The Immunisation Advisory Centre

2016 Academic Review for the New Zealand National Immunisation Schedule:

Pneumococcal – ten-valent vaccine effectiveness and safety

Prepared as part of a Ministry of Health contract for services by the Immunisation Advisory Centre, Department of General Practice and Primary Health Care, University of Auckland

This review is part of a series of antigen reviews commissioned by the Ministry of Health to help inform the National Immunisation Programme.

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Executive summary

This review was conducted to consider the safety of the ten-valent pneumococcal conjugate vaccine (PCV-10; Synflorix®) in infant schedules and its effectiveness in preventing pneumococcal disease, in particular invasive pneumococcal disease (IPD), in target age groups and wider community. The impact on otitis media incidence and non-invasive pneumococcal infections is also considered. Literature published between January 2013 and November 2016 is evaluated.

PCV-10 contains polysaccharides for ten pneumococcal serotypes (1, 4, 5, 6B, 7F, 9V, 14, 23, 18C and 19F) which are conjugated to either non-toxic tetanus toxoid or diphtheria toxoid carrier proteins or non-typeable *Haemophilus influenza* (NTHi) protein D. These proteins enable the immune system to mount a T cell-dependent immune response and generate long-lived memory. This vaccine differs from the seven valent and 13-valent vaccines (PCV-7 and PCV-13; Prevenar® and Prevenar®13) in which all the pneumococcal polysaccharides are conjugated to the diphtheria toxoid carrier protein, CRM_{197}.

New Zealand epidemiology

The introduction of PCV-10 immunisation for infants as part of the New Zealand National Immunisation Schedule during 2011-2014 resulted in a significant decline in vaccine-serotype IPD across all age groups. In 2006, prior to the introduction of pneumococcal conjugate vaccines (PCVs) to the infant schedule, the rate of PCV-10-serotype IPD in children aged younger than 5 years was 44.2 per 100,000. This rate decreased by 95.6% to 1.9 cases per 100,000 in 2014. In late 2014, PCV-10 was replaced by 13-valent vaccine, PCV-13.

Most recently, during September 2015 to September 2016, no cases of PCV-10-type IPD were identified in infants aged under 2 years – this age group received PCV-13 immunisation as part of their primary series. Only one PCV-10-type IPD infection (serotype 4) was notified in children aged 2-4 year olds compared with 10 cases with disease caused by the additional PCV-13 serotypes (type 3 and 19A). However, over this period, a 21.8% increase in non-vaccine serotype IPD occurred, predominantly in those over the age of 5 years.

In July 2017, PCV-10 will replace PCV-13 on the infant immunisation schedule, and surveillance will continue to monitor this vaccine's effectiveness and safety in target populations and the indirect effect on non-target populations. PCV-13 will remain available for children and adults at high risk of IPD.

Safety

PCV-10 continues to be shown to be safe and well tolerated in infants and toddlers, when used in a range of schedules globally and when given concurrently with other infant schedule vaccines. It has a similar safety profile to other pneumococcal conjugate vaccines. Fever of over 38°C is the most common adverse event following concomitant administration with infant schedule vaccines, particularly DTaP-containing vaccines, and has been reported after around one third of doses.

Effectiveness

Although, there are fewer countries that have previously included or currently include PCV-10 on their national immunisation schedules than those who use PCV-13, there is good evidence of its effectiveness against pneumococcal disease.

Invasive pneumococcal disease (IPD)

Surveillance in New Zealand reported that IPD notifications reduced by around two-thirds in infants following the switch from PCV-7 to PCV-10.

PCV-10 has excellent vaccine effectiveness (VE) against culture-confirmed vaccine-serotype IPD. The largest study to be conducted on PCV-10 was conducted in Finland. The FinIP clinical trial found VE was 100% (95% CI 83-100%) following a three-dose primary series and a booster in the second year of life (3+1 schedule). Rates of non-laboratory confirmed IPD in children aged 3-42 months declined by two-thirds following the introduction of PCV-10 in Finland. In Latin America, during the COMPAS study, 100% (95% CI 74.3-100) VE was also shown against IPD.

Age-appropriate PCV-10 immunisation was shown to be 83.8% (95% CI 65.9-92.3) effective overall against IPD in Brazil, including 82.2% (95% CI 10.7-96.4) effectiveness against cross-reactive serotype 19A. Following the initiation of the PCV-10 vaccination programme, mortality from pneumococcal meningitis decreased by 69% in infants aged <2 years and the number of cases halved, particularly in those aged 6-11 months.

In Canada, at least one dose of PCV-10 was shown to be 97% (95% CI 84-99%) effective against vaccine-type IPD in children aged under 5 years, 72% (95% CI 46-85%) effective against any IPD, and had a 71% cross-reactive VE (95% CI 24-89%) against serotype 19A IPD. When comparing at least two doses of PCV-7, PCV-10 or PCV-13, VE did not differ against vaccine-type IPD.

Pneumonia

Decreases in pneumonia hospitalisation in infants were observed in Brazil, Latin America and Finland following the introduction of PCV-10 immunisation of infants. VE against all infant pneumonia hospitalisations was calculated to be around 25% (95% CI 2.6-42.6) in the FinIP trial.

Otitis media

PCV-10 has been shown to provide protection against pneumococcal acute otitis media in Latin American and Indigenous Australian children.

In New Zealand, a decline in incidence of otitis media in children aged under 6 years has been observed since the introduction of PCV to the infant schedule in 2006. During the PCV-7 usage time period OM incidence declined by 55%, then by 66% during the PCV-10 period and 81% during the PCV-13 period. These declines were greatest in the children of Māori and Pacific ethnicity, resulting in little ethnic disparity between the main ethnic groups.

Following the introduction of PCVs in New Zealand, the dominant pathogen associated with otitis media became NTHi, which was detected in 95% of children requiring surgery for otitis media. Due to conjugation of two of the vaccine-type polysaccharides with NTHi protein D, it has been suggested that PCV-10 might also protect against this major cause of acute otitis media in children. However, the data is not conclusive.

There is evidence that PCV-10 immunisation initiated prior to 12 months of age may reduce the frequency of tympanostomy tube placements (TTP, also known as grommets). Reductions in TTP were reported in the FinIP trial following the vaccination of infants aged under 7 months or as a catch-up at age 7-11 months with PCV-10 (VE 13% [95% CI -2% to 26%] and 11% [95% CI -7to 26%], respectively). The FinIP study also found that there were fewer outpatient prescriptions for antimicrobial drugs used to treatment AOM following immunisation with PCV-10 (VE ranging from 3-8% across the study cohorts) which could

lead to over 12,000 fewer antimicrobial purchases per year in children aged under two years in Finland.

Nasopharyngeal carriage

Vaccination with PCV-10 reduces nasopharyngeal carriage (NPC) of vaccine-type pneumococci. The FinIP trial found that NPC was reduced by 19-56% in toddlers immunised with PCV-10 (as 3+1 schedule). The COMPAS study showed a 25.6% (95% CI 12.7-36.7) reduction in NPC for vaccine-serotypes. Following a 3-dose primary series in Brazil, NPC was reduced by 44% (95% CI 14.2-63.5). Carriage of vaccine-type pneumococci declined from 34% to 13% in vaccinated Kenyan children following the introduction of PCV-10 to the infant schedule. The reductions in NPC were shown to persist for at least 28 months following a 3+1 infant schedule of PCV-10 in the Czech Republic.

PCV-10 immunisation was not found to reduce NTHi carriage in the COMPAS, FinIP and other studies. A Dutch study also found that effect of PCV-10 on NTHi NP colonisation in healthy children was no greater than that from PCV-7 vaccination.

In New Zealand, the carriage of PCV-10 serotypes, but not NTHi, declined in children aged under 3 years following the introduction of the vaccine to the infant schedule. There was an increase in NP carriage of non-vaccine type 19A in New Zealand children.

Herd immunity

PCV-10 immunisation has been shown to have indirect population-wide effects (herd immunity) on vaccine-specific disease, including in New Zealand. A reduction in IPD cases of 48% (95% CI 18-68) among unvaccinated children aged 2-5 years was observed following the introduction of the PCV-10 vaccination programme in Finland. In Kenya, the PCV-10 had 66% effectiveness (95% CI 38-82) among unvaccinated individuals aged ≥5 years against NP carriage of pneumococcal vaccine-serotypes. This reduction in transmission may lead to a reduction in vaccine-type IPD in all age groups.

In New Zealand, significant reductions of 60.0% and 69.9% were observed in vaccine-serotype IPD notifications in those aged 5-64 years and over 65 years, respectively, between 2006 and 2014. However, no corresponding decline was seen in the overall IPD rate for the non-target age groups.

Conclusions

- PCV-10 provides excellent protection against vaccine-type pneumococcal disease in vaccinated young children, particularly against invasive disease such as meningitis.
- There are no safety concerns around its use when given concurrently with other routine vaccinations in infants, although in around one-third of doses given with DTaP-containing vaccine, there is an increased risk of mild-moderate fever. No data were identified for PCV-10 alone.
- The most effective immunisation schedule was a 3+1 schedule, however, 2+1 also provided excellent protection (100% versus 92%, respectively in the FinIP study) against vaccine-type invasive pneumococcal disease.
- This vaccine also provides good protection for infants against hospitalisation with pneumococcal pneumonia.
- Protection provided against pneumococcal otitis media, could reduce the incidence of surgery and antimicrobial drug usage to treat otitis media.
- Reduced transmission and herd immunity effects on vaccine-serotype IPD were observed in unvaccinated children and older age groups following the introduction of PCV-10 programmes.

Contents

Figures and Tables

Acknowledgements

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Abbreviations

ACIP	Advisory Committee on Immunization Practices
AE	Adverse events
AEFI	Adverse Events Following Immunisation
AOM	Acute otitis media
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
COMPAS	Clinical Otitis Media and Pneumonia Study
DTaP-IPV-HepB/Hib	Combined diphtheria, tetanus, acellular pertussis, inactivated poliovirus, hepatitis B and *Haemophilus influenzae* type b vaccines.
ED	Middle ear discharge
ESR	Institute for Environmental and Scientific Research
EU	European Union
GSK	GlaxoSmithKline Ltd
FinIP	Finnish Invasive Pneumococcal disease Study
Hib	*Haemophilus influenzae* type b
IPD	Invasive pneumococcal disease
NP or NPC	Nasopharyngeal / nasopharyngeal carriage
NTHi	Non-typeable *Haemophilus influenzae*
NZ	New Zealand
PCV	Pneumococcal conjugate vaccine
PCV-10	10-valent pneumococcal conjugate vaccine with serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F
PHiD-CV	PCV-10 as designated in literature: pneumococcal-non-typeable *H. influenzae* protein D conjugate vaccine.
RCT	Randomised clinical trial
RR	Relative risk
SAE	Serious adverse events
SAGE	Strategic Advisory Group of Experts on Immunization
TTP	Tympanostomy tube placements
UK	United Kingdom
US	United States of America
VAERS	Vaccine Adverse Event Reporting System
WHO	World Health Organization

1 Background

Pneumococcal immunisation of infants was made possible with the development of pneumococcal conjugate vaccines (PCV). Linking the pneumococcal polysaccharides to an immunogenic protein enabled children under the age of 2 years to mount a good immune response. The first PCV vaccine to be licensed in 2000 by Wyeth Pharmaceuticals (now Pfizer) in the United States (US) was a seven-valent PCV (PCV-7, Prevenar®), in which seven pneumococcal polysaccharide serotypes are conjugated to a non-toxic diphtheria toxoid carrier protein CRM_{197}. PCV-7 was succeeded in 2010 by a 13-valent PCV (PCV-13; Prevenar® 13) in response to an increase in non-vaccine serotype invasive pneumococcal disease (IPD).

GlaxoSmithKline Ltd developed a ten-valent PCV (PCV-10, Synflorix®), which was first licensed in 2009 in the European Union (EU) for immunisation of infants against pneumococcal disease (invasive pneumococcal disease [IPD], acute otitis media [AOM], and subsequently, in children up to 5 years of age and against pneumococcal pneumonia). Of the pneumococcal polysaccharide serotypes contained in PCV-10, eight are conjugated to non-typeable *Haemophilus influenzae* protein D - serotypes 1, 4, 5, 6B, 7F, 9V, 14 and 23; whereas, 18C and 19F are conjugated to tetanus toxoid and diphtheria toxoid carrier proteins, respectively (see section 0 for details). As such, PCV-10 differs from the Prevenar® brand of pneumococcal conjugate vaccines (PCV-7 and PCV-13) which solely conjugate using diphtheria toxoid carrier protein.[1] Pivotal European clinical trials had demonstrated PCV-10 to be non-inferior in immunogenicity against the seven serotypes in common with PCV-7 (serotypes, 4, 6B, 9V, 14, 18C, 19F and 23F) and both vaccines have similar safety profiles.[2, 3]

In New Zealand (NZ), pneumococcal conjugate vaccines (PCV) were first introduced to the National Immunisation Schedule in June 2008. PCV-10 replaced PCV-7 on the childhood immunisation schedule in 2011, and in July 2014, PCV-10 was replaced by PCV-13, as illustrated in Figure 1 . As of July 2017, PCV-10 will be used again as part of the infant immunisation schedule and PCV-13 will remain available for eligible individuals at highest risk of invasive pneumococcal disease and for private purchase.

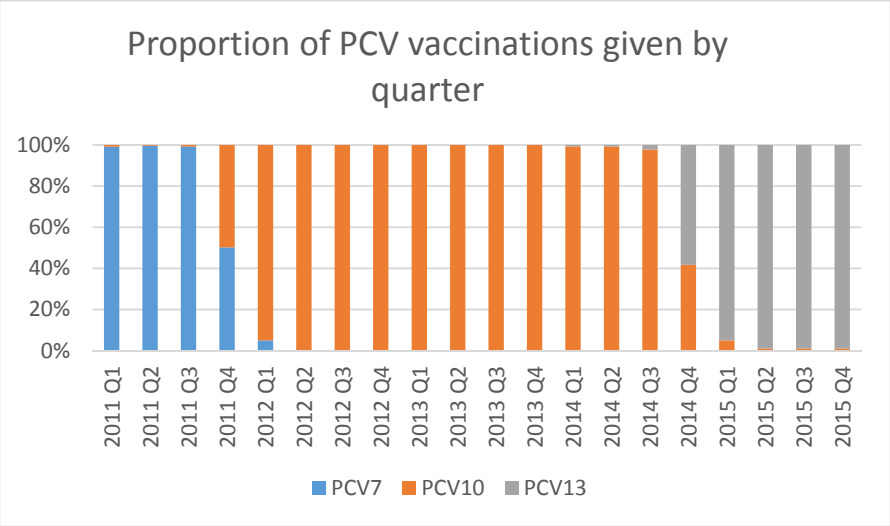

Figure 1 Proportion of PCV vaccinations given by quarter. Source: National Immunisation Register

This academic literature review will consider the safety of PCV-10 in infant schedules and the effectiveness of this 10-valent vaccine in preventing invasive pneumococcal disease of the target age groups and wider community. Also considered will be impact on non-invasive pneumococcal infections namely non-bacteraemic pneumococcal pneumonia (NPP) and otitis media, and other bacterial infections. Literature published between January 2013 and November 2016 will evaluated.

2 Methodology for review

2.1 Objectives

The objectives of this literature review are to evaluate the safety and effectiveness in disease control of PCV-10 vaccine (10-valent pneumococcal conjugate vaccine) for use in National Immunisation Schedule in infants and children. The objectives have been informed by the general specifications for the 2016 New Zealand (NZ) antigen literature review and the specific specifications for PCV-10 vaccine as listed below. The dates for eligible publications are between January 2013 and November 2016.

1. Safety
2. Effectiveness in disease control
3. Different options for placement on the schedule, based on international findings and best practice
4. Current international research and evidence around use of vaccines.

This is neither a systematic review nor a critique of the literature. The choice of articles reviewed is based on the purposeful selection of recent reviews and studies that may best inform policy discussions around the use of PCV-10 vaccine.

2.2 Literature search strategy

From a large literature search conducted on pneumococcal vaccines as a whole, papers specifically related to PCV-10 studies were reviewed. Below is the literature search strategy for the creation of the whole library.

Medline

MeSH term: Pneumococcal Vaccines AND conjugate

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

Cochrane Library search terms and strategy

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

Limit to Cochrane Reviews, Other Reviews, 2013-present = 6

Scopus search terms and strategy

"Pneumococcal vaccine" Published 2013 – present

All documents excluding physical and social sciences

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

Grey literature

One conference abstract was used in this review.

Additional searches

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

Final Endnote Library 974 Articles

Where systematic reviews and/or meta-analysis were available the preceding literature has been excluded from the review. From the final library, 50 were identified by their title or abstract as being specifically PCV-10 related. Two relevant review articles were found, since these were not systematic reviews then preceding literature were included for further information.

2.3 Participants / populations

This review considers infants and children who were administered PCV-10 as part of their routine infant series or as part of a catch-up programme. The population-wide effect of infant vaccination programme using PCV-10 on older individuals is also presented.

2.4 Interventions

Synflorix®

PCV-10 (Synflorix®, GlaxoSmithKline; also designated PHiD-CV10) is a 10-valent polysaccharide-protein conjugate vaccine. Each dose contains 1µg each of pneumococcal polysaccharide serotypes 1, 5, 6B, 7F, 9V, 14 and 23F conjugated to Protein D derived from non-typeable *Haemophilus influenzae*, 3µg of serotype 4 conjugated to Protein D, 3µg of serotype 18C conjugated to tetanus toxoid and 3µg of serotype 19F conjugated to diphtheria toxoid (CRM_{197}). Each dose contains aluminium phosphate adjuvant and 4.3mg of sodium chloride as a buffer with water for injection.

2.5 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.

3 New Zealand epidemiology

Between 2006/7 and 2014, the rate of PCV-10-serotype invasive pneumococcal disease (IPD) decreased by 95.6% (44.2 to 1.9 cases per 100,000 population) in children < 5 years of age in New Zealand. The overall rate of IPD due to any serotype also decreased by 66.7% in this age group (53.5 to 17.8 per 100,000 population). Indirect effects have been observed following the introduction of routine PCV vaccination of infants in 2008 in New Zealand. Significant reductions of 60.0% and 69.9% were observed in vaccine-serotype IPD notifications in those aged 5-64 years and over 65 years, respectively, between 2006 and 2014. However, unlike for the <5-year-olds, no corresponding decline was seen in overall IPD and non-PCV serotype IPD cases in these age groups, and in 2014, the overall IPD rate remained at around 6.1/100,000 for those aged 5-65 years and 33.5/100,000 in those aged ≥65 years.

During 2011 and 2013, the rate of IPD due to PCV-10 serotype 7F increased in the 5-64 years and ≥65-year age groups, despite falling rates of this serotype in vaccinated infants. However, by 2014 the rate had decreased and was attributed to the delayed indirect effect in older age groups of switching from PCV-7 to PCV-10 in the infant schedule in late 2011.[4]

According to the ESR July-September 2016 quarterly surveillance report, for the year ending September 2016, there were a total of 486 notified cases of IPD in NZ (rate of 10.6/100,000 population). The highest incidence was seen in the ≥65-year age-group (29.4/100,000).

There were 20 cases in infants age <2 years (rate 16.9/100,000), none of these cases were due to PCV-10 serotypes and six were due to additional PCV-13 types, the remainder were non-PCV-13 types. In children aged 2-4 years, there were 22 cases, one case due to a PCV-10 type (serotype 4), ten due to additional PCV-13 types (serotype 3 and 19A) and the remainder non-vaccine types. The most prevalent serotypes causing IPD were 19A, 22F, 7F and 3, although the total number of cases due to these decreased between 2014/2015 and 2015/2016. During these last two 12-months periods, there was a 21.8% increase in non-PCV-13 serotypes, which was predominantly seen in the ≥5-year age groups.[5]

3.1 Summary of epidemiology

The introduction of PCV-10 immunisation of infants as part of the New Zealand Immunisation schedule during 2011-2014 resulted in a significant decline in vaccine-serotype IPD across all age groups. No cases of PCV-10-type IPD were seen in infants aged <2 years from September 2015 to September 2016 – this age-group would have received PCV-13 immunisation as part of their primary series – only one PCV-10 type IPD infection was notified in children aged 2-4 years compared with 10 cases with additional PCV-13 serotypes disease. However over this period, a 21.8% increase in non-vaccine serotype IPD has been reported across all age groups.

4 Safety

4.1 Background

Pneumococcal vaccines have excellent safety profiles. As highlighted in the 2012 Pneumococcal Antigen Review, PCV-10 has a similar safety profile to PCV-7 in infants and when co-administered with a variety of DTaP-based and meningococcal vaccines: no safety concerns were detected in full term or preterm infants.[6]

The objective of this section is to review the most recent safety data for currently licensed 10-valent pneumococcal vaccine (PCV-10) with particular focus on administration as part of routine childhood immunisations and when given concurrently with other childhood vaccines. Only Adverse Events Following Immunisation (AEFI) considered subsequent to the pivotal clinical efficacy trials are reviewed here.

4.2 Review

A systematic review by Esposito and Principi in 2016 found that PCVs are considered safe for use in children, and serious adverse events (SAE) are very rarely detected by post-market surveillance. Pooled evaluation of data derived from several clinical trials found PCV-10 to be very well tolerated and safe with a similar safety profile to other PCVs. Mild-moderate irritability, injection site redness and fever were most commonly reported following around 55%, 41% and 30-35% of all doses, respectively.[7]

4.2.1 Concurrent administration

Co-administration with other schedule vaccines was been shown to be associated with fever. As reviewed, data from five pivotal clinical trials (published in 2009) reported that fever of ≥38°C occurred in approximately one third of primary or booster vaccine doses coadministered with DTaP-based vaccines. No data was provided around giving PCV-10 without coadministered vaccines. No other AEs were described for PCV-10.[2, 7]

A review of clinical trials for the PCV-10 vaccine, Synflorix®, found it to have a similar safety and tolerability profile to other pneumococcal conjugate vaccines. No further studies were highlighted other than those reported from clinical trials presented on the European Medicines Agency licensure documents, in which, PCV-10 was administered concurrently with other routine infant vaccines. To summarise, the majority of common adverse events were mild-moderate in severity and the frequency or severity of these events did not increase with subsequent doses of PCV-10.[1]

Two studies in South-East Asia found no serious adverse events associated with three-dose concurrent administration of PCV-10 with DTaP-containing vaccines. In a Japanese study, 360 infants were randomised 2:1 to receive PCV-10 with DTaP or DTaP alone as part of the primary series at 2, 3 and 6 months plus 17-19 month booster with DTaP. *Haemophilus influenzae* type b (Hib) and hepatitis B vaccines were also given concurrently. The incidence of unsolicited AEs were comparable between groups, apart from fever following the booster dose in the PCV-10 group, in which the incidence of fever >39.5°C (classed as grade 3) was 2.6%. However, only one case was considered to be related to vaccination. None of the 47 SAEs reported during the 15 month study were considered vaccine-related (28 in PCV-10 and 19 in control group).[8]

In the other Asian study, infants were coadministered PCV-10 with DTaP-IPV-HepB/Hib at 2, 3 and 5 months in Singapore (n=298) and 2 and 5 months in Malaysia (n=168). Booster doses were given at 18-21 months. Oral rotavirus vaccine was also received at 2 and 3 months of age. The incidence of each grade 3 solicited AE was ≤11.1% in both primary and booster phases of the study; the most frequent AE were injection site pain and diarrhoea following primary dose and pain and irritability following booster. No grade-3 unsolicited AE and none of the 25 SAEs reported were considered causally associated with primary vaccination. Following the booster dose in toddlers, one causally-related solicited AE (urticaria) was reported and of the four SAE reported, none were considered vaccine-related.[9]

PCV-10 was shown to have an acceptable safety profile in 199 Vietnamese infants (age 2, 3 and 4 months) when coadministered with DTaP-IPV-HepB/Hib (Infanrix®-hexa) when compared with 99 controls who received DTaP-IPV-HepB/Hib alone in a phase III open-label RCT. Within 31 days of vaccination, the incidence of unsolicited symptoms was comparable between those who received both vaccines and the control group; only a rash in the PCV-10 group and a case of vomiting in the control group were causally related to vaccination. No SAEs were considered vaccine-related.[10]

4.2.2 Booster and Catch-up doses

In an open-label RCT, PCV-10 was coadministered as a booster dose (following 3-dose primary series) with a tetravalent meningococcal conjugate vaccine (MenACWY-TT; Nimerix®) in healthy Taiwanese and Mexican toddlers with clinically acceptable safety profiles. A total of 363 toddlers aged 12-23 months were randomised 2:1:1 to receive either both vaccines at the first visit, MenACWY-TT at the first visit and PCV-10 a month later, or PCV-10 then MenACWY-TT a month later. Solicited and unsolicited symptoms were recorded on days 4 and 31 post-vaccination, respectively. SAEs were recorded throughout the study. Injection site pain was the most frequently reported local symptom and irritability was the most frequent general symptom. Fever occurred in 11% - 19.8% of infants after each vaccination. One toddler (out of 91) developed a high fever (rectal 40°C) following a dose of PCV-10 one month after MenACWY-TT, which was causally associated with the vaccination. No SAE were considered related to vaccination.[11]

Mild fever and injection site swelling were the most frequently reported adverse events following two catch-up doses of PCV-10 given in the second year of life to 67 Malian children. There were no SAE or trial withdrawals due to AE during this phase III open-label study.[12]

A similar open label study was conducted in Nigeria in which 68 primed children received PCV-10 booster co-administered with DTaP at 15-21 months and 36 unprimed children received two catch-up doses (dose 1 with DTaP) at 15-21 and 17-23 months. As seen previously, solicited mild vaccine-site pain and fever were observed. No vaccine-related SAE were reported and PCV-10, given as booster dose or as catch-up doses, was assessed to be well-tolerated.[13]

4.3 Summary of vaccine safety

PCV-10 continues to be shown to be safe and well tolerated in infants and toddlers when used in a range of schedules globally and when given concurrently with other infant schedule vaccines. Fever is the most common adverse event following concomitant administration with infant schedule vaccines, and is particularly associated with DTaP-containing vaccines in around one third of doses.

5 Effectiveness in disease control

5.1 Background

Fewer countries have included PCV-10, (replaced PCV-7 with PCV-10), on their infant schedule than those who have introduced PCV-13. According to GlaxoSmithKline, as of December 2015, 45 countries included or are currently using PCV-10 as part of their national immunisation programme or for high-risk programmes, including Brazil, a few territories in Canada, Finland, Kenya, the Netherlands, New Zealand, the Northern Territory of Australia and other Latin American countries.[14] However, there is less literature considering the efficacy and effectiveness of this vaccine than for PCV-7 and its successor PCV-13. Some studies were conducted in lower income countries, such as Brazil and Kenya, where the living conditions, nutritional status, HIV status and health outcomes of infants may differ from those seen in the New Zealand population as a whole, but study outcomes may have relevance for the high risk infants living in deprivation and those of Māori or Pacific ethnicity for whom the risk of IPD is greatest.

In PCV-10, the serotype-specific polysaccharides are conjugated to different proteins (specifically, non-typeable *H. influenzae* protein D, tetanus toxoid or diphtheria toxoid carrier proteins) than the polysaccharides in PCV-7 and PCV-13, which are conjugated solely to a diphtheria toxoid carrier protein. These differences could influence effectiveness against disease for certain serotypes despite comparable immunogenicity data.

The effectiveness of PCV-10 immunisation of infants in the prevention of pneumococcal disease, including IPD, meningitis, pneumonia and otitis media is considered in this section. The effectiveness of PCV-10 on reducing nasopharyngeal carriage of pneumococci and other bacteria will also be reviewed. The impact of PCV-10 on *S. pneumoniae* serotype prevalence is not discussed in this part of the review, because the majority of the published literature on this topic consider the role of both PCV-10 and PCV-13 together or is predominantly around the use of PCV-13.

5.2 Invasive pneumococcal disease (IPD)

A literature review by Plosker in 2014 highlighted the protective efficacy and effectiveness of PCV-10 against pneumococcal disease as determined by two key RCTs (COMPAS and FinIP) and various post-marketing studies.[1]

The efficacy of PCV-10 in protecting against IPD was compared with control hepatitis vaccines as part of a secondary outcome of the Clinical Otitis Media and Pneumonia Study (COMPAS) phase III trial in Latin America (Argentina, Colombia and Panama). Approximately 24,000 infants received PCV-10 or hepatitis B vaccine at age 2, 4, 6 months and PCV-10 or hepatitis A vaccine at age 15-18 months. The study showed that VE of PCV-10 was 100% (95% CI 74.3-100) against pneumococcal vaccine-serotype IPD and 65% (95% CI 11.1-86.2) against any IPD. The primary focus of this study was pneumococcal pneumonia (see section 5.3).[1, 15]

The Finnish Invasive Pneumococcal disease (FinIP) study investigated two or three-dose infant series plus toddler booster (2+1 or 3+1, respectively in infants younger than 7 months) as well as investigating catch-up doses (see section 5.2.2). In total, the double-blind cluster-randomised phase III/IV study enrolled 47,366 children aged <19 months. Clusters were determined by 78 regions in Finland in proportion to the population. Infants enrolled before 7 months of age, received three-dose (at a minimum of 4 week intervals) or two-dose (minimum interval of 8 weeks) primary vaccinations and a booster dose at least 4 months after last primary dose and not before 11 months of age. Control groups younger than 12 months of age received hepatitis B vaccine. Study vaccines were given concomitantly with national vaccination programme vaccines at scheduled visits. Refer to Table 1 for summary of trial cohorts.[16]

Table 1: FinIP study vaccination cohorts (adapted from Palmu et al. 2013)

	Primary infant schedules		**Catch-up schedules**	
Age at enrolment	<7 months		7-11 months	12-18 months
Schedule	3+1	2+1	2+1	2
Number of Primary doses	3	2	2	2
Interval between doses	>4 weeks	>8 weeks	> 4 weeks	>6 months
Booster	4 months after last primary dose			none
Control vaccine	Hepatitis B			Hepatitis A
Study vaccines administered concomitantly with age appropriate national vaccination programmes.				

Vaccine effectiveness (VE) against culture-confirmed vaccine-serotype IPD was shown to be 100% (95% CI 83-100) following the 3+1 schedule and 92% (95% CI 58-100) for the 2+1 schedule. Based on national hospital discharge register data, VE against non-laboratory-confirmed IPD was 50% (95% CI 32-63), increasing to 71% (52-83) for patient file-verified non-laboratory-confirmed IPD. The absolute rate-reductions were higher in these cases than

culture-confirmed IPD. Plosker noted that these findings imply a greater public health value from pneumococcal vaccines than previously reported.[1, 16, 17]

In subsequent paper published by Palmu et al., the rates of register-based non-laboratory-confirmed IPD (or unspecified sepsis) hospitalisations in children aged 3-42 months was 32 in 100,000 person-years for the target vaccine-eligible cohort (born between 2010-2013) compared with 94 in a two-season, age-matched reference cohort (born between 2003-2008) prior to the introduction of PCV-10. The absolute rate-reduction was 62 in 100,000 person-years (relative rate-reduction of 66% [95% CI 59-73]). The results, as shown in Table 2, demonstrated that the PCV-10 vaccination programme in Finland had a nationwide impact on clinically suspected IPD. The greatest absolute rate reductions were seen in the non-laboratory confirmed IPD or unspecified sepsis compared with laboratory-confirmed (absolute rate reduction: 122 episodes versus 50 episodes/100,000 person-years). Palmu reported that a considerable proportion of IPD cases are under reported due to the poor sensitivity of blood-culture detection (out of the ~80% of patients who had samples cultured, only 31% tested positive for pneumococci).[18]

Table 2: Numbers and rates of register-based IPD episodes and the associated vaccine-prevented disease burden by the Finnish National PCV-10 vaccine programme (with permission Palmu et al 2015).

Case Definition	No. of Episodes		Episodes/100 000 PY		Relative Rate Reduction		Absolute Rate Reduction
	NVP-Eligible Cohort[a]	Before NVP[b]	NVP Eligible	Before NVP	Point Estimate (%)	95% CI	Episodes/100 000 PY (95% CI)
Register-based non–laboratory-confirmed IPD or unspecified sepsis[c]	791	2333	237	359	34	29–39	122 (100–144)
Register-based non–laboratory-confirmed IPD[d]	106	608	32	94	66	59–73	62 (52–71)
Laboratory-confirmed IPD[5]	43	409	13	63	80	72–85	50 (43–57)

NVP, national vaccination program; PY, person-years.
[a] Born in 2010–2013, follow-up 334 088 y.
[b] Cohort born in 2003–2008 follow-up 649 877 y.
[c] Any of the following ICD-10 codes in any discharge notifications: A40.3, A40.9, A41.9, A49.9, G00, G00.1, G00.9, I30.1, M00, M00.1, M00.9, B95.3, or B95.5. Culture-confirmed IPD cases were excluded.
[d] Any of the following ICD-10 codes entered as final discharge diagnosis: A40.3, G00.1, M00.1, or B95.3. Culture-confirmed IPD cases were excluded.

A matched case-control study conducted in Brazil found that, following the introduction of PCV-10 to the national immunisation schedule (3+1), the adjusted effectiveness against vaccine-serotype IPD was 83.8% (95% CI 65.9-92.3) for an age-appropriate PCV-10 schedule. For the most common serotypes, VE was 87.7% (95% CI 60.8-96.1) for serotype 14 and 82.8% (95% CI 23.8-96.1) for serotype 6B, and 82.2% (10.7-96.4) for cross-reactive serotype 19A. The study included 316 cases of IPD and 1219 neighbourhood age-matched controls. Age-appropriate PCV-10 immunisation was up-to-date for 94 (30%) cases and 521 (43%) of the controls.[1, 19]

The effectiveness of PCV-10 among young children, as examined by an indirect cohort method in Brazil, was similar to that found with the matched-case control study. Multivariate logistic regression was used to compare PCV-10 vaccination among children with vaccine-type or vaccine-related IPD with children with non-vaccine type disease. Adjusted VE of at least 1 dose of PCV-10 was 72.8% (95% CI 44.1-86.7) against vaccine-type disease and 61.3% (14.5-82.5) against vaccine-related serotypes. Significant protection was seen against the vaccine-related serotype 19A and individual vaccine types 14, 6B, 23F and 18C.[20]

A Canadian case-control study investigated the effectiveness of three PCVs used sequentially to prevent IPD in Quebec. PCV-7 was introduced in December 2004 as part of the infant schedule in a 2+1 schedule for low risk infants at age 2 months, 4 months and 12 months (with a catch-up for children <5 years). PCV-7 was replaced by PCV-10 in June 2009 and

then by PCV-13 in January 2011 in 2+1 schedules with no catch-ups. More than 90% of children receive the recommended doses from the start of the PCV programme. During 2005-2013, 889 IPD cases were reported in children <5 years, of which, 516 cases participated in a parental interview and immunisation status review and were compared with 1767 age-stratified controls. Against vaccine-type IPD, VE of ≥ 1 dose of PCV-7 was 90% (95% CI 82-95%), 97% (84-99%) for PCV-10 and 86% (62-95%) for PCV-13. For any type-IPD, VE was 50% (29-64%), 72% (46-85%) and 66% (29-83%) for PCV-7, PCV-10 and PCV-13, respectively. Of the cases and controls immunised with ≥1 dose, 305 cases and 1035 controls received only PCV-7; 34 and 114 received PCV-10; and 44 and 178 received PCV-13, respectively. The most frequent serotype in IPD cases (32% of total cases) was 19A. PCV-10 showed VE of 71% (95% CI 24-89%) in cross-protection against serotype 19A-specific IPD, compared with VE of 42% (-9 to 69%) for PCV-7, and for PCV-13 that contains 19A serotype, VE was 85% (55-94%). For ≥2 doses, there was no difference in VE against PCV-13 serotype-IPD with PCV-10 only (VE 85% [66-94%]), PCV-13 only (85% [55-94%]) and mixed PCV-10+PCV-13 (89% [58-97%]) schedules.[21]

5.2.1 Pneumococcal meningitis

A decrease in pneumococcal meningitis morbidity and mortality was observed two years after the introduction of routine PCV-10 vaccinations in Brazil in under two-year olds, based on data obtained from the Information System on Notifiable Diseases from 2007 to 2012. Overall, the incidence of pneumococcal meningitis decreased by 50% from 3.7/100,000 in 2007 to 1.84/100,000 in 2012. Mortality decreased by 69% from 1.3/100,000 to 0.4/100,000. Approximately 30% of cases each year were fatal, although in the second year post vaccination this decreased to 22%. During the study period, there were 1,311 cases and 430 deaths attributed to laboratory-confirmed pneumococcal meningitis (serotypes not determined). The greatest impact of PCV-10 vaccination was seen in the 6-11-month age-group for which there was 73% reduction in pneumococcal meningitis incidence (incidence ratio: from 7.46 to 2.02 cases/100,000) and 85% reduction in mortality (mortality ratio: 3.25 to 0.49 deaths/100,000 inhabitants from 2007 to 2012; no confidence intervals given). PCV-10 vaccination coverage was 73% in 2011 and 89% in 2012.[22]

Similar findings were observed in a study conducted the Parana state of Brazil during 1998-2011, follow the introduction routine PCV-10 vaccination in 2010. The number of cases reduced from 6.01 cases to 2.49 /100,000 and mortality from 1.85 to 0.47 deaths/100,000. A significant reduction from 80.7% to 53.3% was shown in vaccine-serotype cases in under 2 year-olds (p=0.03).[23]

5.2.2 Catch-up doses

In the matched-case-control study in Brazil, a single catch-up dose of PCV-10 significantly protected children aged 12-23 months against vaccine serotype IPD with adjusted VE of 68.0% (95% CI 17.6-87.6; based on 29 cases/44 controls) and 40.6% (-190.2 to 87.8; 11 cases /15 controls) against vaccine-related IPD, but was not protective against non-vaccine type IPD (VE -72.6% [-972.1 to 72.2]; six cases / ten controls). As mentioned previously, for the same study, the up-to-date-for-age primary course adjusted VE against vaccine-type IPD was 83.8%.[1, 19]

VE of catch-up doses of PCV-10 was 100% (95% CI 79-100) in the FinIP study. The study investigated two catch-up cohorts: those aged 7-11 months at enrolment received two doses of PCV-10 as primary vaccination plus a booster (n=3880); and those aged 12-18 months at the time of the first dose received two doses, at least 6 months apart (n=6,534). Controls groups received either hepatitis B vaccine at age 7-11 months (n=1907) or hepatitis A if older than 12 months (n=3126). Refer to Table 1. For these catch-up cohorts,

a total of seven IPD cases were reported in the control groups only – one case in the 7-11-month cohort and five cases for the 12-18-month group.[16]

5.3 Community-acquired Pneumonia (CAP)

Clinical Otitis Media and Pneumonia Study (COMPAS) was a phase III trial, conducted in urban centres in Argentina, Colombia and Panama (Latin America), comparing the efficacy of PCV-10 in protecting against bacterial CAP with the control vaccines (hepatitis B for primary vaccination and hepatitis A as booster). Approximately 24,000 infants received PCV-10 or hepatitis B vaccine at 2, 4, 6 months and 15-18 months. An interim analysis of the primary endpoint, conducted when 535 first bacterial CAP episodes were identified, found VE against first bacterial CAP episode to be 22.0% (95% CI 7.7-34.2, one-sided p=0.002) after a mean follow-up of 23 months for the per-protocol cohort (PCV-10 group n=10,295; control group n=10,201). At the end of the study in the intent-to-treat analysis, VE against WHO-defined consolidated CAP was 21.8% (95% CI 7.7 – 33.7%). The mean incidence rates of first episodes of consolidated CAP in the intent-to-treat cohorts were 2.1% (1.9-2.4) and 2.7 (2.4-3.0) for the PCV-10 and control groups, respectively. Findings were consistent between the per-protocol and intent-to-treat analyses.[1, 15]

Significant reductions in all-cause pneumonia hospitalisations among children aged 2 months to 2 years were seen in three out five Brazilian cities following the introduction of PCV-10 to the infant schedule (3+1 schedule, with catch-up for those aged 7-11 months and 12-24 months) in March 2010. Following the introduction of PCV-10 immunisation, the rates of pneumonia hospitalisations changed by -40.3% (95% CI -50.9 to -27.4), -37.6% (-49.6 to -22.7) and -49.3% (-61.6 to -33.1) in Belo Horizonte, Curitiba and Recife, respectively (p<0.001). Non-significant reductions were also observed in São Paulo and Porto Alegre (-13.4% [-26.0 to 1.4; p=0.74] and -23.5% [-41.6 to 0.2; p=0.52], respectively) – in São Paulo, this was attributed to lower vaccination coverage (≤80% compared with >90% - 100% in the other cities). Reductions of 11-22% in non-respiratory-cause hospitalisation were also observed during the post vaccination period across all five cities, and the best-estimate of vaccination effect was calculated to be: -28.7% in Belo Horizonte, -23.3% in Curitiba, -27.4% in Recife, -1.8% in Sao Paulo and -2.3% in Porto Alegre (p=0.002, 0.011, 0.007, 0.827 and 0.845, respectively).[24]

Between 2009 and 2012, a 40% reduction in the prevalence of CAP was observed in two cities in the state of Mina Gerais, Brazil following the introduction of PCV-10 (prevalence ratio=0.60; 95% CI 0.46-0.78; p<0.05). The prevalence of CAP was 70% lower (prevalence ratio = 0.30; 95% CI 0.24-0.37; p<0.05) in children vaccinated as recommended compared with those with delayed vaccination. No reduction in prevalence of otitis media or sinusitis was observed.[25]

Data from the FinIP trial, presented at a European Paediatric Infectious Disease annual meeting in 2013, showed VE for PCV-10 three-dose infant series against all pneumonia episodes in infants in Finnish hospitals was 25.2% (95% CI 2.6-42.6) and 27.6% (5.5-44.6) for two-dose series commenced before 7 months of age (refer to Table 1 for cohorts). For the combined catch-up schedules (aged >7-18 months), VE against hospital-diagnosed pneumonia was 24.1% (8.8-41.8%). It was concluded that PCV-10 provided protection against pneumonia in both the 3+1 and 2+1 schedules.[1, 26]

A study in children aged <4 years showed a significant decrease of 12.65% (p<0.001) in all pneumonia hospitalisations in Brazil when comparing the pre-vaccination (2002-2009) and two-years post PCV-10 vaccination periods (2011-2012). No reduction in non-respiratory-cause hospitalisation were observed for the same time period (p=0.39).[1, 27]

Further studies in Brazil have continued to show significant reductions in pneumonia in under 2-year-old infants following the introduction of PCV-10 to the infant schedule. Active population-based surveillance studies were conducted in Central Brazil (across 17 paediatric hospitals) to investigate pneumonia hospitalisations in children <36 months of age before and after the introduction of PCV-10. The relative rate-reduction was 13.1% for clinical and 25.4% for x-ray-confirmed pneumonia in children age 2-24 months. Three years after the introduction of PCV-10, the highest prevented pneumonia burden was seen in the 2-11-month age group: the incidence of clinical pneumonia reduced by 853/100,000 (95% CI 838-873; from 6788 to 5835/100,000) and x-ray-confirmed pneumonia decrease by 729/100,000 (95% CI 703-752; from 2871 to 2142/100,000). The overall vaccine coverage for completed PCV-10 three-dose primary series by 12 months of age was 58%. Coverage in children aged 24-35 months was lower than those age 2-23 months (50.3% [46.47-54.0] versus 61% [58.2-62.8]).[28]

A Brazilian ecological study conducted across 26 municipalities in the Regional Health Superintendence of Alfenas showed a significant reduction in hospitalisation for CAP in children aged <1 year post-PCV-10 vaccination. The overall prevalence ratio was 0.81 (95% CI 0.74-0.89; $p<0.05$) – representing a 19% reduction in CAP hospitalisations (from 828 to 624 cases from 2007 to 2013). However, this reduction was not significant in all 26 municipalities.[29]

5.4 Otitis media

A secondary outcome of the COMPAS trial in Latin America was to assess VE of PCV-10 against clinically-confirmed acute otitis media (AOM). Participants were only recruited in Panama for this outcome. At the end of the study, the intent-to-treat analysis found that VE against AOM was 19.0% (95% CI 4.4-31.4; one-sided p=0.007; n=254 vaccinated, 308 controls). When the cause of the AOM was investigated further, VE was calculated as 55.7% (95% CI 21.5-75; n=17 PCV-10, 38 controls) against pneumococcal AOM and 69.9% (29.8-87.1; n= 7 vs 23) against vaccine-serotypes. For non-typeable *H. influenzae* (NTHi)-confirmed AOM, VE was given as 21.5% (-43.4 to 57.0; n=19 vaccinated, 24 controls), however, the numbers of bacteriologically-confirmed cases were too low to confirm any effectiveness.[1, 15]

In New Zealand, significant declines in otitis media-related hospitalisations were observed following the introduction of PCV to the infant schedule as shown in Figure 2. During the PCV-7 usage time period OM incidence declined by 55%, then by 66% from 2011-2014 during the PCV-10 period and 81% during the PCV-13 period in children under the age of 6 years. These declines were greatest in the children of Māori and Pacific ethnicity, resulting in little ethnic disparity between the main ethnic groups. (Unpublished data supplied by the Immunisation Advisory Centre).[30]

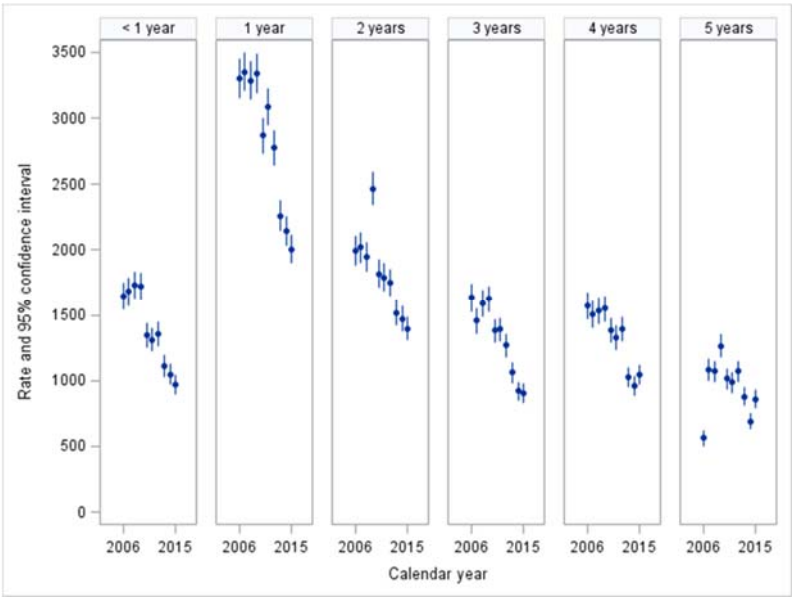

Figure 2: Rate and 95% confidence interval per 100,000 of initial otitis media hospitalisations among children less than 6 years of age, by calendar year and age.

Australian Indigenous children aged <36 months who were vaccinated with PCV-10 were shown to have less suppurative OM than those vaccinated with PCV-7 (odds ratio 0.6, 95% CI 0.4-0.8; p=0.001). Data was collected through routine surveillance during 2008-2012. PCV-10 was used as part of the Australian Immunisation Schedule for children <2 years from October 2009 to September 2011 in the Northern Territory; it was replaced with PCV-13 country wide in October 2011.[31]

To investigate these findings further, a cross-sectional study investigated whether the reduced prevalence of suppurative OM, seen since the replacement of PCV-7 with PCV-10 in Australia, was associated with changes in nasopharyngeal (NP) carriage and middle-ear discharge (ED) microbiology. The study examined swabs from vaccinated Indigenous children in the Northern Territory (mean age 18 and 20 months, respectively). NP swabs were obtained from 421 children who received PCV-7 and 443 children who received PCV-10 vaccine. Pneumococcal carriage was seen in 76% of PCV-7 group and 82% of PCV-10 group, and NTHi was found in 68% and 73% of PCV-7 and PCV-10 groups, respectively. In ED samples from PCV-7 and PCV-10 vaccine recipients, pneumococci were cultured from 25% and 18% of perforations (p=0.38) and NTHi was cultured in 61% and 34% (p=0.008), respectively. The study concluded that in the PCV-10 vaccinated children, the prevalence of NTHi-ED infection was lower than for those who were vaccinated with PCV-7. It is unclear why there was a discrepancy between carriage and middle-ear infection, but it may be due to the adherence characteristics of the cells in each compartment and/or the presence of anti-*H. influenzae* protein D antibodies.[32]

A study in NZ did not find any significant changes in the rate and ratios of NTHi culture and molecular detection in middle ear fluid (MEF) samples of children with established ear disease following the implementation of PCV-10 on the national immunisation schedule. The two-phase study compared the microbiology of MEF and NP carriage in two cohorts of children aged ≤3 years undergoing ventilation tube (VT insertion; also called tympanostomy tube placement). Phase 1 was conducted during 2011 following the introduction of PCV-7 to the infant immunisation schedule and phase 2 was conducted during 2014 following the introduction of PCV-10. Vaccine coverage for at least three doses of PCV at time of enrolment was 96% and 94%, respectively. Samples were collected from 325 children

(median age 21.6 months [16.9-27.4]) during phase 1 and 319 children (median age 22.3 months [16.9-27.3]). Serotyping of the *S. pneumoniae* in MEF isolates showed that non-vaccine type 19A was the dominant serotype in phase 2, whereas 19F was the most dominant type during phase 1. Therefore, in MEF, these data did not support a role for PCV-10 serotype 19F in cross-protection against 19A. Serotype 19A was also strongly associated with penicillin and multidrug resistance. PCR and culture detection of NTHi in MEF did not differ between the two phases (53% by PCR for both phases). Over both time periods, 95% of the *Haemophilus* isolates were confirmed as NTHi and this was found to be the dominant otopathogen in these children. When compared with non-otitis prone children, children undergoing VT insertion had higher rates of NP carriage of *H. influenzae* or *S. pneumoniae* serotypes in both study phases.[33] (see section 5.5 for NP carriage findings)

5.4.1 FinIP study

One of the outcomes of the FinIP and blinded follow-on studies was to investigate the effectiveness of PCV-10 against otitis media.

5.4.1.1 Acute otitis media

Vaccine effectiveness was assessed against parent-reported physician-diagnosed AOM during the FinIP trial in a cohort of 4117 vaccinated infants, over a mean follow-up of 18 months from first vaccination. At least 1 AOM episode was reported in 1162/1846 (63.0%) of infants who received PCV-10 in 3+1 schedule, 589/942 (62.5%) in the 2+1 schedule group and 892/1329 (67.1%) in the control group. In reducing the number of infants who had ≥ 1 AOM episode, vaccine effectiveness in the 3+1 groups was 6.1 % (95% CI -2.7 to 14.1), 7.4% (-2.8 to 16.6) in 2+1 group and when both schedule were combined was 6.7% (-1.3 to14.0). Overall VE against all AOM episodes was 2.8% (-9.5 to 13.9), 10.2% (-4.1 to 22.9) and 6.4% (-5.5 to 17.2) for the 3+1, 2+1 schedule and both schedules combined, respectively. The study concluded that there was a trend towards decreased numbers of AOM episodes after PCV-10 vaccination, although there was no significant effectiveness in reducing AOM rates.[34] The bacterial cause of the infection was not determined in this study and cases may have been due to non-pneumococcal infections.

5.4.1.2 Tympanostomy tube placements

One such outcome was effectiveness of PCV-10 was evaluated against tympanostomy tube placements (TTPs, commonly known as grommets) used in the treatment and prevention of recurrence of AOM. Out of 30,527 infants (aged <7 months when enrolled), 4369 TTPs were reported in 3594 participants. Refer to Table 1 for cohort vaccination details. In the control cohort (who received hepatitis B vaccine not PCV-10), the incidence of TTP was 7.9/100 person-years. The highest incidence of TTP was during the second year of life. Estimated VE was 13% (95% CI -2% to 26%; p=0.08) combined for both 3+1 and 2+1 PCV-10 infant schedules. In these cohorts, the absolute reduction in TTP was 1.1 per 100 person years: to prevent one procedure, 44 needed to be vaccinated during the two-year follow-up. For the catch-up schedule at 7-11 months of age, VE was 11% (95% CI -7to 26%; p=0.21; 2+1 doses) and catch-up at 12-18 months, VE was -1% (-21 to 16%; p=0.91, after 2 doses PCV-10). The study concluded that PCV-10 immunisation initiated prior to 12 months of age may reduce TTP frequency. However, primary analysis did not reach significance.[35]

5.4.1.3 Antimicrobial drug usage

Another part of the FinIP phase III/IV study examined VE of PCV-10 against outpatient prescriptions for antimicrobial drugs recommended for the treatment of AOM. Refer to Table 1 for cohorts. In the control clusters, the incidence of antimicrobial drug purchase was 1.69 per person-year. A total of 98,436 outpatient antimicrobial purchases were reported for

30,527 infants who were aged <7 months at enrolment for FinIP. During a 2-year follow-up after PCV-10 vaccination (combined for 3+1 and 2+1 schedules), the incidence rate difference from controls was 0.12 per person-year and VE was 8% (95% CI 1-14): this corresponded to a need to vaccinate 5 (3-67) infants to prevent one antimicrobial drug purchase. VE was identical for the two infant schedules. VE estimates increased with the higher number of purchases per child, indicating greater vaccine effect for those most susceptible to infection. This effect started soon after the first dose of vaccine and was sustained during the third year of life. In the catch-up cohorts, VE was 4% (-5 to 12) for the age 7-11-month cohort and 3% (-4 to 10) for the age 12-18-month cohort, incidence rate difference was 0.05 (-0.07 to 0.17) and 0.04 (-0.05 to 0.12), respectively. The conclusion of this analysis was that PCV-10 vaccination could lead to over 12,000 fewer antimicrobial purchases per year in children younger than 24 months in Finland (with birth cohort of around 60,000 compared with approximately 50,000 in New Zealand).[36]

5.5 Summary of FinIP findings

A summary of the findings from the FinIP study were presented by A Palmu in Auckland, November 2016 as shown in the table below. [16-18, 26, 35]

Outcomes	VE 3+1 95% CIs	VE 2+1 95% CIs	VE 3+1/2+1 95% CIs	Incidence per 100 000 Control 3+1/2+1	VPDI per 100 000	Contribution of all VPDI reduction
IPD (invasive pneumococcal disease)[1]	100% 88 to 100	88% 55 to 98	**94%** **77 to 99**	80	75	0.6%
Non-laboratory-confirmed IPD [2]	38% 13 to 56	62% 43 to 75	**50%** **32 to 63**	422	207	1.5%
Pneumonia[3]	25% 3 to 42	27% 5 to 44	**26%** **8 to 41**	1262	341	2.5%
Tympanostomy tube placement[4]	14% -4 to 29	13% -5 to 28	**13%** **-2 to 26**	7887	1100	8.1%
Antimicrobial purchases [5]	8% -1 to 15	8% 0 to 15	**8%** **1 to 14**	154900	11800	87.3%

Table 3: The disease burden caused by S. pneumoniae *in infants and the vaccine-preventable disease incidences following immunisation with PCV-10 in the FinIP study. (Source: presentation by A Palmu, 2016, reproduced with permission)*

5.6 Nasopharyngeal Carriage

5.6.1 Vaccine serotype *S. pneumoniae*

Reductions in nasopharyngeal carriage (NPC) of pneumococcal vaccine serotypes have been reported following vaccination with PCV-10 in various geographical locations. Some of these studies were reviewed by Plosker in 2014.[1]

Reductions in NPC of PCV-10 vaccine-serotypes were shown in a FinIP nested study. When compared with control vaccine, PCV-10 given as a 2+1 infant series reduced NPC by 23-38% and 19-56% for a 3+1 series, over 3 months in children aged 18-22 months. The effectiveness of PCV-10 in reducing NPC was largely due to reductions in serotypes 6B, 14, 19F and 24F. Reductions in carriage were also observed in a satellite study of the older siblings of the FinIP vaccinated children. PCV-10 did not appear to reduce NPC of

Staphylococcus aureus, *Moraxella catarrhalis* or NTHi (which had a low overall rate of carriage).[1]

Data from the COMPAS trial supported the FinIP study data. VE against NPC for vaccine-serotypes was 25.6% (95% CI 12.7-36.7) across all time points. PCV-10 had no significant effect on NPC of non-vaccine serotypes and NTHi (VE -6.6% [-26.0 to 9.7] and 8.3% [-13.7 to 26.1], respectively). Other studies in the Czech Republic and the Netherlands further supported these findings.[1]

PCV-10 VE in reducing vaccine-serotype NP carriage was shown to be 35.9% (95% CI 42-57.1, p=0.03) in infants age 7-11 months following two-dose primary series (2+0) and 44.0% (14.2-63.5; p=0.008) in infants aged 15-18 months following 3-dose primary series (3+0) in Brazil. No significant effect was observed in infants following 1-dose catch-up vaccination given at age ≥12 months (VE -2.8% [-62.5 to 35.0; p=0.905).[1, 37]

Reduction in vaccine-serotype carriage was observed to persist for at least 28 months after a PCV-10 booster dose in 4-year olds (previously primed with 3-dose primary series) in the Czech Republic.[1, 38]

Findings from annual cross-sectional carriage studies among an age-stratified, random population sample in Kenya, showed PCV-10 was associated with reductions in NP carriage of vaccine-serotypes and NTHi with a modest increase in non-vaccine serotypes. At baseline in 2009-2010, carriage prevalence was 34% for vaccine-serotype *S. pneumoniae*, 41% for non-vaccine type *S. pneumoniae* and 54% for NTHi in children <5 years. Following the introduction of PCV-10 to the infant schedule in 2011, prevalence was 13%, 57% and 40%, respectively, in 2011-2012. Carriage VE for vaccine serotypes was 64% (95% CI 49-47) among children aged <5 years and was 66% (95% CI 38-82) for those aged ≥5 years.[1, 39]

An RCT in Kenya found no changes in prevalence or relative abundance of *S. pneumonia*, NTHi or other potential pathogens (*M. catarrhalis* or *S. aureus*) following randomised vaccination with two doses of either PCV-10 or control hepatitis A vaccine in 60 children aged 12-59 months. The study concluded that PCV-10 vaccination did not significantly alter the species composition or diversity of the NP microbiome in this population.[40]

A multicentre NZ study (as described in section 5.4) found that vaccine-serotype *S. pneumoniae* in NP samples declined from 11% to 1% of children <3 years of age undergoing VT insertion for otitis media and 8% to 0% in non-otitis prone children between 2011, following the introduction of PCV-7 to the infant schedule, and 2014 following the introduction of PCV-10 (p≤0.001, for both groups). The NP carriage of non-vaccine serotypes increased for both VT groups (98/316 [31%] in 2011 to 151/316 [48%] in 2014, P≤0.001) and non-otitis groups (29/137 [21%] to 49/154 [32%]; p≤0.05). However, no significant changes were observed for other otopathogens or for those with carriage of more than one pathogen (*S. pneumoniae*, *H influenzae* or *M. Catarrhalis*) in either group.[33]

5.6.2 Non-typeable *Haemophilus influenzae* carriage (NTHi)

A Dutch study examined NP colonisation with NTHi following PCV-10 or PCV-7 vaccination at 2, 3, 4 and 11-13 months of age. The study was initiated 2 years after PCV-7 was introduced to the schedule in the Netherlands. NP colonisation with NTHi increased with age in both groups from 33% at 5 months to 65% at 24 months of age. VE against NTHi colonisation was 0.5% (95% CI -21.8 to 18.4%) at 3 months post-booster and VE against NTHi acquisition was 10.9% (-31.3 to 38.9%) for PCV-10 compared with PCV-7. Colonisation patterns for *S. pneumoniae*, *M. catarrhalis* and *S. aureus* were similar between groups. The study concluded that PCV-10 immunisation did not affect NP colonisation or density of NTHi

in healthy children up to 2 years of age, when compared with PCV-7, and these data implied that herd immunity for NTHi was not expected with PCV-10 vaccination.[41]

As described above (section 5.4), a study in NZ did not find any significant changes in the culture and molecular detection rate and ratios in nasopharyngeal (NP) samples of children with established ear disease following the implementation of PCV-10 on the national immunisation schedule. The two-phase study compared the microbiology of NP carriage in two cohorts of children aged ≤3 years undergoing ventilation tube insertion (VT; also called tympanostomy tube placement). NTHi was detected in NP samples of 62% of children following the introduction of PCV-7 vaccination, and 61% of children during following the introduction of PCV-10. When compared with non-otitis prone children, children undergoing VT insertion had higher rates of NP carriage of *H. influenzae* or *S. pneumoniae* serotypes in both study phases. The study concluded that the introduction of PCV-10 following PCV-7 appears not to have a significant impact on nasopharyngeal microbiology in New Zealand children.[33]

5.7 Indirect and herd immunity

A systematic review by Loo et al. in 2014 investigated the indirect effects of PCV dosing schedules on pneumococcal disease and bacterial colonisation among non-targeted age groups, including unvaccinated family members and high-risk populations, such as Indigenous and immunocompromised populations. The review found evidence that 3+1 dose PCV schedules demonstrate indirect effects on vaccine-type IPD, vaccine-type nasopharyngeal carriage and syndromic pneumonia. Almost all the studies investigated PCV-7 (95%). However, this review found no studies that investigated the indirect effects of PCV-10 and concluded that more data is required around 3+0 and 2+1 schedules and for PCV-10 and PCV-13.[42]

A population-based study, conducted following the introduction of PCV-10 to the national immunisation schedule in Finland in September 2010, observed a 48% (95% CI 18-68) reduction in IPD among unvaccinated children aged 2 to 5 years during 2012-2013 (i.e. 2-3 years after vaccination programme began). This reduction equated to an absolute rate reduction of 7.9 cases (95% CI 3-13) per 100,000 children per year and was mostly attributed to the ten vaccine serotypes.[43]

A population effect was observed in NP carriage of vaccine serotypes in both children <5 years of age and older individuals, following the introduction of PCV-10 to the infant schedule in Kenya. In unvaccinated individuals aged >5 years, adjusted prevalence ratios for vaccine-type and non-vaccine-type carriage were 0.34 (95% CI 0.18-0.62) and 1.13 (0.92-1.38), respectively. VE against vaccine-serotype carriage was calculated to be 64% (49-74) in those <5 years of age and 66% (95% CI 38-82) among those aged ≥5 years. For NTHi, VE for carriage was 38% in those aged <5 years and 29% in the older age groups – post hoc analysis determined this decline to be non-significant two years after the introduction of PCV-10. The study concluded that the childhood PCV-10 programme reduced transmission of vaccine-serotype pneumococci within the whole population and is likely to lead to reduced vaccine-type IPD across all age groups.[39]

5.8 Summary of efficacy and effectiveness

Invasive pneumococcal disease (IPD)

PCV-10 has excellent vaccine effectiveness against culture-confirmed vaccine-serotype IPD. The FinIP clinical trial found VE was 100% following a three-dose primary series and a

booster in the second year of life (3+1 schedule) and 92% for the 2+1 schedule (which is now used routinely in Finland). Rates of non-laboratory confirmed IPD in children aged 3-42 months declined by two-thirds following the introduction of PCV-10 in Finland. Efficacy of 100% against IPD was also shown in the COMPAS study in Latin American. Surveillance in New Zealand found that IPD notifications reduced by around two-thirds in infants following the switch from PCV-7 to PCV-10.

Age-appropriate PCV-10 in Brazil was shown to be 83.8% effective overall against IPD, including 82.2% effective against cross-reactive serotype 19A. Following the initiation of the PCV-10 vaccination programme, mortality from pneumococcal meningitis decreased by 69% in infants aged <2 years and the number of cases decreased by 50%, particularly in those aged 6-11 months.

In Canada, at least one dose of PCV-10 was shown to be 97% effective against vaccine-type IPD in children <5 years, 72% effective against any IPD, and had a cross-reactive VE of 71% against serotype 19A-IPD. When comparing at least two doses of PCV-7, PCV-10 or PCV-13, VE against vaccine-type IPD did not differ.

Pneumonia

Decreases in pneumonia hospitalisation in infants were observed in Brazil, Latin America and Finland following the introduction of PCV-10 immunisation of infants. VE against all infant pneumonia hospitalisations was calculated to be around 25% in the FinIP trial.

Otitis media

PCV-10 has been shown to provide protection against pneumococcal acute otitis media in Latin American and Indigenous Australian children. However, no significant vaccine effectiveness was determined during the FinIP studies in overall AOM. In New Zealand, there was a 66% decline in OM-related hospitalisation in children under 6 years of age during the period of PCV-10 use in the infant schedule.

PCV-10 immunisation initiated prior to 12 months of age may reduce tympanostomy tube placements (TTP) frequency. Reductions in TTP were reported in the FinIP trial in infants vaccinated aged <7 months or as a catch-up at age 7-11 months with PCV-10 (VE 13% and 11%, respectively). The FinIP study also found that there were fewer outpatient prescriptions for antimicrobial drugs used to treatment AOM following immunisation with PCV-10 (VE 8% 3+1 or 2+1 schedules from <7 months, 4% following catch-up at 7-11 months, 3% following catch-up at 12-18 months compared with control cohorts), which could lead to over 12,000 fewer antimicrobial purchases per year in under-2-year old children in Finland.

Significantly fewer middle-ear discharge samples, from PCV-10-vaccinated Australian Indigenous children with suppurative AOM, contained non-typeable *H. influenzae* than those who had been vaccinated with PCV-7, although nasopharyngeal carriage was similar between the groups. However, a New Zealand study did not find any difference in NTHi in the middle ear fluid of PCV-7 or PCV-10 vaccinated children aged <3 years with otitis media.

Nasopharyngeal carriage

Vaccination with PCV-10 reduces nasopharyngeal carriage (NPC) of vaccine-type pneumococci. The FinIP trial found that NPC was reduced by 19-56% in toddlers immunised with PVC-10 (3+1 schedule). The COMPAS study showed a 25.6% reduction in NPC for vaccine-serotypes. Following a 3-dose primary series in Brazil, NPC was reduced by 44%. Carriage of vaccine-type pneumococci declined from 34% to 13% in vaccinated Kenyan children following the introduction of PCV-10 to the infant schedule. The reductions in NPC

were shown to persist for at least 28 months following a 3+1 infant schedule of PCV-10 in the Czech Republic.

PCV-10 immunisation was not found to reduce NTHi carriage in the COMPAS, FinIP and other studies, including in children with otitis media in New Zealand. A Dutch study also found that effect of PCV-10 on NTHi NP colonisation in healthy children was no greater than that of PCV-7.

Herd immunity

PCV-10 immunisation has been shown to have indirect population-wide effects (herd immunity) on vaccine-specific disease, including in New Zealand. A 48% reduction in IPD cases among unvaccinated children aged 2-5 years was observed following the introduction of the PCV-10 vaccination programme in Finland. In Kenya, the PCV-10 VE was 66% among unvaccinated individuals aged ≥5 years against NP carriage of pneumococcal vaccine-serotypes. This reduction in transmission may lead to a reduction in vaccine-type IPD in all age groups.

6 Conclusions

The main conclusion of this review are presented below:

- PCV-10 provides excellent protection against vaccine-type pneumococcal disease in vaccinated young children, particularly against invasive disease including meningitis.
- There are no serious safety concerns around the use of PCV-10 when given concurrently with other routine vaccinations in infants. Fever was a commonly reported adverse event, when given as part of the primary series or as a booster dose with other vaccines. No data were identified for PCV-10 alone.
- The most effective immunisation schedule was a 3+1 schedule, however, 2+1 also provided excellent protection (100% versus 92%, respectively in the FinIP study).
- This vaccine also provides good protection to children against pneumococcal pneumonia.
- Protection provided against pneumococcal otitis media (VE 56%), may reduce the incidence of tympanostomy tube placements and antimicrobial drug usage to treat otitis media.
- Reduced transmission and herd immunity effects on vaccine-serotype IPD were observed in unvaccinated children and older age groups following the introduction of PCV-10 programmes.

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