The Immunisation Advisory Centre

Review of evidence to inform the New Zealand National Immunisation Schedule, 2019: Pneumococcal

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Abbreviations

ACIP	Advisory Committee on Immunization Practices
AE	Adverse events
ATSI	Aboriginal Torres Strait Islanders – indigenous people of Australia
CAP	Community-acquired pneumonia
95% CI	Confidence interval
COPD	Chronic pulmonary obstructive disorder
CRM	Cross-reactive material derived from diphtheria toxin, used as conjugate protein
DTaP	Combined diphtheria, tetanus, acellular pertussis vaccine
ELISA	Enzyme-linked immunosorbent assay
ESR	Institute for Environmental and Scientific Research
GMT / GMC	Geometric mean titre / concentration
GSK	GlaxoSmithKline Ltd
Hib	*Haemophilus influenzae* type b
HIV	Human immunodeficiency virus
HSCT	Haematopoietic stem cell transplant
IPD	Invasive pneumococcal disease
IRR	Incidence risk ratio
aOR	Adjusted odds ratio
PCV7, 10 or 13	Pneumococcal conjugate vaccine 7-valent, 10-valent or 13-valent
PPV23	Pneumococcal polysaccharide vaccine 23-valent
NTHi	Non-typeable *Haemophilus influenzae*, used as conjugate protein in PCV10
NZ	New Zealand
RCT	Randomised controlled trial
Tdap	Combined tetanus toxoid, reduced antigen diphtheria toxoid and acellular pertussis vaccine
TT	Tetanus toxoid
UK	United Kingdom
US	United States of America
WHO	World Health Organization

Overview Summary

A primary aim of pneumococcal immunisation programmes is to prevent invasive pneumococcal disease (IPD), defined as infection of *Streptococcus pneumoniae* in the blood or other normally sterile sites, with associated hospitalisations and deaths. Pneumococci also cause respiratory tract infections without bacteraemia; the most severe of which is pneumococcal pneumonia, but also include middle-ear infection (acute otitis media) and sinusitis.

Building on our previous reviews of the pneumococcal literature conducted in 2016 and 2017, which examined use of ten-valent pneumococcal conjugate vaccine (PCV10), high-risk groups requiring pneumococcal vaccination and the placement of PCVs in childhood on the National Immunisation Schedule,[1-3] this review is limited to literature published between January 2016 and April 2019. It examines the scheduling of pneumococcal conjugate vaccines (PCV10 and PCV13) and the use of 23-valent polysaccharide pneumococcal vaccine (PPV23) in high-risk groups and older adults, focussing on questions relevant to pneumococcal immunisation in New Zealand (NZ). The evidence presented has not been formally graded as in a systematic review, and cost effectiveness of pneumococcal vaccines is not included.

Globally, it is estimated that 200–300,000 deaths in children result from pneumococcal infections each year, and among survivors of pneumococcal meningitis, at least a quarter suffer long-term sequelae, such as hearing loss, seizures and cognitive or motor deficits.[4]

In NZ, there were 557 cases of IPD during 2018 (overall incidence of 11.4 cases per 100,000 population), with the highest incidence in adults aged 65 years or older (31.3/100,000). Between 2017 and 2018, increasing incidence of non-PCV13 vaccine-types was observed for all age-groups, most notably vaccine-eligible ages 2-4 years. The most prevalent serotypes were 19A, 12F, 22F, 8, 3 and 7F.[5]

Pneumococcal conjugate vaccines have been included in the National Immunisation Schedule since 2008. In the Auckland region from 2009 to 2016, IPD incidence declined by 32% in young children aged 0-4 years, with lower reductions in older age-groups (12% aged 65 years or older). However, in 2011, there was a sharp rise in 19A IPD in children aged 0-4 years and there has been a gradual and continual rise in 19A in the elderly such that in 2016 this age group had the highest rates.[6] There has been insufficient time since July 2017 to assess trends in 19A-type IPD after PCV13 was replaced with PCV10 on the childhood Schedule. However, 19A IPD did increase by 27% from 56 cases in 2017 to 71 cases in 2018 in persons over 5 years of age, while remaining the same in children aged under 5 years, so continued monitoring will be important.[5]

Since the completion of the literature search in April 2019, more literature has been published and further discussions are underway internationally around pneumococcal vaccination recommendations, particularly for immunocompetent older adults. Continual monitoring of the evidence, especially around adult pneumococcal immunisations, is required.

Timing and vaccine choice for primary immunisation in infants and toddlers

The World Health Organization (WHO) released a position statement in February 2019 for PCV10 and PCV13 in children aged under 5 years, recommending three doses of a PCV by 18 months of age as either three primary doses (3+0) or two primary and one booster (2+1).[4]

WHO noted that choice of schedule for PCV10 or PCV13 in any specific region must take into account prevalent serotypes and ages with the highest IPD incidence, as well as the spacing of other vaccines on the schedule.[4]

Further to this, there are several questions surrounding the use of PCVs – i.e. how many primary doses are required, is the interval between primary doses important, what are the benefits of booster doses and is there an optimum interval between primary and booster doses? Other issues include the choice of PCV (10 versus 13) and whether indirect serotype-specific protection (herd immunity) is demonstrated in other age groups. Also, particularly in the NZ context of commencing primary immunisations at 6 weeks of age (rather than 8 weeks or later), does the presence of maternal tetanus or diphtheria antibodies in the infants of mothers who receive tetanus-diphtheria and pertussis (Tdap) vaccination in pregnancy influence the immunogenicity and the effectiveness of PCVs against some or all serotypes?

Note that, since completing this literature review, on 30 July 2019 PHARMAC announced changes to the routine childhood immunisation schedule to commence in July 2020. The proposed childhood schedule will provide three doses of PCV10 as a 2+1 schedule, at 6 weeks, 5 months and 15 months of age.[7]

What is the optimal number of primary doses and spacing of doses PCV for the childhood immunisation schedule in New Zealand?

Immunogenicity data suggest that both PCVs (PCV10 and PCV13) induce good responses in a 2+1 schedule. PCV13 generates higher antibody levels against 10 shared serotypes after two doses, but these levels wane to become similar to PCV10 by 9 months of age.[8, 9]

Data is limited around optimal spacing of primary doses (either two or three). Choice of spacing is influenced by the schedule for other vaccines, in particular pertussis, and choice of timing by the age of highest IPD risk.[10]

The levels of bactericidal antibodies required for protection against IPD varies by serotype, and is highest for 19A, 19F and 3.[11] The recent endorsement of a 1+1 routine schedule in the UK was based on a randomised controlled trial that demonstrated higher booster responses after a single primary dose against serotypes 1, 4, 14 and 19F than after two priming doses. Although for these serotypes, the booster response following a single priming dose was higher than when two priming doses were given, infants aged between 4 and 12 months of age could be vulnerable under this reduced schedule if vaccine-serotypes continue to circulate.[11] Therefore, a single priming dose would only be worth considering if all vaccine serotypes had been virtually eliminated from the population.[11]

Current immunogenicity data is insufficient to compare 1+1 schedules for PCV10 and PCV13, and clinical outcomes are unknown for this reduced schedule.[8] Further, even if it was shown to be clinically effective, such a reduced schedule is not currently an option in NZ where vaccine-serotypes remain in circulation across all age-groups.[12]

Are booster doses required and what is the optimal timing between primary and booster doses?

A 2+1 schedule is expected to provide adequate protection during the first year of life if circulation of vaccine serotypes is low. However, in some infants, seroprotection after two primary doses may be inadequate prior to the third (booster) dose.

A further issue for the 2+1 schedule in NZ is that the current schedule, with the second dose at 3 months and the booster dose at 15 months, increases the time between doses to 12 months compared with 8 months in most other 2+1 schedules.[8, 9] This gap in protection will be short-lived if herd immunity is generated against 19A after the third dose of PCV10, but will need to be monitored carefully.

The reviewed literature indicates that booster doses of PCV13 in the second year of life provide indirect protection to other age groups and unvaccinated children by reducing vaccine-type pneumococcal carriage in toddlers.[9] Although direct cross-protection from PCV10 serotype 6F was observed against 6A, no net cross-protection from 19F and reduction of 19A IPD or 19A carriage were observed in Canada, Finland and Belgium.[9, 13, 14]

Australian experience using PCV13 in a 3+0 schedule provided strong evidence that, especially for serotype 19A, the lack of a booster dose in the second year of life leads to inferior long-term immunity.[15] No recent data were found examining the effectiveness of PCV10 in a 3+0 schedule compared with 3+1 or 2+1 schedules.

Conclusions: timing and vaccine choice of primary series

Questions remain around the spacing of PCV doses, notably between primary and booster doses in a 2+1 schedule. For healthy infants, a 2+1 schedule is sufficiently protective against vaccine-type IPD but does leave a potential “immunity gap” between the second and third doses, exaggerated by the current NZ schedule 15 months dose.

This immunity gap is particularly relevant for infants with greater exposure to circulating serotypes or with risk factors associated with IPD, such as those living in poorly ventilated and/or overcrowded homes, attending day-care or exposed to tobacco smoke.

Although for some serotypes, the booster response following a single priming dose (as in a 1+1 schedule) is higher than when two priming doses are given, the balance of risks and benefits depends on the prevalence of circulating vaccine types, and 19A in particular is likely to circulate more widely with a PCV10 than a PCV13 schedule.[14]

Does the presence of maternal antibodies affect primary response to pneumococcal conjugate vaccines?

The relevance of higher levels of maternal tetanus or diphtheria antibody in infants of mothers who received Tdap vaccination in pregnancy is uncertain. Immunogenicity data is limited and varies between PCV serotype and vaccine. The clinical outcomes have not yet been determined, especially in the context of commencing the primary series at 6 weeks of age and following a 2+1 schedule.

Interference from maternal anti-diphtheria antibodies with infant immune responses to diphtheria-derived protein CRM-conjugated serotypes (all PCV13 serotypes and PCV10 serotype 19F) is greater than for serotypes conjugated to other proteins (other PCV10 serotypes). This could impact on protection against vaccine types that continue to circulate among infants prior to a toddler booster dose under a 2+1 schedule, particularly for PCV13.[11, 16]

Conclusions – interference from maternal antibody

Although clinical advantage has not yet been demonstrated, PCV13 provides greater antibody responses than PCV10 (including PCV13-type 19A), especially post the toddler dose.[8] However, there is a potential for greater interference from maternal anti-diphtheria antibody with responses to PCV13 up to 3 months of age.

Should the schedule and vaccines used for high-risk children differ from routine childhood schedule?

Continued analysis of the most recent IPD notifications in NZ is required to identify which are the most prevalent serotypes and risk factors for IPD in children.

From the limited literature, a three-dose primary series plus a dose in the second year of life (3+1) could provide the greatest protection to high-risk children under the age of two years.[10]

WHO recommends a booster dose to be given in the second year of life for human immunodeficiency virus (HIV)-positive infants and infants born prematurely who receive three primary vaccines doses before 12 months of age.[4]

Conclusions: schedule for high risk children

Limitations of a 2+1 schedule are heightened for children with medical conditions that predispose them to pneumococcal disease, justifying an additional dose before the age of 12 months. Data from the UK suggest that infants born prior to 35 weeks gestation, even in the absence of additional high-risk medical conditions, are also at higher risk of IPD.

Summary - Timing and vaccine choice for the primary immunisation schedule in infants and toddlers

- A 2+1 schedule is expected to provide adequate protection to most children
- The 2+1 schedule will widen the immunity gap, especially for 19A, to between 3 and 15 months of age.
- Three doses of PCV before 12 months of age are recommended for those predisposed to pneumococcal disease, including infants born earlier than 35 weeks gestation.
- Monitoring for potential interference from maternal antibody is required.

Herd immunity

Since young children and toddlers are a significant reservoir, reduced circulation of vaccine-serotype pneumococci is expected to reduce exposure, and risk of vaccine-type IPD, in older people.

Does childhood immunisation provide enough indirect protection to older adults and high-risk children to obviate the need for vaccine-type direct protection?

PCV vaccine programmes have had a significant impact on IPD incidence in children, but NZ data from Auckland and nationally suggest that declines in IPD in older adults have been lower than described elsewhere, with increases in non-vaccine serotypes.[6, 12, 17] In the Auckland region, between 2009 and 2016, overall IPD incidence declined by 32% in children aged 0-4 years, but declined least (12%) in adults aged over 65 years.[6]

In 2016, 37.4% of the IPD cases in NZ adults aged 65 years and older were PCV13 serotypes (68/182 cases), notably serotype 19A (31 cases), and 69.2% were due to PPV23 serotypes.[12]

In the 5 years following the introduction of PCV13 or PCV10 programmes in children in Europe, the incidence of PCV-serotype IPD decreased by up to 50% in adults aged over 65 years but there was only a moderate decline in IPD overall due to increases in non-vaccine-type IPD.[18] Following the introduction of PCV10 in infants in Finland, declines in all-cause and pneumococcal pneumonia hospitalisations were observed in older adults (6.7% and 14.5% annually, respectively).[19]

Serotype 3 causes much of the remaining PCV13-type IPD in adults in the US. Protection against this serotype requires much higher antibodies levels than other serotypes and seroprotection wanes more rapidly in children, reducing the potential for indirect protection.[20]

Conclusions and Summary – Herd immunity

Although PCV programmes have significantly reduced IPD incidence in vaccinated and unvaccinated children, reductions in older age groups depend on serotype prevalence.

- The extent to which PCV childhood programmes provide indirect reductions in IPD among high-risk children and older adults varies among reports and settings.
- A longer data series is required to evaluate any impact on the incidence of IPD by serotype in NZ adults following the change to PCV10 in the childhood programme.
- Direct protection against vaccine-type IPD continues to be necessary for those at highest risk of IPD.

High risk groups and those at increased risk of pneumococcal disease

For adults and those at high risk of IPD, key questions remain as to the relative value of lower immunogenicity, but broader serotype coverage provided by PPV23, versus direct administration of PCV13 or indirect reductions through childhood PCV13 programmes.

Funded pneumococcal vaccines in New Zealand for high-risk groups include:

- Pre and post solid organ and haematopoietic stem cell transplant
- Human immunodeficiency virus infection
- Primary immunodeficiencies – pneumococcal vaccines also used for diagnosis
- Immunosuppressive and radiotherapy recipients, including corticosteroids (for more than 2 weeks or equivalent dosage of 2mg/kg per day)
- Functional and anatomic asplenia, pre and post splenectomy
- Complement deficiency (acquired or inherited)
- Undergoing renal dialysis
- Cochlear implants

Funded for children aged under 5 years (PCV13 plus PPV23) for the following conditions:

- Intracranial shunts
- Cerebrospinal fluid leakage
- Chronic pulmonary disease (including asthma with high-dose corticosteroids)
- Preterm infants, born before 28 weeks gestation
- Cardiac disease with cyanosis or failure
- Diabetes

- Downs syndrome
- Renal failure and nephrotic syndromes

For further details refer to the Immunisation Handbook 2017.[21]

The role of PCV in high risk groups was examined previously in 2016.[2] Additional findings from more recently published literature are discussed below.

What is the ideal schedule for PCV in high-risk children? Should it differ from routine childhood schedule?

Literature around the use of PCVs in high-risk children, especially for PCV10, is limited. It is known that children with high-risk medical conditions are often less well immunised than their healthy counterparts; this highlights a need for increased awareness around the benefit in these children of being fully immunised.[2]

Evidence from the limited literature shows that a three-dose primary series of PCV plus a dose in the second year of life (3+1) would provide the greatest protection to high-risk children under the age of two years.[10] WHO recommends a booster dose of PCV to be given in the second year of life for HIV-positive infants and infants born prematurely who receive three primary vaccines doses before 12 months of age.[4]

Although PPV23 contains more serotypes than PCVs, it is unsuitable for children under 2 years of age due to their immature immune response, hence, PCV13 provides the broadest protection available currently for this age group.

Premature infants

Infants born prematurely are at higher risk of IPD than those born at term but are not considered at special risk unless born before 28 weeks gestation or have specified underlying medical conditions. Currently, in NZ only children born prior to 28 weeks gestation are eligible to further doses of pneumococcal vaccines (PCV13 and from age 2 years, PPV23). Other fully immunised premature infants are likely to be adequately protected by the current 3+1 PCV schedule.

In the UK, under the 2+1 schedule (PCV13 at ages 8, 16 weeks and 12 months), the incidence risk ratio of IPD was found to be increased from 2.9 in those born before 35 weeks to 8.8 in infants born younger than 28 weeks as compared with infants born at term.[22]

Conclusions – schedule for children at higher risk of IPD

- Three primary doses before 12 months of age, plus a booster in the second year of life is recommended for children with increased risk of IPD.
- Infants born prematurely, between 29 to 35 weeks gestation without high-risk medical conditions, may be at increased risk of IPD under a 2+1 schedule.

Should pneumococcal vaccine be routinely recommended for older adults?

Older age is associated with increased risk of pneumococcal disease as immunity and effective respiratory clearance mechanisms decline. Many countries recommend pneumococcal vaccination for adults from 65 years of age. Indigenous peoples are known to have a higher risk of IPD at a younger age than non-indigenous people. In Australia and Canada, First Nations peoples are recommended pneumococcal vaccine from 50 years of age. Similarly, IPD incidence among adults aged 50 to 64 years who have a single non-immunocompromising medical condition twice that of the general population.[2]

Most recently, US ACIP has been re-evaluating its recommendations for PCV13 to be administered routinely to immunocompetent adults aged 65 years and older in a setting of

sustained indirect effects of PCV13 given to children. Revised recommendations are anticipated in 2019.[23]

Which other groups are at potential risk of IPD and pneumonia?

Recommendations to receive pneumococcal vaccination may be beneficial for other individuals at increased risk of IPD and pneumococcal pneumonia, including previous pneumococcal pneumonia and/or IPD episodes.[2]

Life-style factors, such as environmental and work-place air pollution, smoking and alcoholism, can increase the risk of severe disease, especially for those with chronic illnesses that predispose them to infections, for example, asthma, dementia, mental illness and diabetes.[2, 24] Socioeconomic deprivation, particularly unemployment and low income, as well as homelessness and overcrowding have also been associated with increased risk of IPD.[25]

Risk stacking

In 2016, we reported that certain individuals are at increased risk of IPD but not currently eligible for funded vaccines through the concept of risk stacking.[2] Two classifications of risk were identified: 'high-risk' conditions which on their own are associated with significantly higher incidence of pneumococcal disease, and 'at-risk' conditions, which when combined together or with other factors such as age, alcoholism, tobacco smoke, air pollution or socio-economic deprivation, significantly increase the incidence of IPD or pneumococcal pneumonia.[26] Risk in children and adults with two or more comorbidities can be high as in those with a recognised high-risk condition.[2, 27]

Prevalence of at-risk conditions in Māori or Pacific people might make eligibility to pneumococcal vaccination from age 50 years appropriate. Consideration of the risk and benefits in terms of reducing pneumococcal disease burden is needed when recommending pneumococcal vaccination (PCV13, PPV23 or both) for those with two or more risk factors, particularly those under the age of 65 years with multiple comorbidities and increased risk due to ethnicity.

In the US, one dose of PPV23 is recommended for adults aged 19-64 years with chronic medical conditions, including chronic heart (excluding hypertension), lung or liver disease, diabetes, alcoholism or cigarette smoking.[28] However, in the US, a quarter of pneumonia cases aged 65 years of older were classified as being at low risk of pneumococcal disease.[29]

Conclusion: Which additional groups could be considered for pneumococcal vaccination?

For certain ethnicities, such as indigenous populations, similar incidences of IPD are observed at a younger age than for non-indigenous people. This risk is confounded by poverty, overcrowded multi-generational housing and underlying health conditions. It is therefore important to assess the need for pneumococcal vaccination in these adults from 50 years of age, especially for those with health conditions not currently eligible for funded vaccine, where pneumococcal vaccination is generally recommended at age 65 years.

There is good evidence that PCV13 provides protection for healthier older adults against community-acquired pneumonia (CAP) due to vaccine serotypes. For adults with chronic medical conditions and other risk factors that increase risk from pneumococcal infections, broader protection can be gained from PPV23 against IPD.

Summary – At-risk groups

Expanded eligibility for pneumococcal vaccination, or additional doses may include:

- Adults aged from 50 years with comorbidities, low socioeconomic status and/or ethnicity associated with higher incidence of IPD and pneumonia
- Infants born between 29-35 weeks gestation
- Children aged younger than 5 years at high risk of exposure to circulating serotypes: living in overcrowded home, attending day-care or exposed to tobacco smoke.
- If additional vaccines and/or doses are recommended for groups at increased risk of IPD, it is important to monitor compliance.

Pneumococcal polysaccharide vaccine in older adults and high-risk groups

Increasing incidence of non-PCV serotype IPD in older adults have been observed in some countries. In NZ, just over two-thirds of IPD cases in adults age 65 year or older were caused by PPV23-serotypes in 2016.[12] The incidence of non-PCV13 serotype IPD in Europe increased by 63% from 2009 to 2015 following the introduction of PCV10 and PCV13. In 2015, 22-54% of the IPD in older adults in European sites was caused by 11 PPV23-non-PCV13 serotypes.[18]

Although PPV23 does not induce immune memory, antibodies generated provide protection for 2-5 years against IPD caused by a wider range of pneumococcal serotypes than the currently available PCVs. The key questions are whether the increased coverage provided by PPV23 is needed to protect high-risk and older adults against IPD or pneumococcal pneumonia, or whether sufficient protection is provided through PCV13 in high risk groups directly and indirectly through the childhood schedule.

How effective are single and repeats doses of PPV23 against IPD?

Although PPV23 has been available for nearly three decades, questions remain around how long-lived protection is following PPV23 vaccination and the frequency of repeat doses required for prolonged protection. The antibodies induced by PPV23 appear to be longer lived than the duration of clinical protection, which may be quite short-lived (2.5 – 5 years).[18, 30]

A 2017 systematic review concluded that PPV23 continues to play an important role in protecting adults against IPD. The pooled vaccine effectiveness of PPV23 in older adults against any serotype of IPD ranged from 45-73% depending on study type. Waning protection was indicated with longer follow-up of up to 5 years.[30]

A systematic review of observational studies reported that antibody induced by repeat PPV23 vaccination is likely to be as long-lived as after the primary vaccination, but adequately powered randomised controlled trials (RCTs) with clinical endpoints and clinical effectiveness data were lacking.[31]

Data is limited around the use of repeat doses of PPV23 in the elderly and high-risk groups. Revaccination with PPV23 at least 5 years after the initial dose is immunogenic,[32, 33] but may not provide additional benefit to all ethnic groups and health conditions.[34] The clinical effectiveness and optimal intervals between repeat doses of PPV23 that would provide continued protection against IPD remain unclear.

How effective is PPV23 against pneumonia?

Patients with pneumococcal pneumonia are hospitalised and require greater medical support significantly more frequently than those with non-pneumococcal pneumonia.[35]

PPV23 appears to have low-to-moderate effectiveness against pneumococcal pneumonia without IPD, but the protection wanes rapidly and mortality or all-cause pneumonia incidence are not reduced.[2, 36] The effectiveness of PPV23 in adults aged over 50 years against all-cause CAP was estimated to be 4% (95% CI -26 to 26%) in clinical trials, 17% (-26 to 45%) in cohort studies and 7% (-10% to 21%) in case-control studies by a Canadian systematic review and meta-analysis conducted in 2016.[37] With such wide confidence intervals, this evidence is insufficient to show PPV23 to be effective against all-cause pneumonia.

When effectiveness against any serotype pneumococcal pneumonia was assessed by a 2017 systematic review, the pooled VE of PPV23 in adults age 60 years or older was found to be 48% (95% CI 25-63%) in cohort studies and 64% (35-80%) in RCTs.[30] The upper level of VE estimates in this meta-analysis seem implausibly high.

Despite differences in study methodologies and different settings (such as community-living and residential care), there is some evidence of protection from PPV23 against non-IPD pneumococcal pneumonia in older adults.

How effective is PPV23 against IPD in high-risk groups?

There is limited data around the effectiveness of either PCV13 or PPV23, or both, in those at increased risk of pneumococcal disease with any chronic health conditions.

Immunosuppressive therapies, as well as the comorbidities they treat, can increase the risk of pneumococcal disease. They also affect the immune response to vaccination and potentially reduce vaccine immunogenicity, effectiveness and duration of protection in certain at-risk groups.

Factors affecting cellular immunity in particular, such as certain T cell-modulating immunotherapies, immune-mediated inflammatory diseases or cancer, can lead to poorer immune responses to PCVs than PPV23, since PPV23 induces a predominantly B cell rather than T cell-driven response.[38]

Conversely, concurrent administration of a live vaccine or the presence of interstitial lung disease can affect immunogenicity to PPV23.[39, 40]

Other approaches to reduce the risk of pneumococcal disease in adults.

Preceding acute respiratory tract infection and respiratory illness has been associated with around one-third of pneumococcal colonisation events in adults.[41]

Compared with trivalent influenza vaccine, PPV23 provided significantly better protection against pneumococcal CAP in adults aged 65 years or older.[42] As also shown in an earlier study, both vaccines were less effective against all-cause pneumonia or hospitalised CAP, but they each provided some benefit as compared with no vaccination.[42, 43] Hence pneumococcal polysaccharide and influenza vaccination in adults, particularly for those with increased risk of severe disease, may help to reduce the burden of IPD and pneumococcal pneumonia in older age groups. Direct protection is required against IPD for those at highest risk from pneumococcal infection.

Summary – what is the role for PCV13 and PPV23 in preventing pneumococcal diseases in older adults and high-risk groups?

- There is limited data around the effectiveness of PCVs, PPV23 or both in those at increased risk of pneumococcal disease with chronic health conditions.
- PPV23 provides protection against a broader range of serotypes but this may vary by serotype
- Frequency of repeat doses is likely to be around 5 years apart, but there is uncertainty around the duration of protection of PPV23, particularly in those with poorer immune response.
- The PCV13 programme in US is currently under review. A role for PCV13 in older adults depends on the magnitude of indirect protection provided by PCV13 in children.
- We recommend that NZ continues to review closely the potential place for both PCV13 and PPV23 for adults aged from 65 years and other at-risk adults, as new evidence and data emerge.

Updates for the Immunisation Handbook

The following are suggested updates for the Pneumococcal chapter of the Immunisation Handbook:

15.3.1 Global burden of disease – include global estimates from WHO February 2019 position statement or more recent publications

Herd immunity – herd immunity has not reduced the incidence of serotypes 3 and 19A

Impact of vaccination on non-invasive pneumococcal disease – more recent data has been published but beyond the scope of this review.

15.3.2 New Zealand epidemiology – this whole section needs revision with the most recent ESR data.

Currently 2016 annual IPD report provides the most detail about ethnicities, age groups and risk factors, but quarterly reports give serotype data for children aged under 5 years or for those aged over 5 years. Update figure 15.1 and 15.2 with 2016 data (or later as available).

15.4.2 Efficacy and effectiveness

PCV10 - include findings of Vietnamese head to head study and Kenyan studies

Further data around pneumonia and otitis media is available but was not within the scope of this review

Consider systematic review data for PPV23 effectiveness against pneumococcal pneumonia. Mention serotype prevalence in adults and coverage by PPV23.

15.5.4 Recommended but not funded vaccine

Consideration to be given to 'risk stacking' based on age, multiple comorbidity, lifestyle, and ethnicity.

Note that questions remain that are being considered internationally as the benefits of recommending PCV13 and/or PPV23, particularly for at risk adults and older adults, to protect against pneumonia and IPD. Awaiting further details to be published.

15.9 Variations from the vaccine data sheet

A review of the recommendations around concomitant use of live herpes zoster vaccine and PPV23 is required.

1 Background

A most readily measurable aim of pneumococcal immunisation programmes is to prevent invasive pneumococcal disease (IPD), defined as isolation of *Streptococcus pneumoniae* from blood or other normally sterile sites. IPD is associated with the highest severity of pneumococcal infection - hospitalisations and deaths. Pneumococci also cause a range of infections without IPD, primarily of the respiratory tract, the most severe of which is pneumococcal pneumonia, but also includes acute otitis media (AOM) and sinusitis. There is evidence that pneumococcal vaccines also have an impact on non-IPD infections, but lack of an isolate or infecting serotype means that this must be assessed by indirect means.

In 2016, we conducted two literature reviews concerning the use of pneumococcal vaccines in high risk groups and of 10-valent pneumococcal conjugate vaccine (PCV10).[1, 2] In 2017, we also assessed the role of PCV vaccines in the childhood schedule.[3] The 2016 and 2017 reviews examined literature published between 2013 and 2016. This review of evidence will focus on literature informing the use of pneumococcal vaccines and scheduling of PCV10, PCV13 and 23-valent pneumococcal polysaccharide vaccine (PPV23), in children, high-risk groups and older adults published between January 2016 and April 2019.

The aim this review is to help to inform decisions about the New Zealand National Immunisation Schedule (the Schedule). It is not a systematic review and does not seek to demonstrate that all publications have been identified - the methodology of the literature search is given in the Appendix (8.4). The review does not incorporate formal grading of evidence quality and economic analyses are not included.

Pneumococcal conjugate vaccines (PCVs) have been part of the NZ Schedule for children and for high-risk groups of all ages since 2008, commencing with PCV7, then changing to PCV10 and PCV13. Further details of the history of the use of these vaccines is presented in the Appendix in Table 1.

The pneumococcal polysaccharide serotypes and overlap of serotypes between these vaccines are presented in Figure 1.

Figure 1: Pneumococcal vaccine serotypes

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	

PCV10 and PCV13 have comparable immunogenicity against the serotypes they have in common (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F). Although PCV10 does not contain serotypes 6A and 19A, it has been shown to induce opsonophagocytic antibody against both of these serotypes at lower levels than PCV13, but not against serotype 3.[4]

1.1 World Health Organization position on pneumococcal vaccines in children

The World Health Organization (WHO) released a position statement for the pneumococcal conjugate vaccines, PCV10 and PCV13, in children aged under 5 years in February 2019. The recommendations were based on literature published up to June 2017.[4]

Globally more than 200–300,000 deaths in children are estimated to result from pneumococcal infections each year, and long-term sequelae, such as hearing loss, seizures and mental or motor abnormalities, have been observed in at least one quarter of survivors of pneumococcal meningitis.[4]

The key recommendations are:[4]

- Inclusion of PCVs in childhood immunisation programmes worldwide
- A three-dose schedule either as 2+1 or 3+0, starting from 6 weeks of age.
- Pneumococcal vaccine should be complementary to other disease control measures, including appropriate case management, exclusive breastfeeding for the first 6 months of life, and reducing exposure to air pollution and tobacco smoke.
- Higher antibody levels in the second year of life, supporting indirect (herd) reductions in vaccine-type infection in older age groups, are achieved with 2+1 than with 3+0.
- An interval of at least 8 weeks is recommended between two primary doses for a 2+1 schedule, with a third (booster) dose between 9 and 18 months. There is no defined maximum or minimum interval between primary and subsequent booster doses.
- For a 3+0 schedule, a minimum of 4 weeks is required between doses. This schedule may be superior to 2+1 if disease is frequent in the first 6 months of life or if coverage of a booster dose is low.
- Both PCV10 and PCV13 have substantial impacts against vaccine-type IPD, presumptive vaccine-type pneumonia, and vaccine-type nasopharyngeal carriage.
- Product switching is not recommended unless there are substantial changes in epidemiology or programmatic factors, e.g. an increase in 19A burden.
- The choice of the product should be based on programmatic characteristics, vaccine supply and cost, and regional prevalence of vaccine-serotypes. PCV13 may have additional benefits where serotypes 19A and 6C significantly contribute to disease.

Catch-up vaccination can be as a single dose in children over 24 months of age, although WHO noted more data are needed. Unvaccinated children aged 1-5 years at high risk due to underlying medical conditions require at least two doses separated by 8 weeks.

In children who recover from IPD, the schedule can be resumed without repeating previous doses. Likewise, if a series cannot be completed with the same vaccine type, the available PCV should be used without restarting the series, even for the primary series.

HIV-positive infants and preterm neonates who have received three primary vaccine doses before 12 months are particularly likely to benefit from a booster dose in the second year.[4]

2 Epidemiology

Since the introduction of PCVs to the childhood schedules, many countries have reported significant decreases in IPD among children and the population as a whole. However, in some countries, IPD due to non-PCV vaccine serotypes has increased, particularly in older adults.

In Sweden, 72% of cases in the elderly in 2016 were non-vaccine-types and the overall impact on IPD incidence did not significantly differ between the PCV10 and PCV13 era.[44] Emerging non-PCV13 serotypes were observed in France between 2010 and 2016. Serotypes with highest disease potential (8, 12F, 24F and 33F) were isolated more frequently from patients without underlying conditions, whereas serotypes with lower disease potential (15A, 15BC, 16F and 23B) were rarely involved in bacteraemic pneumonia, but were particularly seen in IPD cases (35.8%) with underlying conditions.[45]

2.1 New Zealand epidemiology

The epidemiology presented here is from the quarterly latest report (to December 2018) and the 2016 annual IPD report from the Institute of Environmental Research and Surveillance (ESR).[12]

According to the 2016 annual IPD report, the age-standardised rate of IPD cases was 7.0 per 100,000 population for those with European ethnicity, 6.5 for Asian, 26.8 for Māori and 40.0 for Pacific (based on 2016 mid-year population estimate). The two cases reported for MELAA (Middle Eastern/Latin American/African) ethnicity were too few to calculate the rate. Figure 2 shows that the burden of disease is in older adults and Figure 3 shows the significant burden of IPD in older Māori and Pacific adults.[12] Deprivation is also associated with greater IPD incidence in children and adults: total rate in 2016 increased from 5.9 to 19.6 per 100,000 from deprivation index quintile 1 to 5 (based on 2013 census data for NZDep13 and population).

In NZ, 37.4% of the IPD cases in 2016 in adults aged 65 years and older were PCV13 serotypes (68/182 cases), notably serotype 19A (31 cases), and 69.2% were due to PPV23 serotypes.[12] In 2015, half of IPD in adults aged 65 years and older was due to PCV13 serotypes (97/208 cases) and 74% to PPV23 serotypes.[17]

During the 12 months to December 2018, a total of 557 IPD cases were notified at an overall incidence rate of 11.4/100,000 population. Annually, a peak in IPD incidence commonly occurs in quarter three (late winter/early spring), with the highest rate in adults aged over 65 years (234 cases, 31.3/100,000). Increases were seen in incidence of serotypes 12F, 19A, 22F and 3. In children age-eligible for PCV vaccination, all cases were due to three PCV13 serotypes (3, 6A and 19A) or non-PCV13 serotypes (eight cases in total). Ethnicity data and deprivation data were not presented.[5]

An increase in non-PCV13 serotypes occurred across all age groups during 2017-2018, with greatest increases in children aged 2-4 years. The six most prevalent serotypes were PCV13-serotypes 3, 19A and 7F and non-PCV types 8, 12F and 22F. Between the two 12-month periods ending December 2017 and December 2018, the greatest increase was seen in type 7F (a PCV10 serotype): 2.4-fold from 22 to 52 cases. In children who had received at least four doses of a PCV vaccine, two cases of PCV13-serotype IPD (3 and 19A) and two cases of non-PCV13 serotypes were reported.[5]

Figure 3: Incidence rate per 100,000 population of invasive pneumococcal disease by age, 2016 (source: ESR)

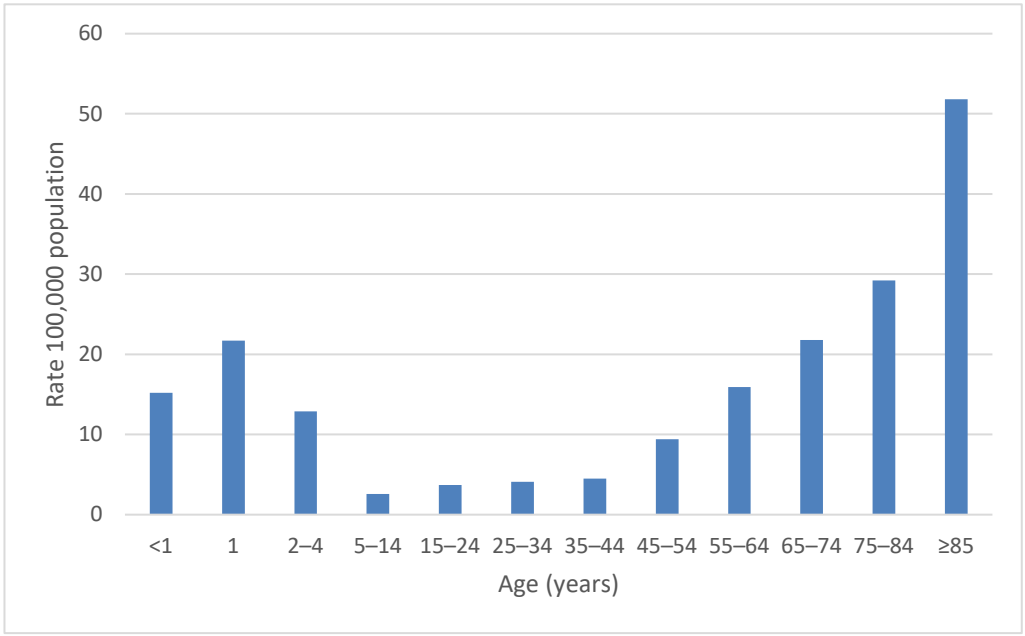
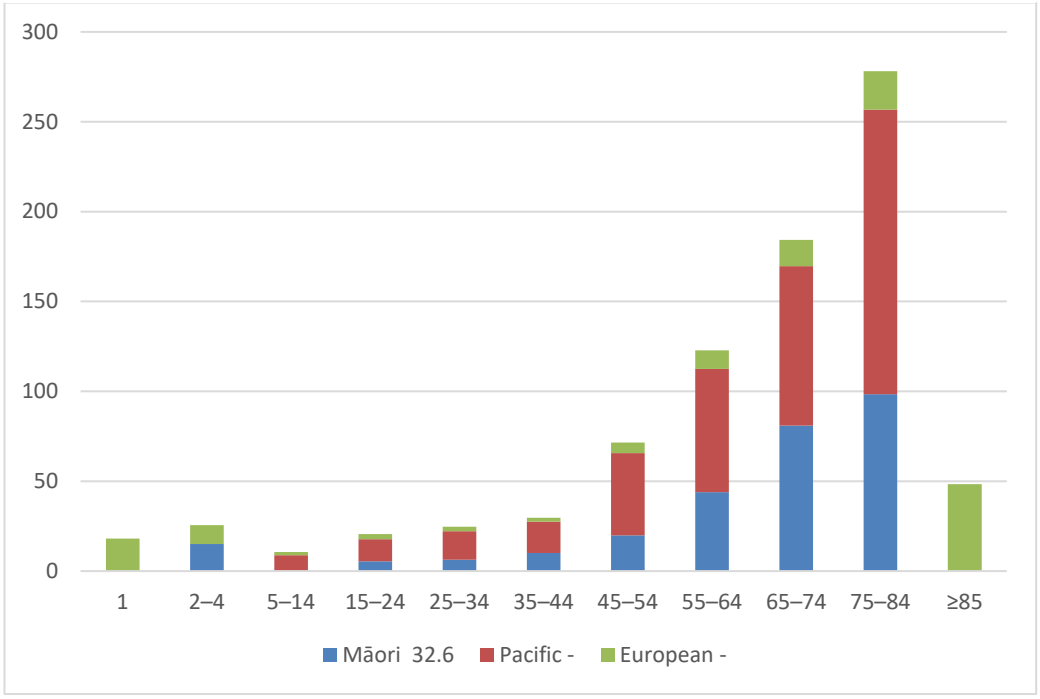


Figure 3: Incidence rate per 100,000 population of invasive pneumococcal disease by age and ethnicity, 2016 (Source: ESR)



2.2 Effectiveness of pneumococcal conjugate vaccination in New Zealand.

A 32% overall decline in IPD incidence in children aged 0-4 years in the Auckland region was reported over 8 years (2009-2016) following introduction of the PCV immunisation programme in children in June 2008.[6] Lower reductions (12%) were observed in adults aged 65 years or older and this age-group had the highest disease burden at 32/100,000 person-years. Ethnic disparities also remained in 2016, particularly for Pacific people. Between 2009 and 2016, the overall incidence rate ratio [IRR] was 2.9 (95% CI 2.61-3.34), $p<0.05$; overall rate 33/100,000) for Pacific people and for Māori (IRR 1.86 [1.61-2.16], $p<0.05$; rate 14/100,000;) as compared with European/Other (rate 3.8/100,000). Although the IPD incidence rate in Pacific people had been decreasing more quickly than for other groups prior to 2016, a noticeable spike was observed in late 2016. Social deprivation was also associated with increased IPD incidence (IRR 3.53 [2.80-4.44]; $p<0.01$ for most deprived compared with least deprived quintile). As deprivation increased, this association has become exponentially more pronounced. Serotype 19A increased sharply in children aged 0-4 years from 3% of cases in 2008 to 33% in 2016. It also increased gradually in the elderly over this time period from 0 in 2008 to 8.2/100,000 in 2016 and is associated with increased disease severity and greater multi-drug resistance. Serotype 15B has emerged as a major variant in 0-4 year-olds, in particular.[6]

A retrospective cohort study demonstrated reductions in the incidence of presumptive IPD and ICD-coded pneumonia, and in disparities between ethnic and socioeconomic groups in NZ following introduction of PCV into the childhood schedule in NZ in June 2008 (3+1 schedule given at 6 weeks, 3 and 5 months and 15 months of age). IPD hospitalisations declined by 75% overall for children aged under 6 years of age (from 26.45 in 2006 to 6.50 per 100,000 person-years in 2015). As expected, the highest rates of disease were observed among Māori and Pacific children and those from socioeconomically deprived areas, but encouragingly the greatest declines in IPD-related hospitalisation were also seen in these children (by 79% in Māori and 67% for Pacific children). All-cause pneumonia hospitalisation declined by 12% and 21% in Māori and Pacific children, respectively, compared with 8% overall and a decline in otitis media of 51% was seen in Māori children compared with 25% overall. These findings are in contrast to increasing hospitalisation rates for other infectious diseases, with increasing ethnic and socioeconomic disparities in NZ.[46, 47]

Literature review

3 Timing of childhood schedule

The timing of the childhood PCV immunisation schedule was considered a previous review.[3] It found that, since NZ has observed a significant decline in a range of measures of pneumococcal disease since the introduction of PCVs (see above)[46], reducing the number of primary doses from three to two as in a 2+1 schedule would maintain protection and be more cost-effective than the 3+1 schedule. Continued surveillance would be required to ensure that any gap in immunity after the second dose (i.e. between 5 and 15 months) does not risk increasing disease.[3] In May 2019, PHARMAC began consultation for a proposal to move to a 2+1 schedule for PCV10, with a subsequent dose of PCV13 in high-risk children up to the age of 5 years, from July 2020.[48]

This section will examine the evidence from the most recently published literature around the scheduling of PCV immunisations in children and proposed changes to the schedule.

3.1 2+1 schedule

Here we examine whether there is sufficient evidence to demonstrate that reducing the number of primary doses of PCV from three doses to two doses would be sufficiently protective in the New Zealand context, any evidence of superiority for either PCV10 or PCV13, and optimal timing between the primary and booster doses.

3.1.1 Comparing immunogenicity of PCV10 and PCV13 in a 2+1 schedule.

Both PCV13 and PCV10 were found to be highly immunogenic when given in a 2+1 schedule in a head-to-head randomised controlled trial (RCT) conducted in Vietnam. Overall, PCV10 induced a better response to shared serotypes after a single dose, whereas PCV13 induced stronger two-dose primary responses, but waned similarly to PCV10 by 9 months of age. PCV13 induced stronger booster responses, but this effect was lost by 18 months of age. The RCT compared the immunogenicity against ten PCV10 serotypes: PCV10 was given either 3+1, 3+0, 2+1 or 2+0 schedules, and compared with PCV13 given as 2+1 schedule (first dose at 2 months and booster at 9 or 9.5 months).[8]

It is unclear yet whether immunogenicity differences for these different vaccines and schedules translate into significant differences in disease outcomes or vaccine-serotype carriage. Immunological advantages for each vaccine varied according to timepoint and serotypes. At 5 months of age, after completion of the primary series, a less than 10% difference in the proportion of infants reaching 0.35 µg/ml antibody titres for any serotype was observed between PCV10 and PCV13. Two doses of PCV13 were non-inferior to three doses of PCV10 (except serotype 6B). At 9 months (pre-booster), 75.4% to 100% of PCV10 groups and 68.9% to 99.1% of the PCV13 group had seroprotective antibody levels to most of the ten shared serotypes, and post-booster, more than 97% of participants had IgG concentrations ≥0.35 µg/ml for all ten shared serotypes. At 18 months the proportion of participants with seroprotective IgG levels was greater than 95% for serotypes 14 and 19F (both groups) and 6B (PCV10 group), and from 59% for all other shared serotypes, with less than 10% relative difference between groups.[8]

3.1.2 Impact and effectiveness of 2+1 PCV schedules

The impact and effectiveness of 2+1 PCV schedules is examined here for both PCV10 and PCV13 with respect to both direct and indirect impact.

Canada, like NZ, has successively changed the PCV used on the schedule as the vaccine serotype content has increased, commencing with PCV7, followed by PCV10 and then moved to PCV13. Unlike NZ and most other Canadian provinces, Québec has used a 2+1 schedule (ages 2, 4, and 12 months) from the start rather than 3+1, and observed an 83% reduction in IPD in children younger than 5 years from 2003 to 2016.[9]

When breakthrough cases of IPD caused by serotype 19A were investigated in Québec, 19 (61%) of 31 cases occurred between 8 and 14 months, following two primary doses of PCV13 and prior to the toddler dose. Although PCV10-serotype 19F showed direct cross-protection against 19A in infants, there was no evidence of reduction in 19A carriage or indirect (herd) reductions in adults, whereas PCV13 did reduce 19A carriage and induce herd effects. It was considered that a recent upswing in 19A may be due to a window of susceptibility in infants under a 2+1 schedule for PCV13 as 19A continues to circulate, but was anticipated to decrease with stronger herd effects over time.[9]

In Finland, a positive impact was also observed against IPD for vaccine-eligible children using 2+1 schedule for PCV10 with a 79% (95% CI 74-83%) reduction in IPD. Direct cross-protection was observed against serotype 6A IPD, but no net reduction for 19A. No notable serotype replacement was observed. In unvaccinated children, indirect impact on IPD was not sustained (33% decrease in all IPD).[13]

Active surveillance data in Germany found that PCV13 demonstrated high overall vaccine effectiveness (VE) against vaccine-serotype IPD for six serotypes added to PCV7 to make PCV13. VE of the German 3+1 schedule was found not be conclusively better for the extra six serotypes in PCV13 than the published VE data of the 2+1 schedule in the UK. However, as the study was based on a small number of reported IPD cases, any improved VE could not confirmed or refuted for the 3+1 schedule.[49]

3.1.3 Conclusions

The choice of schedule for either PCV10 or PCV13 needs to consider prevalent serotypes and age groups with the highest IPD incidence.

While circulation of vaccine serotypes continues, a 2+1 schedule can result in vulnerability in infants between the second primary dose and booster. PCV10 provides direct cross-protection against 6A and 19A, but reductions in carriage and indirect protection of older unvaccinated age groups against these serotypes appears to be superior for PCV13. As reductions in older age groups are numerically large, lesser indirect effects could be important drivers of relative cost-effectiveness.

Immunogenicity data from a recent head to head comparative trial of schedules in Vietnam showed equivalence by 9 months of age but lower antibody levels post the second dose for PCV10 compared with PCV13. In NZ, the booster is given at 15 months which is later than other countries and leaves a greater window of vulnerability. This is particularly an issue where children are at increased risk of exposure (e.g. overcrowding) or may have less robust initial antibody responses (various medical conditions associated with increased IPD risk).

Questions remain over the timing between the primary doses, the optimum age to commence the primary series to avoid potential interference from maternal Tdap vaccination is given, and the gap between primary and booster doses.

3.2 3+0 schedule

There is evidence that a booster dose in the second year of life generates higher antibody responses and greater reductions in nasopharyngeal carriage, leading to less circulation of at least some vaccine serotype pneumococci from toddlers to the wider population. However, to reduce the number of doses given and to ensure adequate protection in countries with high incidence of IPD between the primary series and second year of life, a three-dose primary series is recommended.

A study in Israel found that acquisition rates of vaccine and non-vaccine serotypes at 7-30 months of age were similar for both 3+1 and 3+0 schedules (primary 2, 4, 6 months with or without booster 12 months), despite higher serum IgG in the booster group.[50]

Most evidence around long-term impact of the 3+0 schedule has come from Australia. A cohort study based on 1.4 million births found similarly low rates of IPD among vaccinated and unvaccinated children under two years following the implementation of PCV7 and PCV13 given as a 3+0 schedule (at 2, 4, 6 months of age). No statistically significant difference in vaccine effectiveness was seen between one, two and three doses of PCV13 against PCV13-serotype IPD among non-Aboriginal children under 2 years of age.[51]

For children aged less than 2 years, total IPD declined by 82% from baseline and by 69% in those aged 2-4 years. However, for older age groups and in the longer term, reductions in vaccine-type IPD following PCV13 were inferior to those seen after PCV7. When compared with the UK's 2+1 schedule, lesser reductions in IPD caused by the extra PCV13-serotypes were most evident between ages 5-65 years. Lack of a booster dose was thought to have led to waning immunity to 19A in the second year of life and reduced herd impacts, leading Australia to change to 2+1 from mid-2018.[15]

3.2.1 Conclusions

The Australian experience provides strong evidence that, especially for serotype 19A, lack of a booster dose in the second year of life leads to inferior long-term immunity. No recent data were found considering the effectiveness of PCV10 in a 3+0 schedule compared with schedules including booster doses in in the second year of life.

3.3 Ideal schedule for high-risk children

For infants with medical conditions that affect the humoral immune response to vaccines (e.g. HIV-infected, sickle cell disease, certain primary immune deficiencies), three primary doses are likely to be required to reach adequate antibody levels for protection.

Data is limited around scheduling of PCV vaccines in high-risk children. Only one recent study was found that considered PCV scheduling in high risk infants.

A RCT involving 210 premature infants (born from 23 up to 35 weeks gestation) identified that a reduced 2+1 priming schedule of PCV13 (at 2, 4 and 12 months) resulted in higher post-booster IgG but lower post primary concentrations than either accelerated or extended 3+1 schedules (2, 3, 4 months or 2, 4, 6 months plus 12 months booster, respectively).[10] One month after primary vaccination with reduced, accelerated and extended schedules, 75%, 88% and 97% of participants, respectively, had seroprotective antibody concentrations (>0.35 µg/ml) for at least half of the PCV13 serotypes. The magnitude of the response to booster doses at 12-months was dependent on which primary schedule they had received. Therefore, it was concluded that an optimum schedule for preterm infants and

other high-risk children will depend on when they are at most risk of IPD, either younger than 6 months, between 6 to 12 months (or age of booster) or in the second year of life.[10]

WHO recommends a booster dose to be given in the second year of life for HIV-positive infants and infants born prematurely who receive three primary vaccines doses before 12 months of age.[4]

3.3.1 Conclusions

There are unlikely to be enough IPD cases in NZ, given the relative rarity of many high-risk conditions, to guide policy for specific high-risk groups. From the limited literature, it appears that continuing a three-dose primary series plus a dose in the second year of life (3+1) in high-risk children is justified.

3.4 1+1 schedule

The UK has been actively considering the option of a 1+1 schedule, through immunogenicity clinical trials and analysis of age-specific and serotype-specific IPD incidence.

Pneumococcal conjugate vaccines were introduced to the UK immunisation schedule in 2006 using PCV7 in a 2+1 schedule (at ages 2, 4 and 12 months), continued for PCV13. A recent RCT compared a 1+1 (at 3 and 12 months) with 2+1 schedule.[11] Antibody levels at age 5 months were significantly higher in the 2+1 group (1 month after second dose at 4 months) than 1+1 (at 2 months after the 3-month dose) for all serotypes, except type 3. In contrast, antibody levels following the 12-month dose were significantly greater for the 1+1 schedule for serotypes 1, 4, 14, 19F, but significantly higher under the 2+1 schedule for serotypes 6A, 6B, 18C, 23F. This is consistent with the enhanced boosting after fewer primary doses shown previously for MenC and some PCV13 serotypes. The authors recommended the 1+1 schedule be used only in countries with mature PCV programmes, with little vaccine-type IPD and established herd immunity. In this setting, higher antibody levels in toddlers aged between 12-36 months who are likely to be important spreaders of pneumococci to adults and siblings, are of greater importance than antibody levels in the first year of life.[11]

Although the PCV immunisation programme has lowered IPD incidence in the UK, infants born prematurely remain at higher risk of IPD due to PCV13 and non-PCV13 serotypes than those born full-term. Hence, changes to the schedule from 2+1 to 1+1 are likely to disproportionately affect infants born prematurely.[22]

The opposing view was presented in a dynamic transmission modelling study, supported by the manufacturer of PCV13, Pfizer, which predicted increases in pneumococcal burden (including IPD, non-invasive pneumonia, otitis media). It was estimated that there would be 8777 to 27,807 additional disease cases, including 88-238 more IPD cases, and 241-743 more deaths over 5 years if the UK moved to a 1+1 schedule. This model was based on low vaccine-type pneumococcal transmission.[52]

The previously mentioned RCT in Vietnam also studied responses to a single PCV dose. After a single dose, PCV10 induced protective IgG (>0.35µg/ml) in a greater proportion of participants than PCV13 (relative difference 18.3% [95% CI 11.4 to 25.3]). More than half of the participants had seroprotective levels of IgG at 4 weeks after one dose to serotypes 1, 4, 5, 7F, 14 and 19F in the PCV10 group and to serotype 18C in the PCV13 group, but a single dose of either vaccine elicited no response to shared serotypes 6B, 14, 23G or PCV10-serotypes 6A and 19A compared with pre-vaccination GMCs.[8]

3.4.1 Conclusions

Although immune responses when a booster dose is given with increased intervals following reduced numbers of doses are interesting, there are considerable uncertainties about effects at the population level if a 1+1 routine schedule was implemented. As the immunisation advisory committee (JCVI) in the UK has now recommended to proceed and awaiting a policy decision,[53] it seems prudent to await their experience in a large population.

3.5 Catch-up for children aged under 5 years

WHO recommendations are that catch-up vaccination can be done with a single dose of PCV vaccine for children over 24 months of age, although it was noted that further research was required. Unvaccinated children aged 1-5 years at high risk of pneumococcal infection due to underlying medical conditions should receive at least two doses separated by at least 8 weeks.[4] Recent data around catch-up vaccination are limited for these vaccines.

In a mass immunisation campaign in Kenya, a sharp reduction in annual IPD incidence was observed following the introduction of PCV10 accompanied by a catch-up campaign in 2011. PCV10-type IPD declined from 60.9/100,000 pre-vaccine during 1999-2010 to 3.2/100,000 post-vaccine from 2012-2016 in children aged less than 5 years in the Kilifi district. A decline in PCV-10 IPD was also observed in unvaccinated age-groups, <2 months, 5-14 years and ≥15 years.[54] Vaccine was administered according the GAVI schedule at 6, 10 and 14 weeks of age (3+0) and the national catch-up provided three doses of PCV10 to children less than 12 months of age. In a study conducted in Kilifi, children also received up to two catch-up doses between the ages of 12-59 months in two campaigns. It was predicted that, in the absence of the catch-up programmes, the magnitude of the effect of PCV10 would have taken longer to be achieved.[54] The catch-up campaign prevented an additional 65 cases of IPD across all age groups, compared with PCV-cohort introduction alone. It was estimated that a two-dose catch-up in children under 1 year, then extending a single-dose catch-up to children aged 1 to <2 years and subsequently to 2 to <5 years used an additional 910 (732-1184), 412 (296-606) and 535 (403-763) PCV10 doses per additional IPD cases averted, respectively.[55]

3.5.1 Conclusions

The Kenyan findings have interesting implications for single dose catch-up as part of a mass campaign but have limited application to the NZ setting.

3.6 Effect of maternal Tdap vaccination

There is some concern that presence of maternal antibodies, induced by Tdap vaccination in pregnancy, may influence the immunogenicity of primary doses for vaccines conjugated using tetanus toxoid and diphtheria-derived proteins including PCV. The potential of this interference is particularly relevant to the NZ primary series commencing at 6 weeks rather than 8 weeks and if the NZ programme went from three to two doses of PCV.

When the immunogenicity of 1+1 schedule was investigated in the UK, post primary geometric mean concentrations (GMCs) were lower for antibodies against some PCV13 serotypes (range 6% to 62% lower for serotype 6B and 14, respectively) and significantly lower for serotypes 1, 3, 4, 5, 14, 8C and 19F in infants of mothers vaccinated with Tdap in the 1+1 group. Post-booster responses were not affected in either the 1+1 or 2+1 groups.[11] Furthermore, in a letter, Slack et al (2019) expressed concern that maternal antibody

blunting on the immune response to a single primary PCV13 dose was likely to decrease protection for premature or high-risk infants.[56]

As part of a prospective study in the UK, elevated antibody against serotype 14 was observed at 5 months of age (following primary vaccinations at 8 and 16 weeks) in infants of mothers vaccinated with Tdap in pregnancy, whereas antibody against serotype 7F was higher in infants of mothers not vaccinated in pregnancy. No other differences were observed against pneumococcal or Hib vaccine antigens.[57]

As presented at the International Symposium on Pneumococci and Pneumococcal Disease (ISPDD) in 2018, no blunting in serotype-specific immunity was observed for pneumococcal polysaccharides conjugated with NTHi protein D (serotypes 1, 4, 6, 6B, 7F, 9V, 14, 23F) when PCV10 is given to infants of mothers vaccinated with Tdap in pregnancy compared with CRM-conjugated serotype 19F, for which there were lower post primary and post booster antibody levels compared with infants of unvaccinated mothers (infant schedule not described, PCV recommended at 6-9 weeks, 4 and 11 months in Netherlands). On this basis, it was recommended that infants of mothers who were vaccinated with Tdap in pregnancy should preferably be vaccinated with protein D-conjugated rather than CRM-conjugated vaccines.[16]

An alternative, to overcome the potential interference of maternal Tdap on infant immunity to conjugated vaccines (including PCV), is to vaccinate pregnant women with a pertussis-only vaccine.[58]

3.6.1 Conclusions

The relevance of the presence of higher levels of maternal tetanus or diphtheria antibody in infants of mothers who received Tdap vaccination in pregnancy is uncertain. Immunogenicity data is limited, varies between PCV serotypes and vaccines and clinical outcomes uncertain. The potential interference of diphtheria-derived protein CRM-conjugated serotypes (as used for all PCV13 serotypes and PCV10 serotype 19F) appears greater than for TT-conjugated serotypes (PCV10 serotype 18C) and may have relevance for seroprotection of infants prior to a toddler booster dose if PCV is given as 2+1 schedule (particularly for PCV13, in which all 13 serotypes are conjugated to CRM).

3.7 Summary - timing of childhood schedule for pneumococcal immunisation.

PCV vaccines have made a considerable impact on the incidence of pneumococcal disease and helped to reduce equity gaps in young children. Some vaccine-type serotypes remain in circulation and the timing of the infant schedule may influence this. For some serotypes, herd immunity has not yet been established by PCV10 or PCV13 vaccines and these serotypes remain in circulation. PCV10 demonstrates direct protective effects against 19A through cross-protection with 19F, but indirect / herd immunity against 19A is not observed.

A schedule with a booster dose is likely to provide long-term immunity against circulating pneumococcal serotypes, particularly, when given to toddlers in whom bacterial carriage is greatest. Depending on the predominant serotypes, a 2+1 schedule is likely to be widely protective, although some infants could be at increased risk between primary and booster doses depending on the timing of the booster dose (at 9, 12 or 15 months of age).

For high-risk infants, including those born prematurely, a 3+1 schedule is likely to be required to provide sufficient protection, particularly if a reduced primary schedule is implemented (such as 2+1). High-risk infants, born to mothers who received Tdap in

pregnancy, may be more sensitive to potential interference of maternal antibody if they received only two primary doses of PCV13. As there is less interference with TT and NTHi conjugated serotypes, in this case PCV10 could provide better protection, but the advantage likely to be short-lived. Therefore, a three-dose primary series is advised for these infants in particular.

4 Herd immunity

Since young children and toddlers are significant reservoirs for pneumococci, it was anticipated that immunising young children and reducing nasopharyngeal colonisation would reduce the circulation of vaccine-serotype bacteria. This indirect (herd) immunity derived from child immunisation programmes would lower the risk of vaccine-type pneumococcal diseases in older people. However, data around the magnitude of indirect protection are inconclusive and vary by pneumococcal serotype.

A further concern around the magnitude of vaccine-induced indirect reductions in total IPD is serotype replacement whereby non-vaccine serotypes fill the niche of vaccine-serotypes as they decline. Evidence for herd immunity versus serotype replacement is reviewed.

4.1.1 Mixed schedules with PCV7, PCV10 and PCV13

There is evidence that serotype replacement has occurred in adult groups in some countries since the introduction of PCVs to the child immunisation schedules. For example, in 5 years since the introduction of PCV13/10 programmes in children in Europe, the incidence of PCV-serotype IPD decreased by up to 50% in adults aged 65 years of older. However, an increase in non-PCV-type IPD has been observed, resulting in an only moderate decline in IPD overall.[18]

PCVs had a major effect on the rate of IPD in children in Quebec from 2004-2016 (with successive use of PCV7, PCV10 and PCV13), but this decrease was not also reflected in adults. Although the proportion of IPD cases in older adults caused by PCV13 serotypes declined, the overall IPD rate did not decrease. In 2016, 79% of cases were non-PCV13-type IPD and in those aged 65 years or older, 28% of cases were due to PCV13 serotypes and 62% to serotypes included in PPV23.[9]

A pneumococcal nasopharyngeal carriage study in conducted over 3 years in Belgium found that, after completion of a switch from PCV13 to PCV10 in the childhood immunisation programme, the proportion of PCV13-non-PCV10 serotypes (mainly 19A) increased significantly in children aged 6 to 30 months in day-care visiting a physician for acute otitis media.[14]

4.1.2 PCV10 usage

The impact on all-cause pneumonia hospitalisation rate in adults was assessed following the use of PCV10 in infants in Finland. Prior to PCV10, the annual all-cause pneumonia rate had been increasing annually by 2.4% (from 2004/5 to 2009/10). This declined by 4.7% annually during 2011/12 to 2014/15 following the introduction of PCV10 in 2010. A significant decline of 6.7% annually was seen in adults aged 65 years or older. The rate of pneumococcal pneumonia decreased annually by 8.1% (IRR 0.92 95% CI 0.88-0.97) and significant annual decline of 14.5% was seen in older adults.[19]

4.1.3 PCV7 and PCV13 usage

The findings of a Danish study suggested that toddlers were not the main reservoir for pneumococcal serotypes causing most of the IPD cases in the elderly. By serotyping pneumococci cultured from nasopharyngeal swabs, Danish children aged 8-19 months were found be the main carriers of pneumococcal serotypes causing non-vaccine-type IPD in children aged 0-4 years (mostly 8 and 24F in 2016). However, serotypes causing IPD in the elderly were not found or were found in low prevalence in these children (most were serotype 8, also 3, 7F, 9N, 22F and 12F during 2014-2016). Serotype 8 was found in two children at baseline only. The carriage rate of pneumococci before attending day-care was 26% and increased to 67.4% after 6 months. In Denmark, PCV7 vaccination was introduced in 2007 and replaced with PCV13 in 2010.[59]

Nasopharyngeal carriage of pneumococci was found to be low in adults aged 65 years or older in the US. Vaccine-type carriage was very low and similar between those that were PCV13 vaccinated or not (0.2% vs 0.1%, respectively). Out of 2989 participants, only 55 (1.8%) were found to carry pneumococci and colonisation was associated with respiratory symptoms. This study was unable to conclude whether indirect or direct effects of PCV13 vaccination had an effect on adult carriage.[60]

Serotype 3 causes much of the remaining PCV13-type disease in the US and other countries that routinely use PCV13. No herd immunity has been demonstrated for this serotype since immunisation appears to have little or no effect on carriage. Serotype 3 is more invasive and results in more severe disease, with temporal variations in incidence. This serotype has a thick mucoid capsule that secretes free polysaccharide (in animal studies), interferes with antibody-mediated bacteriolysis and reduces the opsonophagocytic clearance. Higher antibody titre thresholds (2.83 µg/ml compared with the standard seroprotective assay cut-off of 0.35µg/ml) are required for protection against this strain. Unpublished data, presented to the ACIP, showed that VE against serotype 3 in children declines from 12 months after the last vaccine dose.[20]

4.2 Conclusions

PCV vaccination programmes have resulted in a significant impact on IPD incidence in children, and against vaccine-type IPD due to some serotypes in older adults. Reports vary to the extent of herd effects, which may not protect those at increased risk from IPD and may be associated with increases in non-vaccine serotypes which reduce or eliminate reductions in vaccine-type disease.

5 Pneumococcal vaccines in high-risk groups

Funded pneumococcal vaccines are available in New Zealand for those at highest risk with certain medical conditions and severe immunocompromise.

Compromised immunity is a significant risk factor in opportunistic infections like pneumococcus. Mortality with IPD is more than 50% for those with asplenia. Although anti-retroviral treatment has significantly reduced the burden of IPD in individuals with human immunodeficiency virus (HIV), the risk of disease remains 35 times higher in HIV-infected than non-HIV-infected individuals.[61]

Patients with conditions affecting the respiratory and immune systems are also at high risk of IPD and death. Chronic respiratory diseases, including chronic obstructive pulmonary

disease (COPD), cystic fibrosis and lung cancer, are associated with impaired respiratory tract immune responses and increased infection risk. For those with common respiratory diseases like asthma and COPD, the risk of IPD is two to six-fold greater than the general population.[61]

High-risk groups for funded vaccine include:

- Pre and post solid organ and haematopoietic stem cell transplant (HSCT)
- Human immunodeficiency virus (HIV) infection
- Primary immunodeficiencies – vaccines also used to diagnose
- Immunosuppressive therapy and radiotherapy recipients, including corticosteroids (for more than 2 weeks or equivalent dosage of 2mg/kg per day)
- Functional and anatomic asplenia, pre and post splenectomy
- Complement deficiency (acquired or inherited)
- Undergoing renal dialysis
- Cochlear implants

Funded for children aged under 5 years with these medical conditions (PCV13, from 2 years of age plus PPV23)

- Intracranial shunts
- Cerebrospinal fluid leakage
- Chronic pulmonary disease, including asthma with high-dose corticosteroids
- Preterm infants, born before 28 weeks gestation
- Cardiac disease with cyanosis or failure
- Diabetes
- Downs syndrome
- Renal failure and nephrotic syndromes

For further details refer to the Immunisation Handbook 2017.[21]

In Australia and Canada, separate categories for immunisation are delineated for those at high risk of pneumococcal disease. Canada distinguishes immunocompromised and immunocompetent conditions and includes special situations such as alcoholism, living in aged-care and homelessness as risk factors for IPD. Australia has category A and B risk factors for those at high risk or increased risk of IPD. Occupational risk factors and lifestyle factors are also considered in the UK.[2]

This section will examine whether those at high risk of IPD are being adequately protected or if there are other groups that could be better protected by funded pneumococcal vaccines. The most recent literature is considered that adds further information to that obtained by our 2016 literature review on pneumococcal immunisation in high-risk groups.[2]

5.1 Immunocompromised children and children born preterm

Premature infants aged less than 1 year are disproportionately affected by IPD as compared with those born at term for both PCV13 and non-PCV13 serotypes. Under the reduced 2+1 primary schedule (8, 16 weeks and 12 months) in the UK, incidence risk ratio of IPD increased from 2.9 in those born before 35 weeks to 8.8 in infants born younger than 28 weeks gestation as compared with infants born at term. The case-fatality rate for IPD was not significantly different between term and preterm infants ($p=0.62$).[22] An RCT found that the optimum vaccine schedule for preterm infants with PCV13 would depend on the age at which they were at most risk of IPD. Infants who received a two-dose ‘reduced’ primary schedule (2 and 4 months) or ‘accelerated’ schedule (2, 3, 4 months) had higher IgG levels

post-booster (given at 12 months) than those who received an 'extended' (2, 4, 6 months) three-dose primary schedule, regardless of serotype. At one month after the two-dose, accelerated or extended primary series, 75%, 88% and 97% of participants, respectively, had seroprotective antibody levels for at least half of the PCV13 serotypes.[10]

In NZ, infants born prematurely are only currently considered as being a high-risk group if they are born before 28 weeks gestation, unless they have underlying health issues that makes them eligible for further pneumococcal vaccination. These infants are likely to be adequately protected by the 3+1 schedule in place and are therefore not currently observed to be at increased risk. There is a risk however that if a 2+1 schedule is implemented more cases of IPD may emerge in this potentially vulnerable group.

For catch-up vaccinations, WHO recommends that unvaccinated children aged 1-5 years, who are at high risk pneumococcal infection such children with HIV-infection or sickle-cell disease, receive at least two doses given at least 8 weeks apart.[4]

5.2 Older adults

Older age is associated with increased risk of pneumococcal disease as immunity and effective respiratory clearance mechanisms decline, independent of chronic health conditions.

Many countries have followed the lead of the US and recommend pneumococcal vaccination for adults aged ≥65 years.

Indigenous peoples are known to have a high risk of IPD at a younger age than non-indigenous people, therefore, Australia and Canada recommend these groups to receive pneumococcal vaccination from 50 years of age. 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.[2]

Most recently, US ACIP has been re-evaluating its recommendations for PCV13 to be administered routinely to immunocompetent adults aged ≥65 years in a setting of sustained indirect effects of PCV13 given to children. Revised recommendations are anticipated mid-2019.[23]

Indirect protection stemming from childhood immunisation programmes has reduced the circulating vaccine-type IPD cases in older adults in the US. Non-PCV vaccine serotypes are more likely to cause disease, some of which are covered by PPV23. Therefore, the role of PCV13 in adults is unclear. PCV13 does not appear to be directly or indirectly effective against serotype 3 disease in older adults, although the data is inconsistent. Type 3 IPD increased 31% in 10 years <5 year olds, but little change was observed for adults.[20]

In 2016 in NZ, 37.4% of the IPD cases in adults aged 65 years and older were PCV13 serotypes, notably serotype 19a (17%) and 69.2% were due to PPV23 serotypes.[12] Changes in serotype prevalence is illustrated in Figure 4.[12] Further assessment of the prevalent NZ serotypes in adults and children is required to gauge the influence childhood immunisation programmes (using both PCV13 and PCV10 vaccines) have had in more recent years.

5.2.1 Prevention of pneumococcal pneumonia

PCV13 was found to be most effective against CAP and lobular pneumonia in healthier older adults (without high-risk medical conditions). However, the effectiveness of PCV13 was around 6-11.4% against all-cause community-acquired pneumonia (CAP), and only represented 5.1% of all-cause CAP hospitalisations averted in the US.[29]

Community-dwelling adults aged ≥65 years who had received PCV13 or PPV23 before or during a 12-month study period were found to have a reduced risk of pneumococcal colonisation when followed bi-weekly ($p<0.001$). There was no significant decrease in risk of colonisation with the addition of PCV13 compared to those who had received PPV23 alone. The study found that nasopharyngeal and oropharyngeal pneumococcal colonisation was frequent in older adults (as detected by *lytA* polymerase chain reaction analysis).[41]

5.2.2 Conclusions

Adults aged over 65 years are a risk group for IPD. In certain populations, particularly indigenous peoples, a similar level of risk is observed at a younger age than non-indigenous people. It is therefore necessary to assess pneumococcal vaccination for adults from 50 years of age, particularly for those with underlying health conditions not currently eligible for funded vaccine.

PCV13 may provide some protection for healthier older adults against CAP and lobular pneumonia depending on prevalent serotypes in this population. However, PPV23 is likely to be more broadly protective.

5.3 Risk stacking

In a previous literature review that specifically examined pneumococcal immunisation in high-risk groups, the concept of 'risk-stacking' was presented.[2]

From the literature, two classifications of risk were 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 other factors, such as age, alcoholism, tobacco smoke, air pollution and socio-economic deprivation, can significantly increase an individual's likelihood of developing IPD or pneumococcal pneumonia.[24, 25] The risk of life-threatening pneumococcal infections in children and adults with two or more comorbidities can be high as in those with a recognised high-risk condition.[2]

Chronic illnesses, including diabetes, cardiac, pulmonary, liver, renal and alcohol-related diseases, cerebral-spinal leakage and intracranial shunts, are significant risk factors for IPD. In NZ in 2016, 57.7% of cases with a risk factor reported had chronic illness, 23.5% of those aged over 15 years reported smoking as a risk factor and in 61.5% of under 5 year-olds, smoking in the household was a risk factor.[12]

5.3.1 Risk-stacking in children

Children with high-risk conditions were found to be less well immunised than the general population – highlighting a need to increase awareness of the benefit of vaccination in high-risk children against all diseases, where contraindications are not present. Tobacco smoke exposure was shown to increase the risk of IPD, particularly for children with other risk factors such as chronic respiratory disease, compromised immunity and frequent hospitalisation.[2, 12] Attending childcare is also associated with increased risk of IPD.[12]

5.3.2 Risk-stacking in adults

In the US, one dose of PPV23 is recommended for adults aged 19-64 years with chronic medical conditions, including chronic heart (excluding hypertension), lung or liver disease, diabetes, alcoholism or cigarette smoking.[28]

Mortality due to IPD (culture-positive pneumonia, meningitis or bacteraemia) among unvaccinated US adults aged 50 years or older was shown to increase as individual risk

factors were stacked: each additional risk factor increased 30-day mortality by an average of 55% (± 13%) during 2002-2011. Mortality with six stacked indications was double that of two indications. The greatest increase in risk was seen between two and three stacked risk factors (70%). The risk factors assessed included age ≥65 years, alcohol abuse, chronic heart disease, chronic heart failure, chronic liver disease (any severity), chronic respiratory disease, diabetes mellitus, immunodeficiency, and tobacco smoking, as identified by the Advisory Committee on Immunization Practices (ACIP). Increased risk was not however multiplicative for related conditions (e.g. liver disease and alcohol abuse, smoking and respiratory disease). This national case-control study was unable to conclude whether or not smoking alone increased risk, but when associated with other comorbidities, it played a role in risk-stacking.[27]

5.3.3 Risk stacking in older adults

Being resident in long term or other chronic care facility is associated with increased risk of IPD (5.7% of cases with recorded risk factors).[12]

A study presented at the ACIP meeting February 2019 found that the prevalence diabetes or chronic lung disease was 42% of the Medicare population aged ≥65 years who were hospitalised with pneumonia. Around a third of the study cohort (which represented more than half of the US over 65-year-old population) had a condition classified as high risk, in particular chronic kidney disease, generalise malignancy, immunodeficiencies, plus a condition that increased their risk (chronic heart disease, diabetes, chronic lung disease), e.g. diabetes plus chronic kidney disease. A quarter of pneumonia cases were classified as being low risk.[29]

In adults aged ≥65 years with at least one risk factor, the incidence of IPD was almost three-fold higher and the incidence of CAP hospitalisation was two-fold higher than for those without risk factors, according to analysis of data from a population-based prospective study (45 and Up Study) involving 266,951 participants aged 45-85 years in Australia. Case-fatality rate increased with age, but there was limited difference in risk status except for those aged 45-64 years. Risk factors assessed were alcohol consumption, smoking, heart disease, diabetes, asthma, haematological disorders including cancer, non-haematological cancer, renal disease, chronic respiratory diseases and chronic liver diseases. The incidence of CAP hospitalisation varied significantly within risk groups, however since the study was focussed on high-risk groups as a whole details for individual risk groups were not considered. The Pharmaceutical Benefits Advisory Committee (PBAC) recommended PCV13 as a replacement for PPV23 for all adults aged ≥65 years in Australia. The study concluded that it may be worth considering pneumococcal vaccination (e.g. PPV23 following PCV13) for older adults with at least one risk factor, even if additional doses were not deemed to be cost-effective for all adults.[26]

5.3.4 Conclusions

The risk of pneumococcal disease, CAP and IPD, is increased by chronic medical conditions, such as heart disease, diabetes, asthma, renal disease, age or life-style factors, homelessness, living in aged-care, smoking and high alcohol consumption, as well as ethnicity and socio-economic status.

Consideration of the risk and benefits in terms of reducing pneumococcal disease burden is needed when recommending pneumococcal vaccination (PCV13, PPV23 or both) for those with two or more risk factors, particularly for those under the age of 65 years with multiple comorbidities or increased risk due to ethnicity.

It is important to ensure that children with increased risk of IPD through chronic illness, ethnicity or high deprivation are fully immunised. Children exposed to smoke in their household and attending childcare are at increased risk.

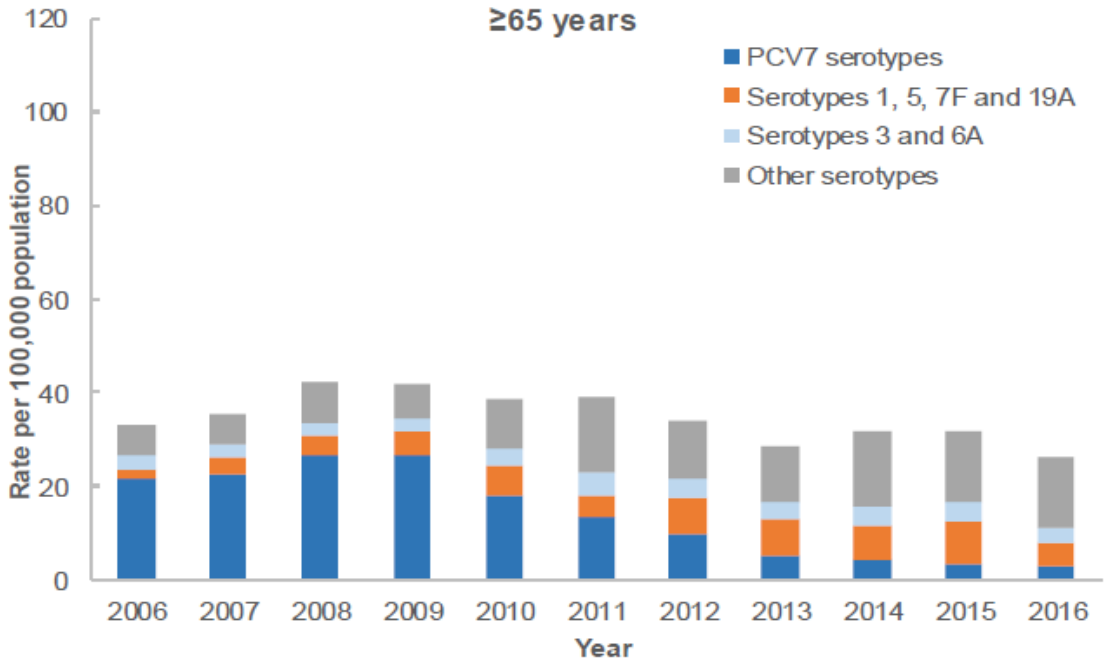
6 Pneumococcal polysaccharide vaccine in high-risk groups and older adults.

Although the 23-valent pneumococcal polysaccharide vaccine (PPV23) does not induce immune memory, it can protect high-risk groups aged from 2 years of age against IPD caused by a broader range of pneumococcal serotypes than the currently available PCVs. As a polysaccharide vaccine, the immune response is only humoral, directly activating B cells to produce polysaccharide-specific antibody, but not activating a T cell response required for memory or long-lasting antibody.

Due to the reduction of PCV10 and PCV13 serotype carriage in children resulting in reduced circulation, adults are at increasing risk from non-PCV serotype IPD some of which are covered by PPV23.

In NZ, 37.4% of the IPD cases in 2016 in adults aged 65 years and older were PCV13-serotypes (68/182 cases), notably serotype 19A (31 cases), and 69.2% were due to PPV23 serotypes.[12] This is fewer than in 2015, when half the IPD cases were PCV13 serotypes and 74% were PPV23 serotypes.[17] Large decreases in PCV7 serotypes have been observed in all age groups since 2006 as shown in Figure 4.

Figure 4: Rate per 100,000 population of invasive pneumococcal disease due to vaccine serotypes and non-PCV13 types in the 65 and older age group, by year, 2006–2016 (Source ESR)



In 2018, 333 cases out of a total of 367 non-PCV13 serotype IPD cases were aged over 5 years,[5] but this time frame is too short to evaluate serotype prevalence in adults since the

change in 2017 from PCV13 to PCV10 in the childhood schedule. This switch may reduce protection against 19A IPD, since although the 19F polysaccharide in PCV10 has cross-protective effects against 19A, these are less than seen with 10A as a vaccine serotype. In Belgium, 3 years following a switch from PCV13 to PCV10 a significant increase in PCV13-non-PCV10 serotype carriage (mainly 19A) was reported in children attending daycare.[14]

Key questions remain as to the comparative benefits of the greater number of serotypes in PPV23 compared with potentially more robust and long-lasting protection against a smaller number of serotypes from PCV13. Our previous review did not specifically examine PPV23 in the prevention of IPD and CAP in at-risk populations.[2] These are considered below.

6.1 Invasive pneumococcal disease

In a meta-analysis of RCT data in adults aged 50 to 95.5 years, the immunogenicity of a single dose of PCV13 was shown to be superior to PPV23 for 10 out of 13 common serotypes (1, 4, 5, 6A, 6b, 9V, 18C, 19A, 19F and 23F),. For serotypes 5, the geometric mean titre ratio was significantly higher in those aged over 65 years than the younger age group. Conversely, for serotypes 7, 19F and 23F, the younger age group responses were higher than those aged ≥65 years. Responses were comparable between pneumococcal naïve individuals and those with prior PPV23 vaccination.[62]

A role for PPV23 vaccination was suggested by meta-analysis of IPD incidence in adults aged 65 years or older in 13 sites in 10 European countries, commissioned by the European Centres for Disease Prevention and Control and European Commission.[18] After 5 years of PCV10 or PCV13 immunisation programmes in children, the incidence of IPD in older adults declined by 9% for all pneumococcal serotypes, 77% for PCV7-serotypes and 38% for additional PCV13 serotypes. However, for non-PCV13 serotypes, the incidence of IPD increased by 63% (95% CI 39-91%). In 2015, 20-29% of IPD cases were PCV13-serotypes in PCV13 sites and 32-53% in PCV10 sites. The difference between sites was especially observed for serotype 19A. Compared with 2009, in 2015 the incidence rate of PPV23-non-PCV13 serotypes had increased by around 50% and these 11 serotypes caused 22-54% of IPD in older adults per site. The authors of the meta-analysis recommended that policy makers take into account the indirect impact of childhood programmes on older adults; and that vaccines given to directly reduce pneumococcal disease in older adults include a wider range of serotypes.[18]

PPV23 induced a robust immune response in adults aged over 50 years to the PPV23/non-PCV13 serotypes 10A, 11A, 15B and 17F associated with high case-fatality or meningitis.[63]

A systematic review and meta-analysis considered the effectiveness of PPV23 against pneumococcal disease in adults aged 60 years of older. Studies deemed to have high bias were excluded. The study found that pooled VE against IPD of any serotype ranged from 45% (95% CI 15-65%) to 59% (35-74%) and 73% (10-92%) in cohort, case-control or clinical trial data, respectively. Pooled VE against any serotype pneumococcal pneumonia was 48% (25-63%) and 64% (35-80%) in cohort studies and clinical trials, respectively. Waning of protection was found between 2.5 years and 5 years follow-up after PPV23.[30]

6.1.1 Conclusions

Several countries and settings have reported an increasing incidence in non-PCV serotype IPD in older adults. PPV23 provides broader protection against IPD and pneumococcal pneumonia, however, although antibody appears longer lived, the duration of clinical protection may be quite short-live (2.5–5 years). There was a very wide range of VE estimates for PPV23, some which are surprisingly high and should be treated with caution.

6.2 Revaccination with PPV23

Due to reported attenuation of immune response, described as hyporesponsiveness, following repeat doses of PPV23, some countries limit the number of doses recommended to a maximum of three life-time doses. Recommendations around repeat boosters are vary. For example, in Canada, revaccination with one life-time booster, given 5 years after the initial dose, is recommended for high risk groups. Other countries recommend repeat doses of PPV23 to be given 5 or 10 years apart, depending on risk.[2]

Data is limited around the use of repeat doses of PPV23 in the elderly and high-risk groups. It is uncertain how long-lived protection is following PPV23 vaccination. One systematic review found in observational studies that revaccination with PPV23 is likely to induce long-lived antibody, comparable to primary vaccination. However, antibody levels within the first two months tended to be lower after revaccination compared with primary vaccination. Adequately powered RCT with clinical endpoints and clinical effectiveness data were lacking.[31]

Revaccination of Aboriginal Torres Strait Island adults with PPV23 did not provide enhanced protection against all-serotype IPD when compared with IPD rates of those who were not revaccinated at least 5 years after the initial PPV23 dose (hazard ratio [HR] 0.77 vs 1.09) and no differences were observed between vaccine-specific serotypes. A retrospective data-linkage study conducted over a 13-year period in North Queensland, Australia, identified 79 confirmed IPD cases among 12,809 adults aged ≥16 years. However, the authors noted that these findings need to be taken with caution as confounding factors, such as health-care engagement and high risk chronic conditions were not included.[34] In the Northern Territory, fewer ATSI adults had adequate responses to a first dose of PPV23 than non-indigenous counterparts (88% vs 100%) and lower IgG responses to a second dose.[64]

In Japan, revaccination of adults aged 70 - 89 years with PPV23 was found to provide continued seroprotection against pneumococcal disease when given at least 5 years after an initial PPV23 dose. Second doses were well tolerated and associated with increases in serotype IgG and OPA geometric mean titres (GMT) at 4 weeks post vaccination. Antibody titres after revaccination were generally comparable to those who received PPV23 for the first time. Baseline antibody levels were generally higher in those who had prior PPV23 vaccination than those who were PPV23-naïve.[32] In a post hoc analysis, subsequent doses given at least 5 years after the first induced comparable IgG for the 14 serotypes measured (serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F) and OPA GMT for all six serotypes (3, 4, 6B, 14, 22F, and 23F) assessed regardless of the interval between PPV23 doses (at 5, 6, 7, 8, 9-11 years). Baseline serotype-specific antibody titres to the 14 serotypes evaluated were comparable regardless of the time interval following the initial PPV23 vaccination. Although the OPA geometric mean fold ratios (GMFR) were lower in those being revaccinated than those in the primary vaccination group, the lower 95% CI level of GMFR for 14 serotypes exceeded one in all groups. Most of the revaccinated participants had underlying chronic medical conditions.[33]

6.2.1 Conclusions

Revaccination with PPV23 at least 5 years after the initial dose is immunogenic but may not provide additional benefit to all ethnic groups, especially in the presence of underlying health conditions. Questions remain around the clinical effectiveness and intervals between repeat doses of PPV23 that provide continued protection.

6.3 Role of PPV23 in preventing pneumococcal pneumonia

Patients are more frequently hospitalised with pneumococcal pneumonia than non-pneumococcal pneumonia (80% vs 66%, p<0.001) and significantly more of those hospitalised require supplementary oxygen and mechanical ventilation, according to a German study.[35]

In our 2016 literature review about high risk groups, limited evidence was found for PPV23 having a protective effect against all-cause community-acquired pneumonia (CAP) in older age groups at increased risk of pneumococcal disease.[2]

In Japan, PPV23 was found to have low to moderate VE against serotype-specific pneumococcal pneumonia in adults aged ≥ 65 years, which differed by vaccine serotype. Overall VE against PPV23-types was 33.5% and PCV13-types 40.1%. VE was highest in those younger than 75 years, in females and those with lobular or healthcare-associated pneumonia. However, this Japanese study using test-negative controls observed no significant effect of PPV23 vaccination against pneumococcal pneumonia mortality and the point estimate of VE declined with time and almost disappeared after 5 years.[36]

Sex- and age-dependent effectiveness of PPV23 on all-cause pneumonia was also shown in a German study and a significant reduction in pneumonia mortality was only observed in adults aged 60 to 79 years.[65]

A systematic review and meta-analysis conducted in 2016 that used Canadian National Advisory Committee on Immunisation methodology, estimated effectiveness of PPV23 in adults aged >50 years against CAP to be 4% (95% CI -26 to 26%) in clinical trials, 17% (-26 to 45%) in cohort studies and 7% (-10% to 21%) in case-control studies.[37]

However, the systematic review and meta-analysis, mentioned in section , which considered the effectiveness of PPV23 against pneumococcal disease in adults aged 60 years of older found that the pooled VE against any serotype pneumococcal pneumonia was 48% (25-63%) in cohort studies and 64% (35-80%) in clinical trials.[30] These VE appear to be higher than those found previously and may reflect differences in study design, pneumococcal detection and settings, such as residential care versus community-living adults.

The difference between these data is whether vaccine effectiveness was against pneumococcal pneumonia in which pneumococci have been isolated or all-cause community-acquired pneumonia, which encompasses pneumococcal pneumonia as well as other infections.

6.3.1 Conclusion

PPV23 appears to have low-to-moderate effectiveness against pneumococcal pneumonia, the protection wanes rapidly and does not appear to reduce mortality or all-cause pneumonia incidence.

6.4 Immune response to PPV23 in high-risk groups

Immunosuppressive therapies used to treat chronic health issues, as well as the comorbidities themselves, can increase the risk of pneumococcal disease and also affect the immune response to vaccination with the potential of reducing vaccine immunogenicity and effectiveness in certain at-risk groups.

The initial serological response to PCV and PPV23 is impaired in patients receiving immunosuppressive medication, as indicated by a PROSPERO-registered systematic review.

This impaired response was more profound after PCV than PPV23, which was hypothesised to be due to immunosuppressive therapies targeting cellular immunity and impairment of T cell-dependent response to PCV; whereas, TNF-α blocking agents were associated with more favourable responses to PCV. A meta-analysis compared seroconversion responses to PCV and PPV with those receiving methotrexate or azathioprine, anti-TNF-α, rituximab (only assessed for PCV) or in combination, and in healthy controls. Impaired humoral responses against PCV were demonstrated in patients with autoimmune disease on immunosuppressive therapy. This study was unable to evaluate current recommendations to vaccinated patients with PCV and PPV23 sequentially.[38]

No additional deleterious effect on the short or long-term immunogenicity of PPV23 was detected due to anti-TNF therapy (etanercept) in patients with juvenile idiopathic arthritis who received conventional disease-modifying anti-rheumatic drug (DMARD) therapy (methotrexate).[66]

The presence of interstitial lung disease was associated with increased risk of pneumonia in 900 Japanese patients with rheumatoid arthritis treated with biological or immunosuppressive therapies (hazard ratio 3.6 [95% CI 1.55-8.40]). The RCT also found that PPV23 did not prevent pneumonia overall in the vaccinated patients compared with placebo control patients (3.7% vs 3.4% developed pneumonia, respectively).[39]

An RCT post-hoc analysis found impaired immunogenicity against PPV23 in patients aged 60-70 years with type-2 diabetes who concurrently received a live-attenuated Oka varicella-zoster vaccine (BVZV, Japanese brand with same viral dose as in varicella vaccine for children). The IgG responder rates at 3 months after vaccination against either or both PPV23 serotypes (6B and 23F) was 68% in those who received both PPV23 and BVZV compared with 85% for those who received PPV23 and placebo.[40]

6.4.1 Conclusions

Factors affecting cellular immunity, such as immunosuppressive therapy and chronic health conditions, result in poorer immune responses to PCV vaccines than PPV23. Other factors appear to affect the immunogenicity to PPV23, such as concurrent administration of live vaccine and the presence of interstitial lung disease. There is limited data around the effectiveness of either PCV or PPV23, or both, in those at increased risk of pneumococcal disease with chronic health conditions.

The Immunisation Handbook 2017 states that herpes zoster vaccine can be delivered concomitantly with PPV23; however, this is a variation from the product information. In light of the impaired immunogenicity seen in Japan (with a similar live vaccine), this may need to be reviewed.[21]

6.5 Other approaches to reduce risk of pneumococcal disease in adults

Adults are frequently unaware of the vaccines available to them to reduce their risk of disease. Positive recommendations from healthcare professionals are the greatest influence on vaccine uptake. Adults with increased risk from IPD and pneumococcal pneumonia, due to multiple morbidities could be better protected if advised to receive pneumococcal vaccine. However, those for whom the vaccine is not funded are less likely to receive this vaccine, particularly in the lower socioeconomic groups.

One challenge for legislators is to determine what level of risk is seen as being appropriate to fund vaccine i.e. whether it would be two or more defined comorbidities or combinations certain co-morbidities?

6.5.1 PPV23 plus influenza vaccination

Other approaches reduce the risk of pneumococcal disease in those at risk, such as influenza vaccination, which is available to much wider at-risk groups and adults aged 65 years plus. One third of pneumococcal colonisation events in adults aged ≥65 years were associated with preceding acute respiratory tract infection and respiratory illness.[41] It follows that a greater uptake of influenza vaccine in adults may help to reduce the risk of secondary pneumococcal infections, particularly pneumonia, while the childhood programme helps to provide herd immunity to reduce circulating pneumococcal serotypes.

Simultaneous administration of PPV23 and quadrivalent inactivated influenza vaccine (QIV) was shown in Japanese adults aged ≥65 years to be acceptably immunogenic and seroprotective against six pneumococcal serotypes (3, 4, 6B, 14, 19A and 23F) and vaccine-type influenza strains as compared with sequential vaccination (2 weeks apart) without any increase in adverse events.[67]

PPV23 vaccination provided significantly better protection against pneumococcal CAP in adults age ≥65 years in Japan than trivalent inactivated influenza vaccine (aOR 0.23 [95% CI 0.08-0.66] vs 0.65 [0.31-1.36], respectively). However, against all-cause CAP, PPV23 and TIV were less effective, but provided some benefit as compared with no vaccination (aOR 0.76 [0.44-1.32] and 0.79 [0.50-1.25]).[42]

An older study in Australia found no incremental benefit against hospitalised CAP of receiving PPV23 and influenza vaccination compared with influenza vaccine alone (RR 0.98 [0.81-1.18]. Point estimates for PPV23 alone vs no PPV23 suggested a small, but not statistically significant benefit, against death associated with HCAP (RR 0.82 [0.66-1.28]) and all-cause mortality (0.82 [0.71-1.20]). [43]

Unfortunately, influenza vaccine is not as effective in older age groups and those with immune compromise as in healthier, younger adults.[68] Also, other respiratory virus infections can lead to severe acute respiratory illnesses. Therefore, direct protection against IPD through pneumococcal vaccination is likely to be required for those at highest risk.

6.5.2 Conclusions

Pneumococcal polysaccharide and influenza vaccination in adults, particularly for those with increased risk of severe disease, may help to reduce the burden of IPD and pneumococcal pneumonia in older age groups. Direct protection is required against IPD for those at highest risk of pneumococcal infection.

7 Appendix

7.1 History of pneumococcal vaccination in New Zealand

Pneumococcal conjugate vaccines were first introduced to the NZ Schedule in June 2006 for high risk children and adults with pre- and post-splenectomy and then in June 2008 as part of the routine schedule. Following the introduction of PCV, a significant decline in vaccine-type IPD was observed.

Table 1: Pneumococcal conjugate vaccine (PCV) immunisation programmes and practices: history in New Zealand (adapted from 2017 and 2006 Immunisation Handbooks, Ministry of Health)

Year	Programmes	Target population
2006	PCV7 PPV23	Funded for certain high-risk children Funded for adults and children pre and post splenectomy and children with functional asplenia
2008	PCV7 – routine 3+1 schedule	Routine schedule for all children at 6 weeks, 3, 5 and 15 months of age
2011	PCV10 replaced PCV7 PCV13 replaced PCV7	Routine schedule for all children (3+1) For some high-risk children
2014	PCV13 replaced PCV10	Routine schedule for all children (3+1)
2015	PCV13	For adults with certain high-risk conditions
2017	PCV10 replaced PCV13 PCV13 retained with PPV23	For all children (3+1) High risk groups, including adults

7.2 Pneumococcal-containing vaccines available in New Zealand

Two PCV vaccines, 10-valent (PCV10) and 13-valent (PCV13), are available in New Zealand from 6 weeks of age. Also available from 2 years of age is a 23-valent pneumococcal polysaccharide vaccine (PPV23) that is funded for certain high-risk groups to provide additional protection from serotypes not covered by PCV13. [21] Refer to Table 2.

Table 2: Pneumococcal capsular polysaccharide-containing vaccines available in New Zealand, licensed by Medsafe (Source: Medsafe data sheets)

Routine schedule
PCV-10 (Synflorix®, GSK) Serotypes 1, 4, 5, 6B, 7F, 9V, 14, 23F conjugated with non-typeable *Haemophilus influenza* (NTHi), 18C conjugated with tetanus toxoid, and 19F conjugated with diphtheria toxin-related carrier protein CRM
High risk groups – children and adults
PCV-13 (Prevenar®13, Pfizer) – all serotypes conjugated with CRM
PPV23 (Pneumovax 23, Merck Sharp and Dohme)

7.3 International policy and practice

Previous literature reviews have reported on the National Immunisation Schedules for pneumococcal immunisation in the US, Canada, Australia and the UK, and selected European countries. Recommendations for pneumococcal immunisations are summarised in Table 3.

No changes internationally were identified to guidance around high-risk groups for pneumococcal vaccination since our previous review in high-risk groups.[2] ACIP are currently reviewing recommendations for PCV13 in immunocompetent adults aged from 65 years.[23]

Table 3: Summary of examples of international immunisation schedules for pneumococcal vaccines, as of May 2019.

Country	Age of vaccination	Vaccine used	Total number of routine doses in childhood	Special recommendations
USA	2, 4, 6, 12-15m Adult >65y	PCV13 PCV13 / PPV23	3+1	PPV23 from 2y for high-risk children Adult ≥65y PCV13 under review.
Canada	2, 4, 12m	PCV13 (PCV10 Quebec)	2+1	3+1 PCV13 schedule (2,4,6,18m) in two territories with high proportion of indigenous peoples
Australia	6w/2, 4, 12m High risk 6m High risk 4 y Adult	PCV13 PPV23	2+1	PCV13 given at 6m to medically at-risk or indigenous (ATSI) children in high risk areas PPV23 for medically at-risk children aged 4 years ATSI 15-49 y with risk factors and >50 years. All adults >65 years, single dose
NZ	6w, 3, 5m, 15m High risk	PCV10 PCV13 + PPV23	3+1	PPV23 from 2 years of age
Denmark	3, 5, 12m 65y (unfunded)	PCV13 PPV23	2+1	No official recommendation, reimbursement for defined at-risk groups
France	8w or 2, 4, 11m	PCV	2+1	Mandatory in children
Germany	2, 4, 11-13m ≥60 y	PCV PPV23	2+1	Adults aged ≥60 recommended booster every 6 years if indicated
UK	2, 4m, 12m 65 y	PCV13 PPV23	2+1	

Abbreviations: w – weeks; m – months; y – years; PCV – pneumococcal conjugate vaccine; PPV23 – 23-valent pneumococcal polysaccharide vaccine; ATSI – Aboriginal Torres Strait Islander

7.4 Methodology for review

7.4.1 Literature search strategy

The aim of the literature review was to find literature to answer certain questions around pneumococcal immunisation in the NZ context. It was not a systematic review. Literature searches were limited to recent data, published since 2016 when a review was conducted on the childhood schedule. Wider searches were conducted as necessary related to specific questions or for literature cited in the articles found.

Medline search terms and strategy

Medline

1. *pneumococcal vaccines/administration & dosage, adverse effects, immunology, therapeutic use 3482
2. Limit English humans 2016-2019 [18/3/19]
3. 10-valent.mp 396
4. Limit English humans 2016-2019 [18/3/19] 127
5. 2+4 = 87
6. Schedule title, limit 392
7. 2+6 – 8, selected 4, removed 1 duplicate

Pneumococcal prevention and control 4

1. Pneumococcal polysaccharide vaccine.mp 1005

2. Limit 128 selected 47

Removed 101 duplicates, remainder 4

Did not select references referring to vaccine use developing countries.

Cochrane Library search terms and strategy

Title, abstract, keyword – pneumococcal vaccine

Jan 2016 –2019 reviews – 4 found, none selected as being relevant for this review.

Scopus

Title, abstract, keyword - pneumococcal AND vaccin*
Article or review
Published >2015-2018
Limited to medical, human and English language
AND Schedule
170 - selected 14
Added AND schedule AND ("2+1") = 29 – selected 2

Grey literature

For any grey literature used, such as conference abstracts, an equivalent peer-reviewed article was sought.

Additional searches

Where questions arose, additional searches were undertaken to ensure there was no further available data. Where articles were missing, they were accessed and added to the library. All duplicates were removed from the final library.

Final Endnote Library 320 articles and reference sources

Where systematic reviews and/or meta-analysis were available the preceding literature has been excluded from the review, unless the reviewed literature was accessed to provide further details. A total of 298 journal articles were included. The remainder were government guidelines, epidemiology surveillance reports, data sheets or official websites.

7.4.2 Study designs

The studies included in this update are meta-analysis, systematic reviews, reviews, randomised controlled trials, case-control studies, case reports and observational studies using database matching.

8 References

1. The Immunisation Advisory Centre. Antigen Literature Review for the New Zealand National Immunisation Schedule, 2016: Pneumococcal disease - ten-valent pneumococcal conjugate vaccine. Auckland: The University of Auckland; 2016 December

2. The Immunisation Advisory Centre. Antigen Literature Review for the New Zealand National Immunisation Schedule, 2016: Pneumococcal disease - in high risk groups. Auckland: The University of Auckland; 2016 November.

3. The Immunisation Advisory Centre. Antigen Literature Review for the New Zealand National Immunisation Schedule, 2017: Childhood schedule. The University of Auckland.; 2017.

4. World Health Organization. Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper - February 2019. Weekly Epidemiological Record. 2019;94(8):85-104.

5. Institute of Environmental Science and Research Ltd (ESR). Invasive Pneumococcal Disease Quarterly Report, October - December 2018. Poirua: Institute of Environmental Research and Surveillance; 2018.

6. Eichler N, Reynolds E, Jackson C, Thornley S, Peters J. Invasive pneumococcal disease and serotype emergence in the Auckland region during the vaccine era 2009-2016. J Prim Health Care. 2019;11(1):24-31.

7. PHARMAC. Changes to funded vaccines in the National Immunisation Schedule: NZ Government; 2019 [updated 30 July]. Available from: https://www.pharmac.govt.nz/news/notification-2019-07-30-immunisation#PCV10

8. Temple B, Toan NT, Dai VTT, Bright K, Licciardi PV, Marimla RA, et al. Immunogenicity and reactogenicity of ten-valent versus 13-valent pneumococcal conjugate vaccines among infants in Ho Chi Minh City, Vietnam: a randomised controlled trial. Lancet Infect Dis. 2019;19(5):497-509.

9. De Wals P, Lefebvre B, Deceuninck G, Longtin J. Incidence of invasive pneumococcal disease before and during an era of use of three different pneumococcal conjugate vaccines in Quebec. Vaccine. 2018;36(3):421-6.

10. Kent A, Ladhani SN, Andrews NJ, Scorrer T, Pollard AJ, Clarke P, et al. Schedules for Pneumococcal Vaccination of Preterm Infants: An RCT. Pediatrics. 2016;138(3).

11. Goldblatt D, Southern J, Andrews NJ, Burbidge P, Partington J, Roalfe L, et al. Pneumococcal conjugate vaccine 13 delivered as one primary and one booster dose (1 + 1) compared with two primary doses and a booster (2 + 1) in UK infants: a multicentre, parallel group randomised controlled trial. The Lancet Infectious Diseases. 2018;18(2):171-9.

12. Institute of Environmental Science and Research Ltd (ESR). Invasive pneumococcal disease in New Zealand, 2016. Porirua: ESR; 2019 5 July 2019.

13. Rinta-Kokko H, Palmu AA, Auranen K, Nuorti JP, Toropainen M, Siira L, et al. Long-term impact of 10-valent pneumococcal conjugate vaccination on invasive pneumococcal disease among children in Finland. Vaccine. 2018;36(15):1934-40.

14. Wouters I, Desmet S, Van Heirstraeten L, Blaizot S, Verhaegen J, Van Damme P, et al. Follow-up of serotype distribution and antimicrobial susceptibility of Streptococcus pneumoniae in child carriage after a PCV13-to-PCV10 vaccine switch in Belgium. Vaccine. 2019;37(8):1080-6.

15. Jayasinghe S, Menzies R, Chiu C, Toms C, Blyth CC, Krause V, et al. Long-term Impact of a "3 + 0" Schedule for 7- and 13-Valent Pneumococcal Conjugate Vaccines on Invasive Pneumococcal Disease in Australia, 2002-2014. Clin Infect Dis. 2017;64(2):175-83.

16. Rots NY, Barug D, Knol M, Pronk I, Sanders L. No blunting of antibody responses against pneumococcal serotypes conjugated to protein D after maternal Tdap vaccination. 11th International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD-11); 15-19 April; Melbourne2018.

17. Institute of Environmental Science and Research Ltd (ESR). Invasive Pneumococcal Disease in New Zealand, 2015. Porirua: ESR; 2017 21 June 2017.

18. Hanquet G, Krizova P, Valentiner-Branth P, Ladhani SN, Nuorti JP, Lepoutre A, et al. Effect of childhood pneumococcal conjugate vaccination on invasive disease in older adults of 10 European countries: implications for adult vaccination. Thorax. 2019;74(5):473-82.

19. Okasha O, Rinta-Kokko H, Palmu AA, Ruokokoski E, Jokinen J, Nuorti JP. Population-level impact of infant 10-valent pneumococcal conjugate vaccination on adult pneumonia hospitalisations in Finland. Thorax. 2018;73(3):262-9.

20. Pilishvili T. 13-valent pneumococcal conjugate vaccine (PCV13) effects on disease caused by serotype 3. ACIP Meeting; February 28: CDC; 2019.

21. Ministry of Health. Immunisation Handbook 2017 (2nd edition) [Internet]. Wellington: Ministry of Health; 2018.

22. Kent A, Makwana A, Sheppard CL, Collins S, Fry NK, Heath PT, et al. Invasive pneumococcal disease in UK children under 1 year of age in the post-PCV13 era: what are the risks now? Clin Infect Dis. 2018.

23. Advisory Committee on Immunization Practices. Summary Report. Atlanta, Georgia: Department of Health and Human Services,, Centers for Disease Control and Prevention; 2018 October.

24. Seminog OO, Goldacre MJ. Risk of pneumonia and pneumococcal disease in people with severe mental illness: English record linkage studies. Thorax. 2013;68(2):171-6.

25. Chapman KE, Wilson D, Gorton R. Invasive pneumococcal disease and socioeconomic deprivation: A population study from the North East of England. Journal of Public Health (United Kingdom). 2013;35(4):558-69.

26. Dirmesropian S, Liu B, Wood JG, MacIntyre CR, McIntyre P, Karki S, et al. Pneumonia hospitalisation and case-fatality rates in older Australians with and without risk factors for pneumococcal disease: implications for vaccine policy. Epidemiol Infect. 2019;147:e118.

27. Morton JB, Morrill HJ, LaPlante KL, Caffrey AR. Risk stacking of pneumococcal vaccination indications increases mortality in unvaccinated adults with Streptococcus pneumoniae infections. Vaccine. 2017;35(13):1692-7.

28. Centers for Disease Control and Prevention. Table 1. Recommended Adult Immunization Schedule for ages 19 years or older, United States, 2019: US Department of Health and Human Services; 2019 [updated 5 February 2019; cited 2019 May 7]. Available from: https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html#table-age

29. Leesa F, Spiller MT. Effectiveness of PCV13 in Adults Hospitalized with Pneumonia Using Centers for Medicare & Medicaid Services Data, 2014-2017 ACIP meeting February 2019; 28 February: National Center for Immunization & Respiratory Diseases,; 2019.

30. Falkenhorst G, Remschmidt C, Harder T, Hummers-Pradier E, Wichmann O, Bogdan C. Effectiveness of the 23-Valent Pneumococcal Polysaccharide Vaccine (PPV23) against Pneumococcal Disease in the Elderly: Systematic Review and Meta-Analysis. PLoS ONE. 2017;12(1):e0169368.

31. Remschmidt C, Harder T, Wichmann O, Bogdan C, Falkenhorst G. Effectiveness, immunogenicity and safety of 23-valent pneumococcal polysaccharide vaccine revaccinations in the elderly: a systematic review. BMC Infectious Diseases. 2016;16(1):711.

32. Kawakami K, Kishino H, Kanazu S, Toshimizu N, Takahashi K, Sterling T, et al. Revaccination with 23-valent pneumococcal polysaccharide vaccine in the Japanese elderly is well tolerated and elicits immune responses. Vaccine. 2016;34(33):3875-81.

33. Kawakami K, Kishino H, Kanazu S, Takahashi K, Iino T, Sawata M, et al. Time interval of revaccination with 23-valent pneumococcal polysaccharide vaccine more than 5 years does not affect the immunogenicity and safety in the Japanese elderly. Hum Vaccin Immunother. 2018;14(8):1931-8.

34. Takashima M, Lambert SB, Paynter S, Ware RS. Relative effectiveness of revaccination with 23-valent pneumococcal polysaccharide vaccine in preventing invasive pneumococcal disease in adult Aboriginal and Torres Strait Islander people, Australia. Vaccine. 2019;37(12):1638-41.

35. Pletz MW, Von Baum H, Van Der Linden M, Rohde G, Schütte H, Suttorp N, et al. The burden of pneumococcal pneumonia - Experience of the german competence network CAPNETZ. Pneumologie. 2012;66(8):470-5.

36. Suzuki M, Dhoubhadel BG, Ishifuji T, Yasunami M, Yaegashi M, Asoh N, et al. Serotype-specific effectiveness of 23-valent pneumococcal polysaccharide vaccine against pneumococcal pneumonia in adults aged 65 years or older: a multicentre, prospective, test-negative design study. Lancet Infect Dis. 2017;17(3):313-21.

37. Kraicer-Melamed H, O'Donnell S, Quach C. The effectiveness of pneumococcal polysaccharide vaccine 23 (PPV23) in the general population of 50 years of age and older: A systematic review and meta-analysis. Vaccine. 2016;34(13):1540-50.

38. van Aalst M, Langedijk AC, Spijker R, de Bree GJ, Grobusch MP, Goorhuis A. The effect of immunosuppressive agents on immunogenicity of pneumococcal vaccination: A systematic review and meta-analysis. Vaccine. 2018;36(39):5832-45.

39. Izumi Y, Akazawa M, Akeda Y, Tohma S, Hirano F, Ideguchi H, et al. The 23-valent pneumococcal polysaccharide vaccine in patients with rheumatoid arthritis: a double-blinded, randomized, placebo-controlled trial. Arthritis Research & Therapy. 2017;19(1):15.

40. Hata A, Ishioka T, Oishi K, Katayama T, Ohkubo T. Altered immunogenicity of 23-valent pneumococcal polysaccharide vaccine in elderly patients with diabetes who revealed lower responses to concomitant administration of BIKEN varicella zoster vaccine: Results of post hoc analysis of a randomized double-blind trial. J Diabetes Complications. 2019;33(3):243-8.

41. Branche AR, Yang H, Java J, Holden-Wiltse J, Topham DJ, Peasley M, et al. Effect of prior vaccination on carriage rates of Streptococcus pneumoniae in older adults: A longitudinal surveillance study. Vaccine. 2018;36(29):4304-10.

42. Suzuki K, Kondo K, Washio M, Nakashima K, Kan S, Imai S, et al. Preventive effects of pneumococcal and influenza vaccines on community-acquired pneumonia in older individuals in Japan: a case-control study. Hum Vaccin Immunother. 2019:1-7.

43. Skull SA, Andrews RM, Byrnes GB, Kelly HA, Nolan TM, Brown GV, et al. Prevention of community-acquired pneumonia among a cohort of hospitalized elderly: benefit due to influenza and pneumococcal vaccination not demonstrated. Vaccine. 2007;25(23):4631-40.

44. Naucler P, Galanis I, Morfeldt E, Darenberg J, Ortqvist A, Henriques-Normark B. Comparison of the Impact of Pneumococcal Conjugate Vaccine 10 or Pneumococcal Conjugate Vaccine 13 on Invasive Pneumococcal Disease in Equivalent Populations. Clinical Infectious Diseases. 2017;65(11):1780-9.

45. Levy C, Varon E, Ouldali N, Bechet S, Bonacorsi S, Cohen R. Changes in invasive pneumococcal disease spectrum after 13 valent pneumococcal conjugate vaccine implementation. Clin Infect Dis. 2019.

46. Petousis-Harris H, Howe AS, Paynter J, Turner N, Griffin J. Pneumococcal Conjugate Vaccines Turning the Tide on Inequity: A Retrospective Cohort Study of New Zealand Children Born 2006-2015. Clin Infect Dis. 2019;68(5):818-26.

47. Baker MG, Barnard LT, Kvalsvig A, Verrall A, Zhang J, Keall M, et al. Increasing incidence of serious infectious diseases and inequalities in New Zealand: a national epidemiological study. Lancet. 2012;379(9821):1112-9.

48. PHARMAC. Proposal for changes to funded vaccines in the National Immunisation Schedule 2019 [updated 9 May 2019]. Available from: https://www.pharmac.govt.nz/news/consultation-2019-05-08-immunisation/

49. Weinberger R, van der Linden M, Imohl M, von Kries R. Vaccine effectiveness of PCV13 in a 3+1 vaccination schedule. Vaccine. 2016;34(18):2062-5.

50. Dagan R, Ben-Shimol S, Simell B, Greenberg D, Porat N, Kayhty H, et al. A toddler PCV booster dose following 3 infancy priming doses increases circulating serotype-specific IGG levels but does not increase protection against carriage. Vaccine. 2018;36(20):2774-82.

51. Gidding HF, McCallum L, Fathima P, Moore HC, Snelling TL, Blyth CC, et al. Effectiveness of a 3 + 0 pneumococcal conjugate vaccine schedule against invasive pneumococcal disease among a birth cohort of 1.4 million children in Australia. Vaccine. 2018;36(19):2650-6.

52. Wasserman M, Lucas A, Jones D, Wilson M, Hilton B, Vyse A, et al. Dynamic transmission modelling to address infant pneumococcal conjugate vaccine schedule modifications in the UK. Epidemiol Infect. 2018;146(14):1797-806.

53. Joint Committee on Vaccination and Immunisation. Minute of meeting held of 06 February 2019 Draft: Crown Copyright; 2019 [cited 09 Jul 2019]. Available from: https://www.gov.uk/government/groups/joint-committee-on-vaccination-and-immunisation

54. Hammitt LL, Etyang AO, Morpeth SC, Ojal J, Mutuku A, Mturi N, et al. Effect of ten-valent pneumococcal conjugate vaccine on invasive pneumococcal disease and nasopharyngeal carriage in Kenya: a longitudinal surveillance study. Lancet. 2019.

55. Flasche S, Ojal J, Le Polain de Waroux O, Otiende M, O'Brien KL, Kiti M, et al. Assessing the efficiency of catch-up campaigns for the introduction of pneumococcal conjugate vaccine: a modelling study based on data from PCV10 introduction in Kilifi, Kenya. BMC Medicine. 2017;15(1):113.

56. Slack M, Vyse A, Madhava H, Ellsbury G, Czudek C, Reinert RR, et al. Burden of invasive pneumococcal disease. Clin Infect Dis. 2019.

57. Rice TF, Diavatopoulos DA, Smits GP, van Gageldonk P, Berbers G, van der Klis F, et al. Antibody responses to Bordetella pertussis and other childhood vaccines in infants born to mothers who received pertussis vaccine in pregnancy- a prospective, observational cohort study from the UK. Clin Exp Immunol. 2019.

58. The immunisation Advisory Centre. Review of evidence to inform the New Zealand National Immunisation Schedule, 2018: Pertussis. Auckland, New Zealand: The University of Auckland; 2019 February 2019.

59. Fjeldhoj S, Laursen RP, Larnkjaer A, Molgaard C, Fuursted K, Krogfelt KA, et al. Probiotics and carriage of Streptococcus pneumoniae serotypes in Danish children, a double-blind randomized controlled trial. Sci Rep. 2018;8(1):15258.

60. Milucky J, Carvalho MG, Rouphael N, Bennett NM, Talbot HK, Harrison LH, et al. Streptococcus pneumoniae colonization after introduction of 13-valent pneumococcal conjugate vaccine for US adults 65 years of age and older, 2015-2016. Vaccine. 2019;37(8):1094-100.

61. Berical AC, Harris D, Dela Cruz CS, Possick JD. Pneumococcal Vaccination Strategies. An Update and Perspective. Annals of the American Thoracic Society. 2016;13(6):933-44.

62. Vadlamudi NK, Parhar K, Altre Malana KL, Kang A, Marra F. Immunogenicity and safety of the 13-valent pneumococcal conjugate vaccine compared to 23-valent pneumococcal polysaccharide in immunocompetent adults: A systematic review and meta-analysis. Vaccine. 2019;37(8):1021-9.

63. Ciprero KL, Marchese RD, Richard P, Baudin M, Sterling TM, Manoff SB, et al. Vaccination of adults with 23-valent pneumococcal polysaccharide vaccine induces robust antibody responses against pneumococcal serotypes associated with serious clinical outcomes. Human vaccines & Immunotherapeutics. 2016;12(8):2135-41.

64. Moberley S, Licciardi PV, Balloch A, Andrews R, Leach AJ, Kirkwood M, et al. Repeat pneumococcal polysaccharide vaccine in Indigenous Australian adults is associated with decreased immune responsiveness. Vaccine. 2017;35(22):2908-15.

65. Kolditz M, Schmitt J, Pletz MW, Tesch F. Impact of pneumococcal polysaccharide vaccine on incidence and mortality after pneumonia in adults aged >/=60 years-a population-based retrospective cohort study. Clin Microbiol Infect. 2018;24(5):500-4.

66. Aikawa NE, Franca IL, Ribeiro AC, Sallum AM, Bonfa E, Silva CA. Short and long-term immunogenicity and safety following the 23-valent polysaccharide pneumococcal vaccine in juvenile idiopathic arthritis patients under conventional DMARDs with or without anti-TNF therapy. Vaccine. 2015;33(5):604-9.

67. Nakashima K, Aoshima M, Ohfuji S, Yamawaki S, Nemoto M, Hasegawa S, et al. Immunogenicity of simultaneous versus sequential administration of a 23-valent pneumococcal polysaccharide vaccine and a quadrivalent influenza vaccine in older individuals: A randomized, open-label, non-inferiority trial. Hum Vaccin Immunother. 2018;14(8):1923-30.

68. Loubet P, Loulergue P, Galtier F, Launay O. Seasonal influenza vaccination of high-risk adults. Expert Rev Vaccines. 2016;15(12):1507-18.