at 12 sites in South Africa and Romania. The study concluded that it supports the recommendation for adults with HIV infection to received one dose of PCV-13.³⁹

8.4.4 Treatments of immune-mediated inflammatory diseases (IMID)

A systematic review conducted by Hua et al. analysed the effect immunosuppressive agents and targeted disease modifying anti-rheumatic drugs (DMARDs), had on the immune response following vaccination with influenza and pneumococcal vaccines in adults with rheumatoid arthritis (mean age 56.9 years). Two studies found that methotrexate (an immunosuppressant) had an inhibitory effect on the immune response to pneumococcal vaccination (PPV-23 and PCV-7) when compared with a control group, for serotypes 6B and 23F. Three studies found that anti-TNF- α DMARD therapy (including adalimumab, etanercept, certolizumab or infliximab) did not have a significant effect on the humoral response to pneumococcal vaccination. Although there was a reduced response rate for both serotype 6B and 23F in patients treated with rituximab (B cell depletion biological DMARD therapy) compared with controls, significance was not reached for 23F (according to a pooled meta-analysis). The review concludes, that although there were few studies to base the meta-analysis on, it suggests that rituximab and methotrexate, but not the anti-TNF- α DMARDs, have an effect on vaccine immune responses. However, protection is still provided for a number of patients receiving these treatments.⁵³

8.4.5 Asplenia

The immunogenicity of PCV-13 was investigated in Denmark in 33 patients (median age 61.5 years [range 11–88 years]) with asplenia following splenectomy. Of these patients, 81% had received at least one dose of PPV-23 within a mean time of 4.6 years (range 0.5–13.0 years) after vaccination. In patients who had PPV-23 immunisation more than a year previously, PCV-13 significantly increased IgG GMCs for 9/12 serotypes common to both vaccines after 4–6 weeks. The study concluded that PCV-13 is immunogenic for serotypes 1, 3, 4, 5, 7F, 18C, 19A, 19F and 23F when used as a booster in asplenic patients with previous PPV-23 vaccination.⁵⁴

8.4.6 Haematopoietic stem cell transplant recipients

The long-term persistence of immunity to pneumococcal vaccination in haematopoietic stem cell transplant (HSCT) recipients was investigated in a European study. Thirty patients (aged 18–55 at transplant) had received three doses of PCV-7 from 3 or 9 months post-transplant plus a dose of PPV-23 at 12 or 18 months in an earlier study. IgG GMCs against all seven PCV-7 antigens and two PPV-23 antigens (serotypes 1 and 5) were assessed 8–11 years post-HSCT and compared with data collected at 24 months post-transplant. GMCs to serotypes 4, 6B, 9V and 19F did not significantly change with time, there was a significant decrease in GMCs to serotypes 1, 14, 18 and 23F and serotype 5 GMCs were unchanged. Persistent antibodies to the PCV-7 type antibodies were seen in 19/29 (65%) of patients at 0.15 $\mu\text{g/ml}$ cut-off and 12/30 (40%) for 0.5 $\mu\text{g/ml}$ cut-off. These were not significantly decreased compared with 24 months post-HSCT ($p=0.46$). Of the 11 patients who received a PPV-23 dose between 4 and 8.5 years post-HSCT, seven had IgG GMCs above the 0.15 $\mu\text{g/ml}$ cut-off for all nine antigens. Three, who were non-responders at 24 months, did not respond further to the PPV-23 dose. The study concluded that, in these patients with no or limited graft-versus-host disease, there was no evidence that an additional dose of PPV-23 given between 2 to 10 years was beneficial to maintain the response.⁵⁵

The immunogenicity of PCV-13 followed by PPV-23 was investigated an international, multicentre open-label study in allogenic HSCT recipients aged ≥ 2 years – 71 years (54

paediatric [median age 10 years] and 162 adults [median age 47 years]). Approximately 3-6 months after HSCT (mean 154.6 ± 33.4 days), three doses of PCV-13 were given at 1 month intervals followed by a fourth dose 6 months later and a dose of PPV-23 was given a month after dose four⁴. Significant increases from baseline in IgG binding and OPA functional antibodies were shown for all PCV-13 serotypes after three priming doses of PCV-13 (GMFR range 2.99-23.85), levels declined over the next 6 months and after dose four, antibody levels increased significantly for all vaccine serotypes to levels greater than those seen after dose three (GMFR range 3.00-6.97). There was little change in PCV-13 serotype antibody levels after PPV-23 (GMFR range 0.86-1.12). Paediatric patients had higher immune responses than adults. This study did not investigate the use of PPV-23 as a fourth pneumococcal vaccine dose instead of dose four PCV-13, and was unable to determine whether a fourth PCV-13 dose gave a clear benefit compared with PPV-23, as was the recommended schedule.⁴⁰

8.4.7 Summary of sequential PCV-13 and PPV-23

Recent data support the current recommendations for PCV-13 to be given prior to PPV-23 for high risk groups. One study concluded that PCV-13 may be better than PPV-23 to re-establish, maintain and generate anti-pneumococcal recall responses in PPV-23-preimmunised older adults (aged ≥ 70 years). RCTs in adults aged 60-64 years showed that initial PCV-13 vaccination augmented functional OPA responses to subsequent PPV-23 doses, whereas, initial PPV-23 diminished responses to PCV-13 for all vaccine serotypes.

One dose of PCV-13 given to adults with HIV-infection was immunogenic. No significant increase in response was seen when two or three doses of PCV-13 or PPV-23 were at given monthly or six-monthly intervals.

Although rituximab and methotrexate were shown to have an effect on vaccine immune responses in patients with rheumatoid arthritis, protection was still provided by PPV-23 and PCV-7 vaccines for a number of patients who received these treatments.

Immunosuppressant therapies and targeted biological DMARDs are also used to treat other IMIDs, such as multiple sclerosis and inflammatory bowel diseases.

PCV-13 was shown to be immunogenic for serotypes 1, 3, 4, 5, 7F, 18C, 19A, 19F and 23F when used as a booster in patients with previous PPV-23 vaccination following splenectomy.

Additional doses of PPV-23 were not shown to be beneficial to maintain IgG titres up to 10 years following three priming doses of PCV-7 plus PPV-23 in HSCT recipients. Patients who were non-responders for the priming doses remained unresponsive. In a separate study, a fourth dose of PCV-13 given 6 months after three priming doses boosted functional antibody levels in HSCT recipients.

8.5 Immunogenicity of pneumococcal vaccines in children

In healthy children, non-inferiority between PCV-13 and PCV-7 has been evaluated in clinical trials for the seven serotypes in common in both vaccines. In one study, investigating immunogenicity of PCV-13 in adolescents (age 10-17 years) who had not received previously received PCV-7 compared with younger children (age 5-10 years) who had previously received at least one dose of PCV-7, non-inferiority of OPA titre data was shown for all serotypes except serotype 3, for which OPA response was lower in adolescents. However, a ≥ 9.7 -fold increase in serotype 3 OPA titres was observed pre- and post-vaccination for both age groups. Immunogenicity of PCV-13 after 1 month was also shown

to be non-inferior for healthy children age 5-10 years compared with toddler booster dose. No long-term immunogenicity data were available at the time of this review.⁵⁶

Few papers described the use of pneumococcal vaccines in children >5 years of age with high risk of IPD.

8.5.1 Children with sickle cell disease

A good immunogenic response to PCV-13 was reported in children with sickle cell disease (age 6-17 years) previously vaccinated with PPV-23. IgG GMC values increased by 1.73-fold to 7.01-fold from pre- to post-vaccination with against all 13 vaccine serotypes following the first PCV13 dose.⁵⁶

8.5.2 Children with nephrotic syndrome

A Swiss study found that high IgG titres (>1 mg/L) were achieved and maintained one year following vaccination with PCV-13 in 42 children with nephrotic syndrome (mean age 7.7 years). All patients showed increases in vaccine-specific IgG for three serotypes tested (14, 19F and 23F) after immunisation. Patients receiving prednisone and alternative immunosuppressive medication had lower specific IgG titres for serotypes 14 and 23F ($p=0.004$ and 0.03 , respectively) at 3 months and for serotype 14 at 12 months post-vaccination than treatment-free patients. The authors recommended that, regardless of previous immunisation history, all nephrotic syndrome patients be vaccinated with PCV-13.⁵⁷

8.5.3 PCV-13 vaccination of children with HIV-infection

Statistically significant increases in IgG GMCs and OPA GMTs were seen for all serotypes following one dose of PCV-13 in 150 children aged ≥ 6 years (mean age 10.3 years) with HIV-infection (CD4 counts ≥ 200 cells/ μ l). Only modest increases in antibody titres were observed following doses two and three of PCV-13 and one dose of PPV-23 given at one month intervals. The phase III open-label study was conducted at 12 sites in South Africa and Romania.³⁹

8.5.4 PCV-13 in children with inflammatory bowel disease

A multicentre study conducted in Poland demonstrated PCV-13 that was immunogenic in children with inflammatory bowel disease (IBD) aged 5-18 years. Although the patients who were receiving anti-TNF agents or other immunomodulators had a significantly lower geometric mean titre rise than those who were on no immunosuppressive therapy ($p=0.037$), no significant difference in the rate of protective vaccine response between patients with IBD and healthy controls (90.4% versus 96.5%; $p=0.53$) was shown at 4-8 weeks after a single dose of PCV-13.⁵⁸

8.5.5 Revaccination of children with PPV-23

A systematic review of literature published up to June 2013 was conducted to determine the optimal dose and timing of PPV-23 revaccination in adult and paediatric populations. This review did not investigate the role of PPV-23 revaccination in those who were initially immunised with conjugate vaccines (PCV). There were few paediatric studies. However in children, antibody levels were seen to decline rapidly following revaccination with PPV-23, but remained higher than the pre-vaccination levels. The optimal interval between doses in high-risk children was found to be at least 5 years. Based on antibody responses, not effectiveness against IPD, the review concluded that an adequate immune response and safety profile was demonstrated following revaccination with PPV-23, given on average 5 years after the previous doses. There was no evidence supporting the use of different intervals for PPV-23 revaccination in children aged <10 years compared with older individuals.⁴⁹

8.5.6 Summary of immunogenicity in children

PCV-13 has been shown to be immunogenic in healthy children and adolescents aged 5-17 years. An anamnestic response to PCV-13 vaccination has been observed in healthy children (aged >5 years) and adolescents in clinical studies. Although, OPA antibody titres were lower for serotype 3 in adolescents than younger children. However, there is little data around the immunogenicity of PCV-13 in children at high risk of IPD or duration of protection in healthy or at-risk children.

High IgG titres have been observed following PCV-13 vaccination of children at high risk of IPD, including sickle cell disease, HIV infection and nephrotic syndrome.

As in adults, the optimum interval for revaccination with PPV-23 in children is 5 years. There was no evidence supporting different revaccination intervals for adults and children. This review did not find any literature on the immunogenicity of booster doses of PCV in high-risk children.

8.6 Summary of immunogenicity

Few studies have investigated the immunogenicity of PCV-13 in adult populations or in children with increased risk of IPD. Data around the long-term persistence of immunogenicity is also lacking in older children and adults.

Most studies found that PCV-13 was immunogenic in PPV-23 naïve and experienced adults with increased risk of IPD, including the elderly and the immunocompromised.

There is no serological correlate of protection and anti-pneumococcal antibody titres may not be a useful measure of protection. The functional ability of these antibodies to opsonise pneumococcal bacteria has greater significance in providing protection. Prior exposure to pneumococcal polysaccharides (through vaccine or disease) may contribute to a decreased effectiveness of PPV-23 in older people as a result of a decline in IgM memory B cells.

The optimal timing between doses of PPV-23 was determined to be at least 5 years in adults and children with increased risk of IPD. There was no evidence that a different timing would be required for children.

Delaying immunisations to improve immunogenicity in those at high risk of pneumococcal infections may not be advantageous when opportunities to vaccinate could be missed. PPV-23 provides extra coverage for those most at risk from IPD; lower antibody concentrations and functional OPA titres should be balanced with clinical risk.

9 Efficacy and effectiveness

Vaccine efficacy is measured as part of pre-licensure or post-marketing clinical trials, under optimum conditions, and is determined as the reduction in disease incidence or similar outcome in a vaccinated group compared with unvaccinated controls. Vaccine effectiveness relates to the ability of a vaccine to prevent disease or other outcomes of interest assessed post-licensure in 'real world' settings.

The effectiveness of pneumococcal vaccines in preventing pneumococcal disease in those most at risk is reviewed. Consideration is given to relevant efficacy and effectiveness studies that contribute to the current understanding in preventing pneumococcal disease high-risk populations, including the elderly and adults and children with underlying medical conditions that increase their risk of pneumococcal disease. The direct impact of pneumococcal vaccination in adults is considered.

Overall, there was a lack of literature reviewing the effectiveness and direct impact of PCV-13 in adult populations, except in age-related studies.

9.1 Effectiveness of PCV-13 in adults ≥ 65 years

9.1.1 Community-acquired pneumonia

The CAPiTA (Community-Acquired Pneumonia Immunization Trial in Adults) RCT was conducted in the Netherlands to investigate the impact of PCV-13 vaccination in reducing vaccine-serotype CAP during 2008-2013. It recruited 85,000 vaccine-naïve elderly aged ≥ 65 years. Initial findings reported that PCV-13 had a 45% efficacy (95% CI 14.2 to 65.3) against first-episodes of vaccine serotype CAP compared with placebo and concluded that PCV-13 had significant efficacy in preventing vaccine-type pneumococcal CAP (bacteraemic and non-bacteraemic), but not did not demonstrate significant efficacy in preventing any cause CAP (VE 5.1%; 95% CI -5.1 to 14.2) among older adults. The study was conducted before the introduction of PCV-13 on the childhood immunisation schedule.^{33, 59}

9.1.2 Invasive pneumococcal disease

As mentioned above, the CAPiTA study was a large RCT conducted prior to the introduction of PCV-13 for children in the Netherlands. Initial findings reported that PCV-13 in adults aged ≥ 65 years has a 75% efficacy in preventing vaccine-type IPD compared with placebo and concluded that PCV-13 was effective in preventing vaccine-type IPD.^{33, 59}

9.1.3 Other outcomes

Preliminary findings of a study investigating the effects of PCV-13 vaccination in adults aged ≥ 70 years in Liguria, Italy, showed a reduction in the incidence of emergency department (ED) access for lower respiratory tract infections in the vaccinated compared with unvaccinated population. When standardised and adjusted for ageing effects, the preventative fraction was estimated to be 24.5% with a decrease in ED access incidence of 1.5/10,000 persons-month. Final results are expected late 2016. The initial findings were published in Italian and then reviewed by Orsi et al in 2016.⁶⁰

9.1.4 Indirect impact of PCV-13 in adults

There are few post-market surveillance studies on PCV-13 that consider the direct effects of vaccination of adults with this vaccine. Rather, several recent studies have provided indirect evidence of impact through herd immunity protection from vaccination of children as part of childhood immunisation programmes. A review of the use of PCV-13 vaccine in adults by G

Plosker in 2015 summarised the impact the vaccine has had through herd immunity. For example, in the US PCV-13 vaccination was associated with significant reductions in pneumococcal disease hospitalisations, in both children and some adult age groups, two years following its introduction on the childhood immunisation schedule. In another US-based study, reductions in overall IPD as well as vaccine-serotype IPD were observed in adults and children when comparing IPD rates before and three years after the introduction on PCV-13 in children. Analysis of these data estimated that PCV-13 had prevented 20,000 IPD cases in adults (30,000 in total) and prevented 3,000 deaths (97% in adults) during the first three years after its introduction on the childhood immunisation schedule. During 2010-2013, following the introduction of PCV-13 in Navarre, Spain, a significant reduction of IPD cases was observed in the overall population compared with 2004-2009, including a 23% reduction in adults aged ≥ 65 years ($p=0.024$). Of the older adult IPD cases, approximately half had comorbidities.⁵⁰

9.1.5 Summary of PCV-13 effectiveness in elderly adults

Although there is limited data in the literature, PCV-13 vaccination appears to be effective in preventing vaccine-type community-acquired pneumonia and IPD in adults over the age of 65 years. Vaccination of children through national immunisation schedules also appears to be reducing the incidence of vaccine-type pneumococcal disease in adults through herd immunity.

9.2 Effectiveness of PPV-23 in the elderly.

9.2.1 Community-acquired pneumonia

A systematic review found no proof that PPV-23 can prevent pneumococcal CAP in a general, community-dwelling elderly population. Out of four studies included in the meta-analysis, three did not show efficacy for PPV-23 in preventing CAP in adults aged ≥ 60 years.⁶¹

A population-based cohort study in Spain found a protective effect for recent PPV-23 vaccination (< 5 years) against pneumococcal and all-cause CAP in adults aged ≥ 60 years through a multivariate analysis compared with those who had never been vaccinated. The effect of the vaccination was shown to wane after 5 years.⁶²

Another systematic review found that PPV-23 VE estimates were around 4% in trials, 17% in cohort studies and 7% in case-control studies in the prevention of all-cause CAP in adults aged > 50 years. The review found that effectiveness of PPV-23 was consistent with previous systematic reviews and similar to estimates reported for PCV-13 in the CAPiTA study (5.1% for all-cause CAP).⁶³

An Israeli retrospective case-control study found that vaccination with PPV-23 was not protective against all-cause hospital-treated pneumonia (adjusted association OR 1.01, 95% CI 0.97-1.04) in a case cohort of 23,441 cases of adults aged > 65 years compared with population based age, sex and risk-matched controls.⁶⁴

9.2.2 Invasive pneumococcal disease

A systematic review found that PPV-23 was around 50% effective in the prevention of IPD in adults aged > 50 years. VE estimates in preventing IPD were 50% in cohort studies and 54% for case-control studies. The review found that the effectiveness of PPV-23 was consistent with previous systematic reviews and similar to estimates reported for PCV-13 in the CAPiTA study (48.5% for IPD).⁶³

An Israeli retrospective case-control study found that vaccination with PPV-23 was effective against IPD in adults aged >65 years (OR 0.58; 95% CI 0.41-0.81) in a case cohort of 212 patients with IPD compared with population-based age, sex and risk-matched controls.⁶⁴

A Taiwanese population-based retrospective cohort study examined the vaccine effectiveness of PPV-23 adults aged ≥75 years with diabetes. The risks of IPD (OR 0.86; 95% CI 0.78-0.94) and respiratory failure (OR 0.84; 0.77-0.93) were lower and the length of hospital stays were shorter (-1.27 ± 0.19 days, $p=0.0012$) in the PPV-23-vaccinated compared with propensity-score-matched unvaccinated patients. The study also found that outcomes were better for patients who received both influenza and PPV-23 vaccines than for those who received PPV-23 only.⁶⁵

9.2.3 Other outcomes in the elderly

A systematic review and meta-analysis was conducted by Vlachopoulos et al to investigate the association between pneumococcal vaccination of adults who received PPV-23 and cardiovascular outcomes. The review included 11 studies with 332,267 participants with a mean follow up of 20 months. A protective role for pneumococcal vaccination was determined by pooled relative risk for total cardiovascular events of 0.86 ($p=0.016$); RR 0.80 in the elderly ($p=0.001$) and 0.92 for those with high cardiovascular risks ($p=0.010$). The primary findings were that patients vaccinated with pneumococcal vaccine had a significantly lower risk for total cardiovascular events and mortality than unvaccinated patients (14% and 8% lower, respectively). This protection was greater in those at high risk of cardiovascular disease and the elderly. In the elderly only, a protective role for pneumococcal vaccination was evident for myocardial infarction and cerebrovascular events.⁶⁶

9.2.4 Summary of effectiveness of PPV-23 in adults

PPV-23 has little effectiveness (5-17%) against all-cause community-acquired pneumonia. Since pneumococcal infection is estimated to cause 30-50% of CAP cases requiring hospitalisation in adults in Europe, PPV-23 vaccination alone is unlikely to be effective in preventing all-cause CAP. PPV-23 has been demonstrated to be around 50% effective in preventing IPD in adults aged ≥50 years.

The protection afforded by PPV-23 in the prevention of pneumococcal pneumonia was seen to wane within 5 years.

PPV-23 vaccination of adults has been shown to have some protective role in preventing cardiovascular outcomes and mortality those with a high risk of cardiovascular disease, in particular for myocardial infarction and cerebrovascular events in adults aged ≥65 years,

9.3 Effectiveness of PCV in high risk children

No recent literature was found that reviewed the effectiveness of pneumococcal vaccination to prevent IPD in children over the age of 5 years at high risk due to chronic health issues.

Pneumococcal pharyngeal colonisation and carriage has been shown to be a precursor for pneumococcal disease. The risk of IPD is more causally linked to underlying medical conditions than to pharyngeal carriage, particularly in children older than 5 years and adults, although there is some evidence of an underlying ecological link.⁶⁷

9.3.1 Oropharyngeal carriage in high-risk children and adolescents

A series of Italian studies have investigated the oropharyngeal carriage (OPC) of *S. pneumoniae* in school-aged children and adolescents aged 6-17 years with chronic medical

conditions. However, a limitation of these studies was that pneumococcal OPC was not assessed in comparison with age matched, geographically matched healthy controls. From these studies in at-risk children, it was not determined whether booster doses of PCV-13 or combination with PPV-23 could help to control colonisation. PCV-7 was not widely used in Italy until 2009, even in children with severe chronic underlying disease.

9.3.1.1 Type 1 diabetes mellitus

One Italian study investigating the OPC of *S. pneumoniae* in school-aged children and adolescents aged 6-17 years with well-controlled type-1 diabetes mellitus (T1DM) found that PCV-7 vaccination as infants and toddlers was not effective in protecting against pneumococcal re-colonisation years later. *S. pneumoniae* was detected in 148/299 (49.8%) patients. Colonisation declined significantly after the age of 15 years and was strictly age related; the number of carriers was highest in children aged <10 years (on average 8 years since last PCV-7 dose) and 10-14 years (11.5 years since last PCV-7 dose). Multivariate analyses determined that the odds ratio (OR) for carriers of any serotype was 0.74 (95% CI 0.44-1.27), 0.74 (0.44-1.26) for any PCV-7-serotype and 0.52 (0.26-1.04) for any of the additional six PCV-13 serotypes. Serotypes 19F, 9V and 4 were the most frequently identified serotypes in both vaccinated and unvaccinated participants (all PCV-7 serotypes). Carriage was influenced by other factors – carriage was higher in males than females, those with Caucasian ethnicity and in those exposed to parental smoking, and less carriage was seen in those children who received antibiotic therapy in the previous 3 months. The study concluded that a booster dose of PCV is needed in children and adolescents with T1DM to maintain protection.⁶⁸

9.3.1.2 Cancer

A further OPC study was conducted to determine the potential protective efficacy of PCV-13 in school-age children (aged 6-17) with cancer. *S. pneumoniae* was identified by PCR from OP swabs in 52/277 patients of whom, 47/235 (20%) had haematological malignancies and 5/42 (11.9%) had solid tumours. As seen in children with T1DM, colonisation significantly declined with increasing age. Among cancer patients previously immunised with PCV-7, 15/58 (25.9%) were colonised with PCV-13-serotypes compared with 26/216 (12%) of those unvaccinated. In these patients, colonisation was not affected by gender, siblings, parental smoking, presence or absence of chemotherapy, hospitalisation, infections or administration of anti-infective treatment within 3 months. Co-trimoxazole prophylaxis was significantly associated with reduced pneumococcal carriage (OR 0.41, 0.19-0.89). The study concluded that because most of the serotypes carried are included in PCV-13, this vaccine should help reduce the risk of IPD in children with cancer.⁶⁹

9.3.1.3 Cystic fibrosis

The same research team also investigated OPC of *S. pneumoniae* in 212 school-age children with cystic fibrosis aged 6-17 years. As seen previously, the highest carriage rate was observed in the younger age groups and declined with age. Fewer carriers had high vitamin D serum levels of ≥ 30 ng/ml than non-carriers (OR 0.35; 0.08-1.49). The most frequently carried serotypes were 4, 5, 9V and 19F in both vaccinated and unvaccinated children (of which 4, 9V and 19F were in PCV-7). The study concluded that PCV-7 vaccination in the first year of life did not reduce the risk of pneumococcal colonisation later in childhood or adolescence in children with cystic fibrosis.⁷⁰

9.3.1.4 Asthma

Pneumococcal colonisation was also evaluated in school-aged children and adolescents with asthma following prior PCV-7 vaccination. OPC of *S. pneumoniae* was found in 192/423

(45.4%) of children with asthma, of which 48.4% were aged <10 years, 46.9% aged 10-14 years and 4.7% aged ≥15 years. Multivariate analysis found no association with carriage and PCV-7 vaccine status (OR 1.05 for any serotype, 1.08 for PCV-7-serotypes and 0.76 for additional six PCV13 serotypes), regardless of asthma severity. As seen in their other studies, serotypes 4, 9V and 19F were the most common serotypes. The study found that around 95% of children were colonised with at least one serotype included in PCV-13.⁷¹

9.3.2 Summary of PCV vaccination of children

Following the introduction of PCV-7 vaccination in infancy, studies found that the highest carriage rates of oropharyngeal carriage of *S. pneumoniae* were seen in the children younger than 15 years in all the groups of children studied (with T1DM, cancer, cystic fibrosis, asthma). In PCV-7 vaccinated children, protection against IPD waned by early adolescence, suggesting booster doses of a PCV vaccine or PPV-23 may be required. The studies were conducted when PCV was not widely used in children and herd immunity is likely to have had little effect. These studies concluded that since most of the carried serotypes are included in PCV-13, PCV-13 could help to reduce carriage and provide wider protection for children with chronic disease against IPD.

9.4 Summary of vaccine effectiveness

Most of the recent studies that investigated immunogenicity and efficacy or effectiveness of pneumococcal conjugate vaccines PCV-7 and PCV-13 have reviewed their use together with the 23-valent polysaccharide vaccine. The most comprehensive study to date in those aged ≥65 years is the CAPiTA study. It found PCV-13 to have 45% efficacy against pneumococcal CAP and 75% efficacy against IPD in the elderly compared with placebo.

When given alone, PPV-23 can provide protection against IPD, reduce hospital stays and reduce cardiovascular outcomes in the elderly. PPV-23 has been demonstrated to be around 50% effective in preventing IPD in adults aged ≥50 years. The protection afforded by PPV-23 in the prevention of pneumococcal pneumonia was seen to wane within 5 years.

PCV-13 plus PPV-23 is effective, but there are issues with non-responsiveness to PPV-23 in some individuals. When used after PCV-13 vaccination, PPV-23 may provide broader, but short-lived, protection against IPD caused by the additional pneumococcal vaccine serotypes in high-risk individuals.

There is very little literature around the impact PCV-13 vaccination of high-risk groups on the incidence of IPD. Much of the research has investigated the indirect effects of vaccination of infants rather than direct effects of vaccination of older children or adults, discussion of which is not within the scope of this review.

Direct protection against oropharyngeal carriage provided by infant vaccinations appears to wane during childhood. In children and adolescents, a benefit of broader serotype protection provided by PCV-13 was identified in high-risk groups when oropharyngeal carriage is considered as a risk for pneumococcal disease.

10 Options for dosing schedules

10.1 Background

A WHO position paper on pneumococcal vaccines in 2012 stated that there was not sufficient evidence to support making policy recommendations for the use of PCVs in older populations. There is also insufficient data to recommend the routine use of PPV-23 in

resource-limited settings to vaccinate elderly and high-risk populations, including HIV infected adults.⁷²

In this section, the options for pneumococcal vaccination is considered for the protection of adults and children at increased risk of developing invasive pneumococcal disease. Consideration will not be given to the childhood immunisation schedule, only the requirement of further doses or valences to provide additional direct protection from more serotypes than provided by routine vaccination.

Extra booster doses and repeat vaccination may be required for individuals who do not adequately respond or generate memory to priming immunisations due to certain medical conditions.

10.2 Vaccine options

The current options for pneumococcal conjugate vaccines available to New Zealand are PCV-10 (Synflorix) or PCV-13 (Prevenar 13). The polysaccharide pneumococcal vaccine, PPV-23 (Pneumovax 23) is available to provide additional protection from a further 10 serotypes not covered by PCV-13 to those at high risk of invasive pneumococcal disease (IPD) but only for those over 2 years of age.

Due to the risk of hyporesponsiveness induced by polysaccharide vaccines, the optimal strategy is to use the conjugate vaccines initially and then to broaden the serotype coverage in those at high risk from IPD.

10.3 Recommended doses

The immune response following initial immunisation with polysaccharide vaccines has been shown to be attenuated against pneumococcal vaccine serotypes and it is therefore recommended to immunise with PCV initially, to generate robust immunity to as many vaccine serotypes as possible prior to PPV-23 vaccination, which provides short-term protection against further serotypes. The optimal time interval between these vaccines is unclear, but in order for memory against the PCV serotypes to be established, at least 8 weeks is recommended prior to giving PPV23.

A review of literature on the impact of PCV dosing schedules found only 5 studies that evaluated vaccine impact on pneumococcal pneumonia in high risk populations (two studies used 3+0 and three used 3+1 schedules, all conducted prior to 2013). One trial in South Africa found 3+0 PCV schedule to have 13-15% efficacy in HIV infected children against radiologically-confirmed pneumonia. A 3+1 schedule in US indigenous people and 3+PPV23 in Australian indigenous people showed no efficacy against pneumonia hospitalisations. Most of these studies evaluated PCV-7, and these cases could have been caused by non-vaccine serotypes. No studies in this review evaluated PCV-13. The investigators noted that many of the studies were conducted in high income countries. However, an impact of routine 3+0 PCV schedules was seen in RCTs in low-middle income countries, which have particularly high levels of underlying health conditions (including HIV infection and sickle cell disease). The review did find that routine PCV-7 vaccination had an impact on pneumonia incidence overall and that it was difficult to identify differences between schedules due to the breadth of the data in different settings and populations. The review's findings supported the WHO recommendations for a 3-dose regimen, and that it is essential to choose a schedule that ensures high coverage of the third dose.⁷³

10.4 Revaccination with PPV-23

The Canadian National Advisory Committee on Immunization (NACI) conducted a literature review in 2015 to evaluate evidence to make recommendations for re-immunisation with PPV-23 in those at risk of IPD. The conclusions were that immunity following PPV-23 declined rapidly and revaccination provides a boost in immunity against IPD. Good immune responses were reported for adults who received one or two doses of PPV-23 before the age of 65 years and little evidence of hyporesponsiveness was seen following one additional dose when given over the age of 65 years.

From this review, the NACI made three recommendations:

- 1) Revaccination with a second dose of PPV-23 should be provided 5 years after the first dose for all individuals from 2 years of age at highest risk of IPD (asplenia, HIV infections, immunosuppression, chronic renal disease and hepatic cirrhosis), who have received age-appropriate PCV-13 vaccination plus one dose of PPV-23 after at least 8 weeks;
- 2) One lifetime booster of PPV-23 was recommended to be given 5 years after the previous dose, since, there was insufficient evidence to determine the optimal timing or number of booster doses of PPV-23 in high risk adults;
- 3) All adults should receive one dose of PPV-23 at 65 years of age, providing 5 years have passed since any previous dose of PPV-23. This recommendation was reached given the increased risk of IPD in the elderly and the rapid decline in antibody levels, and was based on studies reviewed in which PPV-23 was administered at age ≥ 65 years regardless of prior vaccination history. No additional booster doses are currently recommended for those ≥ 65 years without underlying medical conditions.⁷⁴

10.5 Summary

To date there have been very few studies investigating options for administration of PCV vaccines in older high-risk groups other than those evaluating the efficacy of infant schedules. The 2012 pneumococcal antigen literature review found that in adults PCV-13 alone, or as priming dose prior to PPV-23 was consistently supported by literature. No recent data change that position.

Recommendations around the number and interval between PPV-23 doses vary from one life time booster to a maximum of three doses per adult lifetime for those with high IPD risk.

Questions that were previously raised in the 2012 pneumococcal antigen literature review remain unanswered around the use of both conjugate and polysaccharide vaccines in adults and high risk groups.

11 International policy and practice

This section will review the international policies and practices around the use of pneumococcal vaccination in adults and children at high risk of invasive pneumococcal disease. Consideration will be given to the timing of doses and combined use of pneumococcal conjugate and polysaccharide vaccines (PCV-13 and PPV-23, in particular). A review of the childhood immunisation schedule will not be included. Countries will be limited to the US, Canada, Australia, the UK and Europe. The classification of different high-risk groups and the conditions considered within these are highlighted. Where possible the timing between PCV-13 and PPV-23 is given, with booster doses where given.

11.1 Review

11.1.1 United States

Risk group and underlying medical condition	Interval between PCV-13 + PPV-23 by age (years)				Interval between PPV-23 + PCV-13 by age (years)			
	2 -5	6 -18	19-64	≥65	2 -<5	6 -18	19 -64	≥65
No underlying chronic conditions	NA		≥ 1 year		NA		≥ 1 year	
Immunocompetent								
Chronic disease of heart, lungs or liver								
Cirrhosis*	≥8 weeks	NA	NA	≥ 1 year	≥8 weeks	NA	NA	≥ 1 year
Diabetes mellitus								
Alcoholism*								
Cigarette smoking*								
CSF leak	≥ 8 weeks				≥ 8 weeks			
Cochlear implant					≥ 1 year			
Functional or anatomic asplenia								
Sickle cell disease or haemoglobinopathy	≥ 8 weeks				≥ 8 weeks			
Congenital or acquired asplenia					≥ 1 year			
Immunocompromised								
Congenital or acquired immunodeficiency	≥ 8 weeks				≥ 8 weeks			
HIV					≥ 1 year			
Chronic renal failure								
Nephrotic syndrome								
Leukaemia, lymphoma, Hodgkin disease								
Generalised malignancy								
Iatrogenic immunosuppression								
Solid organ transplant								
Multiple myeloma*								
Abbreviations: NA = not applicable, sequential PCV13-PPV23 not recommended for these age and risk groups.								
*Underlying medical condition not included in the recommendation for children aged <6 years.								

Table 5: Summary of recommended intervals between conjugate and polysaccharide pneumococcal vaccines by risk groups and age in the US (adapted from ACIP 2015 recommendations)

The summary of recommended intervals between PCV-13 and PPV-23 for those at high risk of IPD for different age groups is given in Table 5. These recommendations are based on evidence from immunogenicity data since no clinical studies had been conducted to evaluate efficacy in 2015. For those aged ≥ 65 years, it is recommended that there is a gap of at least 1 year between PPV-23 and PCV-13, and vice versa. There should be at least 5 years between doses of PPV-23 if received younger than 65 years of age.⁷⁵

11.1.2 Canada

Table 6: Conditions in adults and children with highest risk of IPD for which pneumococcal vaccination is recommended in Canada (source NACI, Canada)

High risk conditions in adults	High risk conditions in children
Adults ≥ 65 years Adults 18-64 years with high risk of IPD	All children up to 5 years of age, especially those at high risk for IPD Children aged at high risk of IPD aged ≥ 5 years
<i>Non-immunocompromising</i> <ul style="list-style-type: none"> - Chronic CSF leak - Chronic neurological conditions that may impair oral secretion clearance - Cochlear implants (including planned recipients) - Chronic cardiac or pulmonary disease - Diabetes mellitus - Chronic kidney disease - Chronic liver disease (include cirrhosis of any cause) - Asthma that requires medical care in preceding 12 months 	<i>Non-immunocompromising</i> <ul style="list-style-type: none"> - Chronic CSF leak - Chronic neurological conditions that may impair oral secretion clearance - Cochlear implants (including planned recipients) - Chronic cardiac or pulmonary disease - Diabetes mellitus - Chronic kidney disease - Chronic liver disease (including hepatitis B or C) - Asthma in children aged 2 to 17 years (regardless of high-dose steroid use or COPD).
<i>Immunocompromising</i> <ul style="list-style-type: none"> - Haemoglobinopathies (including sickle cell) - Congenital immunodeficiencies involving any part of the immune system - Functional or anatomical asplenia - Immunocompromising therapy (including long-term corticosteroids, chemotherapy, radiotherapy, post organ transplant, certain anti-rheumatic drugs) - HIV infection - Haematopoietic stem cell transplant (recipient) - Malignant neoplasms (incl. leukaemia, lymphoma) - Nephrotic syndrome - Solid organ or islet cell transplant (candidate or recipient) 	<i>Immunocompromising</i> <ul style="list-style-type: none"> - Haemoglobinopathies (including sickle cell) - Congenital immunodeficiencies involving any part of the immune system - Functional or anatomical asplenia - Immunosuppressive therapy - HIV infection - Haematopoietic stem cell transplant (candidate or recipient) - Malignant neoplasms (incl. leukaemia, lymphoma) - Solid organ or islet cell transplant (candidate or recipient)
<ul style="list-style-type: none"> - Adults <65 years in long-term care facilities 	<ul style="list-style-type: none"> - Not previously immunised with PCV-13
<i>Immunocompetent adults in situation or with conditions that increase risk</i> <ul style="list-style-type: none"> - alcoholism - smoking - homelessness - Illicit drug use 	

Pneumococcal vaccination is recommended by the National Advisory Committee on Immunization (NACI) in Canada for all adults aged ≥ 65 years and all children aged up to 5 years of age, and also for adults and children with increased risk of IPD, as listed in Table 6. Immunocompetent adults aged ≥ 65 years with no risk factors and adults aged ≥ 18 -64 years with increased risk of IPD (other than HSCT) are administered either one dose of PPV-23 or one dose of PCV-13 followed by PPV-23 after ≥ 8 weeks (at least 1 year after any previous PPV-23 immunisation). Adults < 65 years in long-term care facilities are recommended one dose of PPV-23. Adults receiving HSCT are given three doses of PCV-13 then PPV-23 at 12 to 18 months post-transplant (up to 12 months after last PCV-13 dose). Revaccination with PPV-23 of adults at continued risk is recommended at least 5 years after last PPV-23 dose.⁷⁶

A booster dose of PCV-13 is recommended for all healthy children at age 3-5 years if they are of Aboriginal (First Nation, Métis and Inuit) descent or attend group childcare and have previously been vaccinated with PCV-7 or PCV-10 or have not completed age-appropriate PCV vaccinations. Children who are at high risk of IPD aged 3 – 17 years are recommended one dose of PCV-13 if they have not received PCV-13 as part of their routine schedule (i.e. a four-dose schedule with PCV) and also to receive a single dose of PPV-23 at 24 months. Revaccination with PPV-23 is recommended for some conditions that place them at highest risk as a once-lifetime booster given five years after the initial dose.⁷⁷

11.1.3 Australia

In Australia, different states and territories have different immunisation schedules using either PCV-13 or PCV-10. Where PCV-10 is used routinely, a booster dose is given in the second year of life to all children.

Where PCV-13 is used, then booster in the second year of life is only given to indigenous children (Aboriginal and Torres Strait Islanders) as they are at higher risk of IPD than non-indigenous people. Adults aged between ages 15-49 years with underlying conditions that increase risk of IPD (refer Table 7) and all indigenous adults aged ≥ 50 years are recommended PPV-23; follow-up doses are given 5 years after previous doses, with no more than three doses in an adult lifetime (from age 15 years is considered an adult dose). Non-indigenous adults without increased risk are recommended PPV-23 from 65 years of age. All children with medical condition associated with increased risk of IPD receive a primary series with PCV-13 plus a booster dose at 12 months of age (depending on age when diagnosed) and PPV-23 at 4-5 years of age.⁷⁸

Table 7: Conditions associated with increased risk of IPD in Australia (Australian Immunisation Handbook 2016; List 4.13.1)

Conditions associated with an increased risk of invasive pneumococcal disease (IPD) in children and adults, by severity of risk.	
Category A: Conditions associated with the <i>highest</i> increased risk of IPD	<p>Functional or anatomical asplenia, including:</p> <ul style="list-style-type: none"> Sickle cell disease or other Haemoglobinopathies Congenital or acquired asplenia (e.g. splenectomy), splenic dysfunction <p>Immunocompromising conditions, including:</p> <ul style="list-style-type: none"> Congenital or acquired immune deficiency, including symptomatic IgG subclass or isolated IgA deficiency (Note: children who require monthly immunoglobulin infusion are unlikely to benefit from vaccination) Immunosuppressive therapy (including corticosteroid therapy ≥ 2 mg/kg per day of prednisolone or equivalent for more than 1 week) or radiation therapy, where there is sufficient immune reconstitution for vaccine response to be expected Haematological and other malignancies Solid organ transplant Haematopoietic stem cell transplant (HSCT) HIV infection (including AIDS) Chronic renal failure, or relapsing or persistent nephrotic syndrome Proven or presumptive cerebrospinal fluid (CSF) leak Cochlear implants Intracranial shunts
Category B: Conditions associated with an increased risk of IPD	<ul style="list-style-type: none"> Chronic cardiac disease particularly cyanotic heart disease or cardiac failure in children excluding hypertension only (in adults) Chronic lung disease, including: <ul style="list-style-type: none"> Chronic lung disease in preterm infants Cystic fibrosis Severe asthma in adults (requiring frequent hospital visits and use of multiple medications) Diabetes mellitus Down syndrome Alcoholism Chronic liver disease Preterm birth at <28 weeks gestation[†] Tobacco smoking[§]
<p>[†] Recommendations differ for those aged >5 years (but not <5 years) between categories.</p> <p>[‡]Up to age 5. Further pneumococcal vaccination recommended only if child has ongoing chronic medical condition that increases IPD risk</p> <p>[§]Tobacco smoking is not a medical condition, but is associated with an increased risk of IPD</p>	

11.1.4 United Kingdom (UK)

Table 8: Groups at-risk of pneumococcal disease in England and Wales (Source: Public Health England)

At-risk group	Examples based on clinical judgement
Asplenia or spleen dysfunction	Including coeliac syndrome and sickle cell disease
Chronic respiratory disease	Including COPD, cystic fibrosis. Conditions in children caused by aspiration or neurological disease (e.g. cerebral palsy). Asthma not an indication unless severe and requires frequent systemic steroids (see immunosuppression).
Chronic heart disease	Chronic or congenital heart disease or failure
Chronic liver disease	
Chronic kidney disease	Nephrotic syndrome, dialysis or transplantation
Diabetes	Requiring insulin or oral hypoglycaemic medication
Immunosuppression	Chemotherapy, bone marrow transplant, HIV, genetic disorders of immune system, systemic steroids >1 month.
Cochlear implants	
Cerebrospinal fluid leaks	Including trauma, major skull surgery

Groups at high risk of pneumococcal disease in England and Wales are listed in Table 8.⁷⁹ The Public Health England recommendations are that all at-risk children should be fully immunised with PCV-13 as per the childhood immunisation schedule with an additional dose of PPV-23 to be given after second birthday (at least 2 months after last dose of PCV-13). For severely immunocompromised individuals from age 5 years, a single dose of PCV13 plus one dose of PPV-23 after at least 2 months are recommended, irrespective of routine childhood vaccinations. Unvaccinated children or adults requiring elective splenectomy or immunosuppressive treatment should be vaccinated according to the schedule for this risk group and age at least 4-6 weeks (minimum 2 weeks) prior to surgery or treatment.

Also included in pneumococcal vaccination recommendations are those with occupational risk from exposure to inhaled metal fumes such as welders.

In Scotland, PCV-13 is part of the childhood immunisation schedule and PPV-23 is offered to individuals aged ≥ 65 years as well as those at high risk of IPD. Children aged between 2-5 years who have had previous IPD are also recommended to receive PPV-23 at the general practitioner's discretion.⁸⁰

11.1.5 European Union

Table 9: Summary of recommendation for pneumococcal vaccination in Europe (adapted from ECDC, 2016)

Country	High-risk group recommendations	Vaccine	Interval between PCV13 + PPV23 [§]	Interval between PPV23 + PCV13 [§]
Austria	Funded for adults aged >50 years <ul style="list-style-type: none"> - Pneumococcal vaccination naïve - Previous PPV-23 - Previous PCV-13 	PCV-13 + PPV-23	≥1 year NA ≤2 years	NA ≤2 years NA
Belgium	High risk adults aged 19-85 years	PCV-13 + PPV-23	≥ 8 weeks PPV-23 booster 5 yearly	≥1 year
	Adults 50-85 years with comorbidity		≥8 weeks	≥1 years
	Healthy adults aged 65-85 years		≥8 weeks	≥1 years
Country	High-risk group recommendations	Vaccine		
Cyprus	High-risk age 2-64 years for specific indications	PPV-23		
Czech Republic	Recommended age 5-64 years: Mandatory for high-risk groups	PCV-13 or PPV-23		
	Age ≥65 years: Mandatory for high-risk groups	1 dose PCV-13 + PPV-23		
Finland	Recommended, not funded at age 50-59 years	PCV-10		
Germany	Specific chronic conditions aged 5-59 years Age ≥60 years	One dose PCV-13 or PPV-23, further doses as necessary One dose PPV-23 Booster only for specific indications		
Greece	High-risk groups age 18-50 years Recommended from ≥50 years	PCV-13 + PPV-23 PCV-13		
Hungary	Recommended ≥60 years	PPV-23		
Iceland	Recommended ≥ 60 years	PPV-23 One dose 10 yearly or 5 yearly if at-risk		
Ireland	Funded ≥65 years	PPV-23		
Luxembourg	Recommended ≥60 years	PPV-23 Boosters 5 yearly if in at-risk group		
Malta	Age ≥65 years No infant schedule	PCV		
Norway	Recommended ≥65 years. Funded for some at-risk groups	PPV-23 One dose if not vaccinated in previous 10 years		
Poland	Recommended ≥50 years	PCV		
Slovakia	Recommended for special groups ≥60 years	PCV		
Slovenia	Recommended ≥65 years, not funded	PCV-13 or PPV-23		
Spain	Recommended ≥65 years	PPV-23 (revaccination only if high risk)		
Sweden	Funded ≥65 years	PPV-23		
§ Where details are given. NA – not applicable				

For a summary of European recommendations for pneumococcal vaccination see Table 9.⁸¹

The Norwegian Institute for Public Health categorises the need to vaccinate high-risk groups according to risk across the whole group or heterogeneity with the group for those aged older than 2 years. Vaccination is recommended for all individuals with conditions that put them at 'very high risk' of IPD, such as asplenia, cerebrospinal fluid leaks, haematological malignancies and B cell deficiency. For those with certain 'high-risk conditions', including primary immunodeficiencies, chronic liver and kidney disease, would be heterogeneous in their risk and individual assessment to vaccinate is required. Whereas those age ≥ 65 years and with cochlear implants would all be vaccinated. Patients with conditions classed as 'moderate risk' are assessed individually, for example diabetes mellitus, coeliac disease, chronic respiratory disease, tobacco smokers.⁸²

11.2 Summary

Internationally, there is a wide variation in the use of pneumococcal vaccines in older adults and at-risk groups. Some countries only recommend PPV-23 not PCV-13 or generic conjugate vaccines, or vice versa.

International recommendations tend to agree with who is at high risk of IPD. Many countries identify those older than 60-65 years of age as being at increased risk of IPD and recommend PCV-13 and/or PPV-23 vaccination. Some countries, including the US, also identify individuals with alcoholism and tobacco smokers as being at-risk from IPD and recommended pneumococcal vaccination. Canada also recognises drug abusers and homeless adults as being at increased risk. However, where pneumococcal vaccination is recommended, it is not necessarily funded for some or all of these conditions.

Healthy indigenous adults in Australia, who are known to be at higher risk of IPD, are vaccinated at an earlier age than non-indigenous adults (from 50 years versus 65 years), and indigenous children are receive an extra booster dose of PCV-13 in the second year of life.

Many European countries recommend vaccination of adults older than 60 or 65 years. Details about special high-risk groups were not available in English and could not be evaluated for this review.

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