Pneumococcal Conjugate Vaccine (PCV) Product Assessment

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PCV Product Assessment

Preface

This technical document provides summary information regarding pneumococcal conjugate vaccine (PCV) products. It synthesizes the epidemiologic and biologic evidence as well as the programmatic considerations surrounding performance, effectiveness, and impact for current PCVs: 10-valent (PCV10) and 13-valent products (PCV13). The availability of multiple pneumococcal vaccines, with overlapping but non-identical characteristics, including formulation, poses challenges. There is a need for comprehensive decision-making framework, inclusive of evidence-based analyses on product performance; to determine which PCV products may best suit different contexts including considerations of supply, logistics, price, cold chain requirements, program impact, and vendor characteristics. The need for such a decision-making framework, populated by unbiased evidence will increase as additional pneumococcal vaccines become licensed and available for use, increasing the complexity of product choices. This addresses a pressing priority for Gavi, the World Health Organization (WHO), and countries on optimizing and sustaining PCV use.

This document provides technical information from review of technical and programmatic evidence that may help countries make PCV product choices and should not be viewed as formal WHO recommendations as it has not yet undergone formal WHO guideline review. The document was developed with direct support of Gavi funds, and leveraged the infrastructure of the PCV Review of Impact Evidence (PRIME) supported by the Gates Foundation.

Materials that can be used to inform product switches including this detailed technical summary:

1. WHO PCV Position Paper, 2012 (http://www.who.int/wer/2012/wer8714.pdf?ua=1)
2. WHO Considerations for PCV Product Choice, 2017 (Available through WHO Regional and Country Offices)
3. WHO Operational Guidance on PCV Product Switches, 2017 (Available through WHO Country Office)
4. Gavi Frequently Asked Questions (FAQ) on Pneumococcal Conjugate Vaccine (PCV) 4-dose vial presentations, 2017 (http://www.gavi.org/library/gavi-documents/guidelines-forms/)

The technical evidence provided in this document comes from *a comprehensive review* of published data on PCV immunogenicity and disease effectiveness and impact of licensed PCV products (PCV10 and PCV13) used in 3-dose schedules (2+1 and 3+0). Evidence from both observational studies and clinical trials is included. Evidence reporting changes in disease incidence (pre- and post- PCV introduction) was prioritized for sections on PCV effectiveness and impact. Case series data and studies providing disease information from only the post-PCV era in sections where there is otherwise severe data paucity, and otherwise are not included.

A *systematic evaluation* of PCV products (i.e. all evidence available, including unpublished data) is underway to inform the policy review process underway by the Strategic Advisory Group of Experts on Immunization (SAGE) PCV Working Group. The results of that evaluation will be used to update the summaries already included in this report and to provide additional analyses. This includes information not presented here, such as: un-published data from surveillance sites; 4-, 2-, and 1-dose vaccine schedules; otitis media; and post-only data.

What is the purpose of this document?

- To assist Gavi in making informed decisions about PCV product requests (including switches) by countries
- To assist countries in making informed decisions around PCV product choice and requests to Gavi

How can countries use this document?

- As a technical tool to inform PCV decision-making on product choice at the time of introduction and within established PCV programs
- As a resource to readily access key evidence, data and tools for PCV product choice

How can Gavi use this document?

- As a technical tool to inform PCV demand forecasts including supply planning for country allocation
- As a resource to readily access key evidence, data and tools for PCV product choice
- As a resource to create country guidance on PCV product choices

Product Choice Considerations

The document provides information that should be considered in a product choice decision but does not itself provide any recommendation for product choice. This document provides specific information about the two currently available, licensed PCV products along with advice about the considerations a country should weigh in making a product choice. The information here focuses on pre-qualified and globally marketed PCVs (i.e. PCV10 and PCV13, see Table 2 for key descriptors of product characteristics) but does not include a systematic review of evidence from previously marketed products (i.e. PCV7), or information on unlicensed products of the past (i.e. PCV9, PCV11), or those that are currently under evaluation. The information is presented in a framework that can be updated as new evidence on existing products and novel pneumococcal vaccine products becomes available. The document is not intended as the primary source of information to support decision-making about *whether to include PCV in the vaccine program* or on dosing schedules; comprehensive documents are otherwise available for those decisions[1-6].

Decision-makers considering a PCV product choice should weigh the evidence aiming to assure a PCV program that is optimized for disease impact and sustainability. That evidence should include an understanding of:

- Pneumococcal disease epidemiology (including pneumococcal serotype considerations)
- PCV performance, and
- PCV programmatic considerations (including product availability, cost, cold chain requirements, product presentation, wastage, product administration and training requirements)
- PCV product supply
- Financial considerations of PCV products

Vaccine performance characteristics are usually ones for which a large amount of data are available on individual products, but few data exist that offer direct product comparisons. Most data come from PCV impact evaluations in routine use settings, and by their nature most often include only the assessment of a single product. The PCV performance measures include immunogenicity, efficacy against disease and colonization (i.e. vaccine impact when given in ideal circumstances), effectiveness against disease and colonization (i.e. vaccine impact when given in routine use circumstances), duration of protection, age of administration, indirect effects (i.e. effects on those who are not immunized), serotype cross-protection, serotype replacement, and safety.

Evidence on PCV impact on pneumococcal colonization and disease from routine immunization program settings is essential for decision-makers to consider, since the question being asked is what vaccine to implement in the routine use program. Not all questions noted here have sufficient evidence to draw conclusions; where data are sparse or not available, this limitation is noted. However, there is a robust, and rapidly growing body of PCV evidence from both trials and of observational studies in routine use settings that policy-makers can rely on to make an informed product choice. To date, although the bulk of evidence remains from high-income settings, there is substantial evidence from middle- and low-income settings.

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List of Abbreviations

ACIP	US Advisory Committee on Immunization Practices
AMC	Advanced Market Commitment
AMR	Antimicrobial resistance
CEA	Cost Effectiveness Analyses
CRM	*Corynebacterium diphtheria*
DT	Diphtheria toxoid
DTaP	Diphtheria-Tetanus-acellular Pertussis vaccine
EMA	European Medicines Agency
FDA	US Food and Drug Administration
GACVS	Global Advisory Committee on Vaccine Safety
GSK	GlaxoSmithKline
GSP	Global Serotype Project
Hib	Haemophilus influenzae type B
ICER	Incremental Cost-Effectiveness Ratio
IgG	Immunoglobulin G
IPD	Invasive Pneumococcal Disease
MDVP	Multi Dose Vial Policy
NP	Nasopharyngeal
NRA	National Regulatory Authority
NTHi	non-typeable Haemophilus influenzae
OPA	Opsonophagocytic Activity
PCV	Pneumococcal Conjugate Vaccine
PCV10	10-valent Pneumococcal Conjugate Vaccine
PCV13	13-valent Pneumococcal Conjugate Vaccine
PCV7	7-valent Pneumococcal Conjugate Vaccine
PD	Protein D
PQ	Pre-Qualification
RCTs	Randomized control trials
SAGE	Strategic Advisory Group of Experts on Immunizations
STs	Serotypes
TPP	Target Product Profile
TT	Tetanus toxoid,
VE	Vaccine Effectiveness
VT	Vaccine Types
VVM	Vaccine Vial Monitoring
WHO	World Health Organization

1. Context and background

1.1 PCV licensure and recommendations

The US Food and Drug Administration (FDA) licensed the first PCV product (PCV7) for use in infants in 2000. A recommendation for inclusion of PCV in the routine infant immunization schedule was made by the US Advisory Committee on Immunization Practices (ACIP) in July 2000, and was implemented in the US later that year [7]. Many countries then licensed and adopted its use. In 2007, WHO adopted a policy, as recommended by SAGE, that all countries should include PCV as part of the routine infant immunization schedule[8]; WHO pre-qualification (PQ) for PCV7 was issued the same year. The WHO recommendation was made with evidence from two large phase III efficacy trials in Africa (the Gambia and South Africa) confirming the generalizability of efficacy beyond that observed in trials from North America and Europe.

Since then, two additional PCV products (PCV10 and PCV13) have received WHO PQ, both of which include more serotypes than those found in PCV7; PCV7 was replaced by PCV13 and is no longer on the market [1]. WHO PQ has been granted for PCV10 2-dose vials and PCV13 1-dose and 4-dose vials. The availability of two licensed PCV products, which differ in several ways, means that countries with PCV need to make product selection decisions for introduction or maintenance of PCV vaccine programs. These decisions are based on a combination of factors that fall into five categories, including: disease epidemiology, product performance, programmatic needs, supply, and financial considerations.

1.2 Pneumococcal disease and serotype epidemiology

WHO country specific and global burden of disease estimates are available from 2000, 2008 and will soon be released for 2015 [9-11]. In the absence of PCV use, pneumococcal disease is the leading vaccine preventable cause of mortality of infancy and childhood. Moreover, in settings where mortality is high, pneumococcus is responsible for an even greater fraction of mortality and morbidity than in lower mortality settings. Plainly stated, where many children die in infancy and early childhood, pneumococcal disease is a main culprit. In settings where mortality is controlled, pneumococcal disease may not cause death but it is a ubiquitous pathogen that causes pneumonia, blood stream infections and meningitis that require immediate, appropriate treatment. Pneumococcal disease, even when not fatal, incurs substantial financial treatment costs to families and to government health care systems, and can incur long-term health consequences to children who survive (e.g. sequelae of meningitis and compromised lung function among those who had pneumonia).

Having decided to introduce PCV, policy-makers will be aware that PCVs contain only a limited number of the more than 96 pneumococcal serotypes, and that immunity to one serotype does not necessarily confer immunity to others (i.e. there is limited cross-protection among serotypes, and always within a serogroup). However, since only a small subset of these serotypes are responsible for the vast majority of disease and deaths, they were targeted for inclusion in PCVs to represent those found across all epidemiologic settings[12]. Both PCV products on the market are considered global products, appropriate for any country setting.

The serotype distribution of pneumococcal disease prior to PCV use was systematically evaluated for all regions. The Pneumococcal Global Serotype Project (GSP) provides a serotype-by-serotype estimate of the fraction of disease, by geographic region, among children under 5 years of age (Table 1) [13]. This analysis formed the basis for the pneumococcal vaccine Advanced Market Commitment (AMC) stipulation that eligible pneumococcal vaccines must account for, at a minimum, 60% of disease causing strains, and include serotypes 1, 5 and 14 [14]. The rationale for the stipulation that PCVs should account for at least 60% of disease was laid out in the Target Product Profile (TPP) document. Serotypes 1 and 5 are common causes of pneumococcal disease outbreaks, and are particularly common in Africa and Asian settings; and serotype 14 was found to be the most common in all regions. Noted also was that the 10 serotypes causing the majority of disease in Africa

were the same as those in Asia, suggesting more similarities than differences between populations. This systematic assessment of serotypes causing disease is considered the reference document for countries.

Table 1. Serotype distribution of the top 20 global serotypes causing invasive pneumococcal disease, by region, pre-PCV among children under-5 years of age

	Africa		Asia		Europe		LAC		North America		Oceania	
	(N=11.181)		(N=4.752)		(N=10.279)		(N=18.788)		(N=11.441)		(N=3.649)	
Serotype	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
1	11.7%	9.5, 13.8	9.5%	6.6, 12.3	5.1%	4.0, 6.2	8.4%	7.2, 9.6	1.1%	0.6, 1.5	1.8%	1.0, 2.6
2	1.9%	1.0, 2.8	2.6%	1.5, 3.7	0.1%	0.0, 0.2	0.3%	0.1, 0.4	0.0%	0.0, 0.0	0.9%	0.0, 1.8
3	1.1%	0.8, 1.5	1.4%	0.8, 2.0	1.9%	1.5, 2.4	2.2%	1.8, 2.6	0.8%	0.6, 1.0	0.4%	0.2, 0.7
4	2.3%	1.7, 3.0	1.6%	1.0, 2.1	3.2%	2.6, 3.8	1.6%	1.3, 1.9	5.7%	4.7, 6.7	4.9%	3.3, 6.6
5	10.7%	7.6, 13.8	6.7%	4.5, 9.0	0.8%	0.5, 1.1	8.5%	7.2, 9.8	0.4%	0.1, 0.7	2.8%	1.5, 4.1
6A	9.4%	7.2, 11.5	3.5%	2.4, 4.6	4.4%	3.8, 5.0	4.5%	3.6, 5.4	3.6%	2.9, 4.3	3.7%	3.1, 4.3
6B	8.5%	6.3, 10.7	11.5%	9.0, 14.0	13.7%	12.2, 15.3	9.4%	8.4, 10.3	13.4%	11.7, 15.1	12.0%	9.3, 14.6
7F	0.8%	0.4, 1.3	2.0%	1.2, 2.8	3.2%	2.4, 3.9	2.5%	2.0, 3.1	1.0%	0.7, 1.4	2.0%	1.1, 2.8
8	1.1%	0.8, 1.5	0.6%	0.3, 0.9	1.0%	0.7, 1.3	0.8%	0.4, 1.1	0.1%	0.0, 0.2	0.9%	0.4, 1.5
9A	0.4%	0.2, 0.7	0.3%	0.1, 0.5	0.1%	0.1, 0.2	0.0%	0.0, 0.1	0.4%	0.2, 0.7	0.1%	0.0, 0.2
9V	2.2%	1.3, 3.1	3.1%	2.2, 4.1	4.2%	3.4, 5.1	2.7%	2.3, 3.1	5.3%	4.5, 6.0	3.9%	3.1, 4.7
12A	0.1%	0.0, 0.1	1.2%	0.7, 1.8	0.0%	0.0, 0.1	0.1%	0.0, 0.1	0.0%	0.0, 0.0	0.0%	0.0, 0.0
12F	1.7%	1.1, 2.3	1.6%	0.8, 2.3	0.7%	0.6, 0.9	0.6%	0.3, 0.9	1.2%	0.7, 1.7	2.2%	0.9, 3.5
14	13.0%	10.0, 16.0	11.6%	8.7, 14.5	23.9%	21.0, 26.8	26.5%	23.2, 29.7	29.2%	26.4, 31.9	23.7%	17.2, 30.1
15B	0.5%	0.1, 0.9	0.8%	0.4, 1.2	0.7%	0.5, 0.8	0.7%	0.4, 0.9	0.3%	0.2, 0.4	0.2%	0.0, 0.4
18C	1.4%	0.9, 2.0	2.4%	1.7, 3.2	6.9%	5.9, 8.0	4.3%	3.4, 5.2	8.0%	6.9, 9.0	5.9%	4.1, 7.7
19A	3.9%	2.5, 5.3	2.6%	1.7, 3.5	5.5%	4.6, 6.4	2.9%	2.3, 3.5	3.0%	2.4, 3.7	3.9%	2.9, 4.9
19F	5.4%	3.6, 7.1	8.1%	6.3, 9.8	8.2%	7.1, 9.3	3.6%	3.2, 4.1	10.3%	9.3, 11.3	8.9%	6.8, 11.0
23F	6.5%	4.5, 8.5	9.7%	7.6, 11.8	7.1%	6.1, 8.2	5.3%	4.4, 6.2	6.2%	4.9, 7.5	5.2%	3.7, 6.6
45	0.5%	0.0, 1.0	0.6%	0.1, 1.0	0.0%	0.0, 0.0	0.0%	0.0, 0.0	0.0%	0.0, 0.0	1.1%	0.1, 2.1
46	1.3%	0.4, 2.1	0.5%	0.1, 0.9	0.0%	0.0, 0.0	0.0%	0.0, 0.0	0.0%	0.0, 0.0	1.0%	0.0, 2.0
All Others	15.7%	12.7, 18.6	18.2%	14.7, 21.6	9.2%	7.9, 10.4	15.3%	12.5, 18.1	10.2%	7.0, 13.4	14.6%	11.1, 18.1
TOTAL	100.0%		100.0%		100.0%		100.0%		100.0%		100.0%	

CI = Confidence Interval; N= Number

Beyond the consideration of serotypes causing disease *prior to the introduction of PCV*, policy-makers may consider several other factors regarding product selection and serotypes:

- **Antimicrobial resistance (AMR):** Some serotypes are more commonly found among strains that exhibit AMR. These are largely those included in available vaccines, but shifts in this epidemiology are possible.
- **Non-PCV7 serotypes including types 3, 6A, and 19A**: This document provides a specific section on the impact of both PCV13 and PCV10 on types 3, 6A, and 19A; the former includes these serotypes in the vaccine formulation while the latter relies on the possibility of cross-protection from 6B for 6A, and 19F for 19A. This issue is often raised for consideration because of the experience with the first generation PCV7. Following the use of PCV7, an increase in the disease incidence of serotypes not included in the vaccine (i.e. serotype replacement) was observed, but the magnitude of that increase was small relative to the reduction in disease incidence from vaccine types (VT). Overall, there was a substantial net reduction in pneumococcal disease with the use of PCV7. However, one non-PCV7 serotype, 19A, was observed to increase in incidence in many countries, and was a serotype commonly associated with AMR. Attention to evidence for PCV10 regarding 19A in particular is a focus for some decision-makers.
- **Country specific serotype distribution**: Most countries have few if any studies to inform local serotype distribution of pneumococcal disease in infants and young children. Even where such data exist, there are many reasons why they may be an unreliable source to estimate the long-term average serotype distribution and should not be a substantial driving factor of product choice. The regional serotype distributions provided by the GSP are considered a more robust reflection of the disease causing serotype

distribution rather than local studies with small numbers of isolates, whose distribution may be substantially biased relative to the true disease distribution in the country.

2. Vaccine characteristics of currently licensed PCV products

Two PCV products are currently licensed, pre-qualified by WHO, globally marketed and available with Gavi support: PCV10 manufactured by GlaxoSmithKline (GSK), marketed as Synflorix, and PCV13 manufactured by Pfizer Inc., marketed as Prevenar-13.

2.1 Serotypes included in products

All of the serotypes included in PCV10 are also included in the PCV13 product. The three additional types found in PCV13 are types 3, 6A, and 19A. Table 2 illustrates the comparison of serotypes in the two products (additional details on products are provided in Table 3). There is some evidence of cross-protection by 6B for 6A and by 19F for 19A for PCV10, which is discussed specifically in Section 3.7.

Table 2: Serotypes included in and specifications of PCV10 and PCV13 product formulations

Product	Formulation Specifications	Serotype & Carrier Protein												
		1	3	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F
PCV10	Vial Size: 2-dose and 4-dose* Preservative: None	1µg PD		3µg PD	1µg PD		1µg PD	1µg PD	1µg PD	1µg PD	3µg TT		3µg DT	1µg PD
PCV13	Vial Size: 1-dose and 4-dose Preservative: None (for 1-dose); 2- phenoxyethanol for 4-dose	2.2 µg CRM	2.2 µg CRM	2.2 µg CRM	2.2 µg CRM	2.2 µg CRM	4.4 µg CRM	2.2 µg CRM	2.2 µg CRM	2.2 µg CRM	2.2 µg CRM	2.2 µg CRM	2.2 µg CRM	2.2 µg CRM

PD=protein D from non-typeable Haemophilus influenzae (NTHi), CRM= *Corynebacterium diphtheria*, TT=tetanus toxoid, DT=diphtheria toxoid
*WHO PQ is expected from late 2017 and implementation from 2018 onwards

Serotype included in the vaccine some evidence of cross protection

2.2 Carrier Protein

Table 2 describes the carrier proteins used for each product. PCV13 uses CRM197 protein as the protein carrier for each of the 13-serotypes. CRM197 is a non-toxic protein derived from *Corynebacterium diphtheriae*. This is the same carrier protein found in several Haemophilus influenzae type B (Hib)-conjugate vaccines.

PCV10 uses protein D (derived from NTHi) as the carrier for eight of the serotypes while one serotype (type 18C) are conjugated to tetanus toxoid and another (type 19F) is conjugated to diphtheria toxoid protein.

2.3 Therapeutic indications

PCV10 and PCV13 were licensed and pre-qualified on the basis of immunogenicity non-inferiority to PCV7, which was licensed on the basis of demonstrated efficacy against invasive pneumococcal disease (IPD). Since the time of licensure both PCV10 and PCV13 have gained approval for indications beyond prevention of IPD.

Each country in which the product is licensed for marketing approves the labeling for that country. The WHO PQ labeling largely mirrors that of the responsible national regulatory authority (NRA); for PCV13 this is the European Medicines Agency (EMA), and PCV10 this is the Federal Agency for Medicines and Health Products in Belgium [15, 16].

The WHO PQ has approved the two vaccines for the following indications:

- PCV10: for IPD, pneumococcal pneumonia, and otitis media, with labelling by the EMA and WHO PQ that includes the prevention of serotypes 19A [16].
- PCV13: for IPD, pneumococcal pneumonia, and otitis media caused by the 13 serotypes in the vaccine [15].

Contraindications, special warnings and precautions for use are outlined in the product labeling documents and relate specifically to those who have allergies to components in the vaccine. There are no substantive distinctions between the products [15, 16].

2.4 Formulations for PCV10 and PCV13

A description of the formulations and packaging characteristics is provided in Table 3.

2.5 Safety Profile

The safety profiles of both PCV10 and PCV13 have been reviewed by multiple national regulatory authorities during the licensure processes, the WHO prequalification process, and the GACVS [17]. Both products have accrued extensive post-marketing safety surveillance data and both are assessed as having excellent safety profiles. There are no issues distinguishing one product from another from a safety perspective.

Table 3: WHO Prequalified, and anticipated PCV product formulation and details [3, 4] [15, 16]

PCV	Serotypes included	Manu-fact.	Trade name	Carrier proteins	Year PQ by WHO	Avail. From UNICEF	Wast-age rate	Storage conditions	Packaging	Volume per dose	VVM
PCV10 1-dose vial, preserv-ative free	1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F	GSK	Synfl-orix	Protein D from NTHi, TT and DT	2009	No	5%	2-8°C, do not freeze.	Cartons of 1, 10 and 100 vials	57.7, 11.5 and 9.7 cm^3 per dose	VVM30: quite stable under high tempera tures
PCV10 2-dose vial, preserv-ative free	1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F	GSK	Synfl-orix	Protein D from NTHi, TT and DT	2009	Yes	10%	2-8°C, do not freeze. An opened 2-dose vial should not be returned to the refrigerator after vaccination session or after 6 hours, whichever comes first.	Cartons of 100 vials	4.8 cm^3 per dose	VVM30: quite stable under high tempera tures
PCV10 4-dose vial, preserv-ative 2-PE*	1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F	GSK	Synfl-orix	Protein D from NTHi, TT and DT	Expect-ed in late 2017	Expect-ed in 2018	10%	2-8°C, do not freeze.	Info. Not Yet Available	2.4 cm^3 per dose	VVM30: quite stable under high tempera tures
PCV1 1-dose vial	PCV10 types plus types 3, 6A and 19A	Pfizer	Prevnar 13, Prevena r 13	CRM 197 protein	2010	Yes	5%	2-8°C, do not freeze	Cartons of 50 vials	12 cm^3 per dose	VVM30: quite stable under high tempera tures
PCV13 4-dose vial, Preserv-ative 2-PE*	PCV10 types plus types 3, 6A and 19A	Pfizer	Prevnar 13, Prevena r 13	CRM 197 protein	2016	Yes	10%	2-8°C, do not freeze	Cartons of 25 and 50 vials	3 cm^3 per dose	VVM30: quite stable under high tempera tures

PQ = WHO prequalified

* 2-phenoxyethanol

3. Performance & impact

Performance factors that decision-makers should consider for product choice decisions include the vaccine's immunogenicity; disease efficacy, effectiveness, impact, and duration of protection; the age at which it can be administered or is most effective; added benefits, such as indirect (herd) immunity and cross-protection against other serotypes; and the vaccine's safety profile.

Existing WHO documents describe these performance measures [2, 18]. For PCV product choice, the focus is on disease and nasopharyngeal (NP) colonization impact since ultimately these are the outcomes of most clinical and policy relevance. This section summarizes the available information on efficacy from randomized control trials (RCTs) and observational studies on each PCV product, effectiveness and impact of PCV products on NP carriage and disease outcomes including on mortality.

3.1 Literature Review Methods

A systematic review of 14 databases (Appendix C) was conducted to include relevant data published in English from January 1, 2010-October 9, 2015, and ad-hoc additions through January 2017. In addition, all relevant citations included in the systematic PCV dosing landscape review (1994-2010) were brought into this analysis and document [19].

- *Types of Studies:*
    - Included: RCTs, non-randomized trials, and observational studies reporting **pre (baseline) and post** vaccine introduction incidence rates for disease outcomes
    - Excluded: Post only incidence data (i.e. no comparison between time points, vaccine products, or dosing schedules made) and case-series data (pre-post or post only)
- *Outcomes:*
    - Included: Mortality (all-cause and pneumonia/IPD specific), IPD, pneumonia, NP carriage, and immunogenicity measured by Immunoglobulin G (IgG) antibody concentrations
    - Excluded: otitis media, immunogenicity measured by opsonophagocytic activity (OPA) or avidity
- *Products and Schedules*:
    - Included: PCV10 or PCV13 in either 2+1 or 3+0 dosing schedules
        -
    - Excluded: Studies evaluating other PCV products and dosing schedules were generally excluded
- *Deduplication*: Families of studies that published data on the same population(s) overtime were identified and 'deduplicated' so that the most recent, comprehensive data was included to allow for maximum time for PCV impact to be evaluated
    - A parent paper was chosen and cited for families of studies within figures and tables
- *Citations*:
    - All included studies are described in Appendix A.
    - All studies that were excluded based on insufficient evidence to draw reliable conclusions on impact are described in Appendix B.

Specific methods for direct effects section: At least 1 year of pre-PCV and 1 year of post-PCV data was required for observational studies.

Specific methods for indirect effects section: At least 3 years of post-introduction data were required to be included in the indirect effects assessment. Studies had to report on an age group that only represented indirect effects, not a mix of direct and indirect effects.

3.2 Immunogenicity

Summary

Serotypes (STs) common to PCV10 and PCV13

- PCV10 and PCV13 are both highly immunogenic in infants for the 10 ST they have in common, for all dosing schedules evaluated, and with or without concomitant Diphtheria-Tetanus-acellular Pertussis (DTaP) vaccine administration. At least one immunogenicity study is available from every WHO region. This evidence includes 6 head-to-head studies, which directly compare PCV10 to PCV13 within a single population and using the same protocol.

ST 3, 6A and 19A

- PCV13 is immunogenic (i.e. induces high concentrations of functional antibody) against ST 3, 6A and 19A, the three additional serotypes in that vaccine but not in PCV10.
- PCV10 induces increases in functional antibody against ST 6A and 19A following the primary series, although the proportion of children achieving the correlate of efficacy is lower than that observed in infants receiving PCV13. After a booster dose, >70% of PCV10 vaccinated infants have antibody concentrations above the efficacy correlate for both serotypes but the absolute concentrations remain lower than in PCV13-vaccinated infants.
    - PCV10 received a positive opinion on cross-protection against 19A on the basis of immunogenicity data and post-marketing surveillance of IPD incidence in Europe [15, 16].
- There is insufficient evidence to evaluate the immunogenicity of PCV10 against serotype 3, a serotype not included in the vaccine.

Modifiers of immunogenicity

- The number of primary doses, age at first dose, dosing interval, age at last dose, geographic region, and DTaP co-administration all influence PCV immunogenicity, when considered one at a time (i.e. in univariate analyses). Since these variables interact with each other, additional multivariable analyses are needed to understand the independent effects of each variable on the immune response.

Regional representation of data

- PCV10 immunogenicity data were available from all regions, though only Asia and Europe had studies using a 2-dose primary schedule. PCV13 immunogenicity data were not available for Africa or South America and did not include any 2-dose primary schedule studies for Oceania.

Immunogenicity Background

In support of the clinical development of extended-valency PCVs (i.e. those licensed after PCV7), the WHO developed guidance for the use of the vaccines based on the immunologic outcomes comparing a novel PCV with a licensed PCV product in head-to-head studies. An immunological correlate of efficacy (% of subjects with serotype specific IgG above 0.35 mcg/mL following a 3 dose primary series when IgG is measured using the Pfizer assay without 22S adsorption; based on immunogenicity bridging studies, when IgG is measured using the GSK assay the correlate of efficacy has been established as 0.22 mcg/mL) was estimated from large randomized controlled efficacy trials from the late 1990's and early 2000's of 7- and 9-valent PCV which demonstrated efficacy against invasive pneumococcal disease. This correlate of efficacy is not an individual correlate --- in other words, individual children whose antibody level is above 0.35 mcg/mL do not necessarily have protection from disease----but instead when a population immunized with a novel PCV results in a proportion of individuals with antibody concentrations above 0.35 mcg/mL that is non-inferior to the proportion among a population immunized with a licensed PCV above this same value, then it is inferred that

the new PCV would have shown similar efficacy against disease to that of the licensed PCV had it been tested for that outcome. Of note, this correlate of efficacy is not serotype specific but was instead inferred based on overall efficacy against all serotypes together. For some serotypes the correlate of efficacy is likely lower and for others higher than 0.35 mcg/mL.

This immunogenicity based licensure process has been accepted worldwide, and used to license PCV10 and PCV13 without efficacy trials.

Because PCV10 and PCV13 RCT immunogenicity data resulted in product licensure, by definition the immunogenicity results showed non-inferiority to PCV7. Here our focus is on not only the RCT data but also updated immunological data generated in post-licensure immunogenicity studies spanning both vaccine products, different regions of the world and differing immunization schedules. The purpose of the immunogenicity section is to link the immunogenicity data to disease impact and vaccine effectiveness (VE) data and to focus on any serotype specific nuances or product nuances that might inform product choice.

Immunogenicity Findings

There was strong evidence to support the immunogenicity of PCV10 and PCV13, in all regions, for both immunization schedules: 2- primary doses with a booster at or after 9-months of age (2+1) and 3 primary doses (3+0). Based on data from 57 PCV10 and 41 PCV13 study groups (Appendix A. Table 21), we can infer that both products:

- Induce a satisfactory immune response after the primary series for both 2-dose and 3-dose primary schedules;
- When administered in a 2+1 schedule, demonstrate a strong response to the booster dose. Because both products also showed antibody *waning* between the primary series and the booster dose, this booster dose may be important for longer duration of protection.
- Perform well across regions.

Although this review was not intended to directly compare products, in the six studies that did, PCV13 induced higher antibody after a 2 or 3-dose primary series to some serotypes common to both products (1, 5, 7F, 23F) but evidence was mixed for other serotypes (6B, 14, 19F) [20, 21]. However, a higher antibody level does not necessarily mean better protection; when comparing the proportions of subjects achieving the correlate of efficacy, the two vaccines were equivalent for at least 8 of the 10 common serotypes. Differences in antibody responses were also seen before and after the booster dose: before the booster dose, PCV13 vaccinees had higher antibody to some serotypes (14, 19F), PCV10 vaccinees had higher antibody to other serotypes (1, 6B, 23F) and evidence was mixed for the remaining serotypes (5, 7F) [22, 23]; (after the booster dose, PCV13 induced higher antibody for four serotypes (1, 7F, 14, 19F) and results were mixed for others (5, 6B,23F) [22-24] [20]. Again, there was no significant difference between products when comparing the proportions of subjects with a concentration of antibody above the correlate for efficacy. For serotypes 3, 6A, and 19A, those that are included in PCV13 but not in the PCV10 formulation, PCV13 was highly immunogenic, meeting all of the evaluation criteria listed above (i.e. non-inferiority, boosting and induction of functional antibodies).

For PCV10, there was insufficient evidence to evaluate immunogenicity for serotype 3, since it was almost never tested for in PCV10 immunogenicity studies, presumably because of PCV10's lack of an antigen that could have an impact on serotype 3 antibody concentrations, either directly or through cross-protection.

However, after primary vaccination with PCV10, >50% of subjects had antibody concentrations to 6A and 19A that were above the efficacy correlate (range 22-79% for 6A and 22-87% for 19A, based on 26 study arms). The percent responders improved to 85% after the booster dose (range 72-99% and 74-96%, respectively). Evidence of boosting of antibodies to 6A and 19A was also reflected in antibody concentrations, which

increased 5-6 fold for each of the two serotypes compared to post-primary levels (based on evidence from 19 studies). These immunogenicity data suggests that PCV10 may demonstrate cross-protection to type 6A and/or 19A disease/colonization which is discussed further in sections 3.2 (NP colonization), 3.4 (IPD) and 3.7 (3, 6A and 19A). There are limited OPA data on the functional activity of the cross-reacting antibodies following PCV10 primary or booster immunization but of those published post booster OPA responses to PCV10 are significantly lower than those following PCV13 boost.

Since countries who are considering product choices are not all using the same vaccine schedule, we compared the immunogenicity of different PCV schedules, investigating the effect of the number of primary doses, age at first dose, interval between primary doses and age at last dose on antibody levels, by product. We also examined immunogenicity by region and among subjects with and without concomitant DTaP vaccination since the concomitant use of whole-cell pertussis vaccines appear to enhance the immunogenicity of PCV. Key inferences from these analyses include:

- For both products, a two-dose primary schedule (most, but not all studies, with 8-weeks between doses)[†] elicits a comparable post-primary immune response to a three-dose primary schedule, except for serotypes 6B and 23F, for which two-dose schedules are significantly less immunogenic than three-dose schedules. At the pre-booster time point, there are no significant differences in proportion of children with antibodies above the correlate of efficacy between schedules for any of the serotypes, however the GMC 's did differ between schedules, for some serotypes for both PCV13 and for PCV10.
- For both products, post-dose 3 antibody levels are higher for children receiving a 2+1 schedule than those receiving a 3+0 schedule for most serotypes. However, this does not lead to significant differences in the proportion of subjects with antibody levels above the correlate of efficacy and may therefore not have implications in terms of prevention of clinical disease.
- Immune responses to PCV10 and PCV13 are generally higher in Africa and Asia than in other regions. However, this finding may be confounded by the fact that children in these regions receive whole-cell rather than acellular pertussis vaccine concomitantly with PCV, the latter lacking the adjuvant effect associated with concomitant wP.
- For PCV13, antibody responses to most serotypes increase with age at first dose, interval between doses and age at last dose, producing differences in antibody concentrations post-primary series and post-dose 3. The effects of the age at immunization on the immune response appear to be less marked for PCV10.

Future analyses including more data will enable development of multivariable models to clarify the adjusted effects of each of these covariates on the immune response and assess if any of these findings differ across the two products. To date we see no evidence of one product performing differently from the other with respect to vaccine schedule choices, interval between doses or age at first dose.

3.3 Nasopharyngeal Carriage

Summary:

Impact on NP carriage of VT:

- Significant reduction in VT NP carriage was seen in both routine use settings and in clinical trials, and for both PCV10 and PCV13, for both 2+1 and 3+0 schedules (n=14 PCV10 and n=15 PCV13 studies). (Appendix A, Table 1)
- Reductions were observed within a year of routine vaccine use (e.g. in the first year of introduction 20-30% carriage compared to 60-80% prior to PCV introduction); however, maximum impact on carriage is not

[†] Among 41 study arms included, 35 had 8 weeks between doses 1 and 2, 4 had only 4 weeks and 2 had 4 months.

realized until after several years of use (e.g., after 5 years in one country, VT carriage was observed to be 1-2%).

- The rate of decline of NP carriage is affected by vaccine coverage, use of a booster, implementation of catch-up schedules, and pre-PCV prevalence of pneumococcal carriage, for example in communities with high HIV prevalence, (e.g., VT carriage was still 22% in Malawi after 5 years of PCV13 use).
- PCV13 impact was also assessed in countries that switched from PCV7 to PCV13 (n=10) and all observed a continued decline in PCV7-type carriage as well as a decline in carriage of the 6 serotypes in PCV13 that are not in PCV7
- No NP studies were conducted in countries that switched from a PCV7 to PCV10 (using a 3-dose schedule).

Impact on NP carriage of STs 3, 6A and 19A:

- Due to low baseline (i.e., pre-PCV introduction) carriage rates of the STs that are in PCV13 but not in PCV10 (i.e., STs 3, 6A and 19A), the ability to assess product specific impact on these serotypes was limited.
- No studies showed impact of PCV10 on ST 3 carriage, although ability to assess was limited by very low ST 3 carriage. Most studies evaluating PCV10 impact on serotype 6A observed small declines (e.g., 10-20%) but none were significant. Studies evaluating PCV10 impact on 19A had heterogeneous results, with some showing increases and some decreases. A study of a 3+1 schedule showed no impact of PCV10 on ST 19A after 5 years of use, which had risen after previous introduction of PCV7; due to low carriage of 19A only one study showed a significant change, and that study showed an increase in 19A.
- Studies evaluating impact of PCV13 on ST3 were insufficiently powered to evaluate an impact. All studies evaluating impact of PCV13 on serotype 6A observed decreases, and two were statistically significant. Similarly, all studies with measureable (>2%) carriage of serotype 19A observed decreases, including returning colonization rates back to pre-PCV rates in settings where ST 19A increased following PCV7 use. However, in a setting with high pneumococcal colonization (e.g. >80% pneumococcal carriage), ST 19A persisted at levels of 3% even after 5 years of PCV13 use (Malawi).

Regional representation of data:

- All WHO regions had data on colonization effects from 3-dose schedules for both PCV10 and PCV13 except PCV10 in the Middle East and PCV13 in Latin America (Appendix A, Table 1)

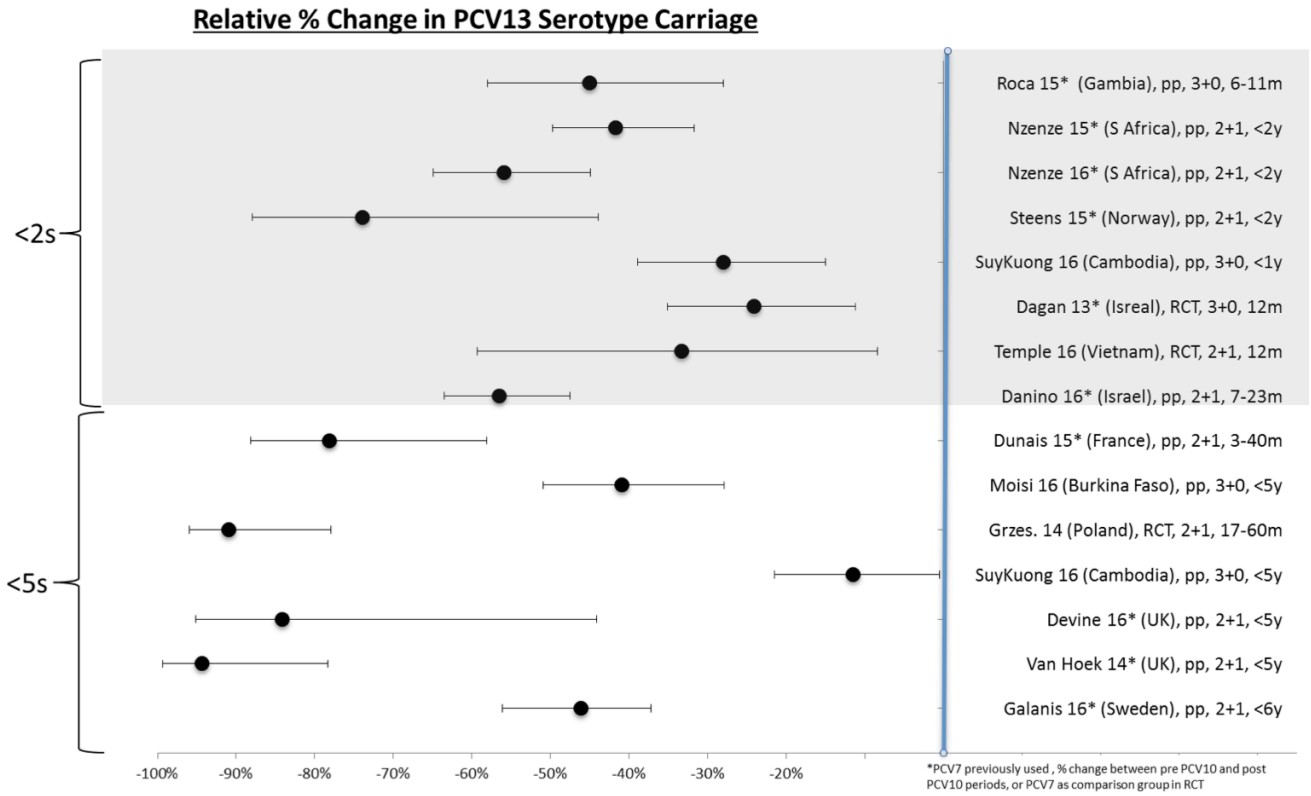
NP Carriage Findings

Impact on VT carriage

PCV13:

Thirty-four studies of 3-dose schedules were assessed; 15 assessed the impact of PCV on VT carriage and were included in further analyses, and all showed reductions (n=9 evaluated a 2+1 schedule and n=6 evaluated a 3+0 schedule). Appendix A Table 2-9 summarizes all studies reporting on VT, and serotype specific pneumococcal carriage. Appendix B Table 1 summarizes all studies that were assessed and not included.

Figure 1. Impact of PCV13 on VT NP carriage



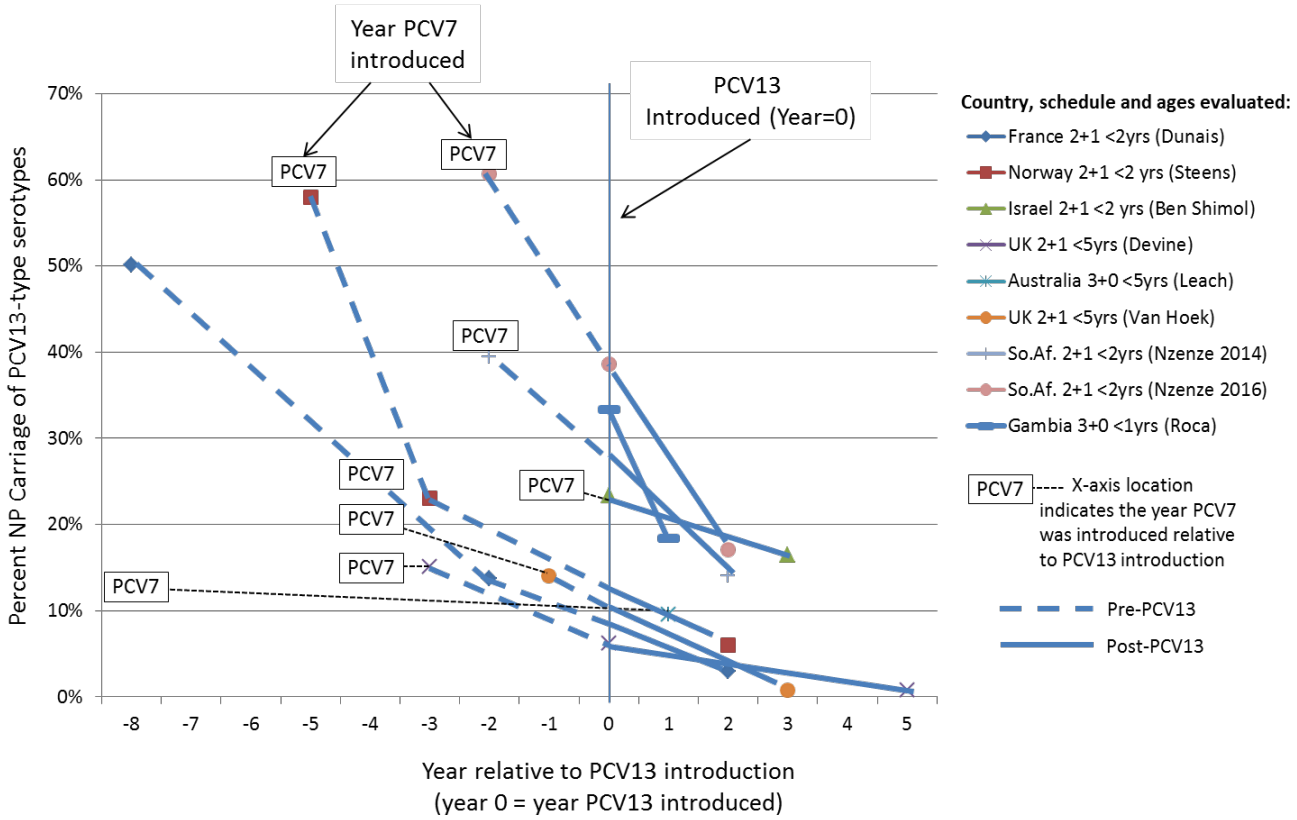
Three of the studies were RCTs [20, 25, 26]. Two were trials of 2+1 schedules that compared PCV13 to unvaccinated children; a large (91%) impact was observed in one (Polish) trial [25], and less impact (33%) was observed in the other (Vietnamese) [20]. A 3+0 trial conducted in Israel compared PCV13-vaccinated children to children who received PCV7 and found a significant 24% reduction in VT carriage (note that the magnitude of impact observed would have been greater if the comparison group had been unvaccinated) [26].

Twelve studies were conducted in settings of routine-use, nine in countries that switched from PCV7 to PCV13 (4 European, 3 African, 1 Middle Eastern and 1 Oceanian) and three in countries that introduced PCV13 *de novo* (2 African and 1 Asian) [27-39]. Of these three studies only two measured a *change* in VT carriage pre- to post-PCV13, both using 3+0 schedules, and significant reductions were seen in both: two years after PCV13 was introduced in Burkina Faso, a 40% reduction in VT carriage was observed in children <5 years of age (from 33% pre to 20% post-PCV13) [29]; a 20% reduction in VT carriage was seen after less than 1 year post introduction in children <2 years of age in Cambodia (from 53% to 42%) [28]. A third study of a 3+0 schedule in Malawi did not evaluate impact by assessing carriage both pre- and post-PCV but rather assessed carriage 5 years post-PCV13 introduction in a setting with high vaccine coverage (85%) that used a catch-up campaign in children <1 year. In that setting, which had high overall carriage as is found in most African studies (81% carried any pneumococcus), 22% of PCV13-vaccinated HIV-negative children 3-5 years old carried a vaccine strain indicating sustained carriage of vaccine-types long after introduction in high-risk populations [27]. It is unknown how high the VT carriage was prior to the introduction of PCV13.

Of the nine studies reporting VT carriage conducted in countries that switched from PCV7 to PCV13, seven evaluated a 2+1 schedule and two evaluated a 3+0 schedule. Years of PCV13 use ranged from 1 to 5 years and all observed reductions in VT carriage after introduction (**Figure 2**). Carriage of the additional 6 ST in PCV13

that are not in PCV7 was reported in 10 studies and all observed declines (measured as a group) as well as continued declines in PCV7-VT carriage.

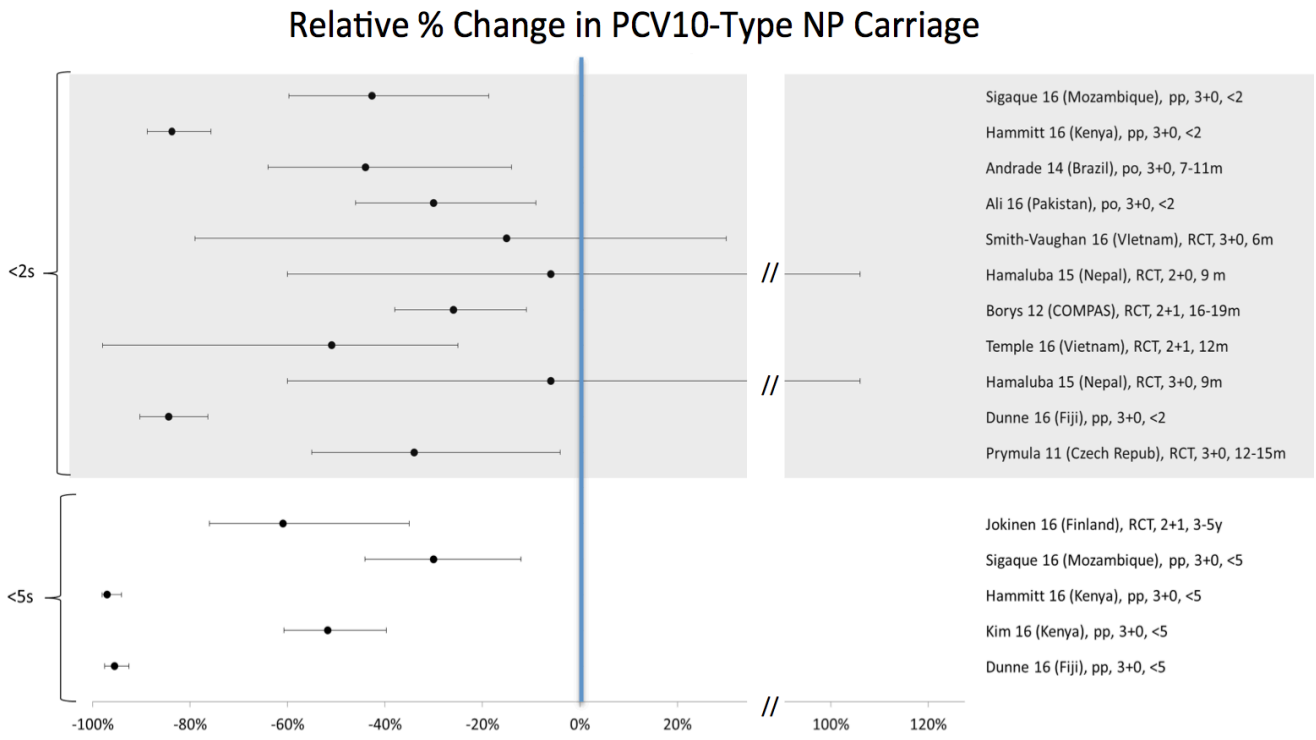
Figure 2. Change in PCV13-type NP carriage after PCV13 introduction in countries that switched from PCV7 to PCV13



PCV10:

Twenty-eight studies of 3-dose schedules were assessed; 14 evaluated VT carriage following PCV10 immunization and were included in the analyses that follow and all showed reductions (n=3 evaluated a 2+1 schedule and n=11 evaluated a 3+0 schedule). Appendix A Table 2-9 summarizes all studies reporting impact of PCV10 on VT, and serotype specific pneumococcal carriage. Appendix B Table 1 summarizes all studies that were assessed and not included.

Figure 3. Impact of PCV10 on VT NP carriage



Seven of these studies were clinical trials (n=3 evaluated a 2+1 schedule and n=4 a 3+0 schedule, plus one trial also evaluated carriage pre-booster after a 2-dose primary series), but none of the clinical trials were conducted in settings with high VT carriage (all had 9-16% VT carriage in the unvaccinated control group) [20, 40-46]. Lower carriage was observed in all PCV10-vaccinated children compared to unvaccinated controls, although none was statistically significant due to the low VT carriage in the controls, the aggregated evidence across trials suggests PCV10 does reduce carriage against VT serotypes, however a formal meta-analysis has not yet been conducted. An additional 4 trials evaluated 3+1 schedules, but these were also in low carriage settings and results were similar [41-44].

Of the 6 studies that evaluated 3-dose PCV10 impact in routine-use, all were conducted in countries that used PCV10 *de novo* (i.e. did not first use PCV7) [47-53]. Studies were conducted in Africa, South America, Asia and Oceania and all used a 3+0 schedule. All observed a decline in VT carriage, as a group, in children who received PCV10 compared to children of a similar age who did not. VT carriage in these studies before PCV10 introduction was low to moderate, ranging from 16% (Fiji) [48, 49] to 40% (Kenya) [47]. Years of PCV10 use assessed ranged from 1 to 4 years and two studies were in the context of a catch-up program. The two studies (Fiji and Kenya) with the largest impact (>80% reduction in VT carriage in children <2 years of age) had the largest number of years of PCV10 use (3-4 years) and the Kenya study also implemented PCV10 catch-up immunization for children <5 years at the time of vaccine introduction. Decline in VT carriage in the other studies ranged from 30-52% after predominantly 1-2 years of PCV10 use. A 7th study, in Ethiopia, assessed the distribution of pneumococcal isolates before (age 6 weeks) and after (age 9 months) vaccination and found that a lower proportion of isolates carried were VT after vaccination (11% at age 9 months compared to 20% at age 6 weeks), suggesting an impact of the vaccine since VT carriage generally increases with age during this period [54]. However, because there was no unvaccinated comparison group, changes in ST distribution due to natural acquired immunity cannot be ruled out in this study.

Only one study assessed the impact of PCV10 on VT carriage following 2-priming doses [52]; a significant 36% decline in vaccine-type carriage prior to the booster dose was observed.

Head-to-head trials of PCV10 vs. PCV13:
Although this review was not intended to directly compare products, two trials compared PCV10 to PCV13, but VT carriage was low in groups that received PCV10 and those that received PCV13 and no meaningful differences were observed (PCV13-type was 13.5% in PCV10 group versus 11.6% in PCV13 group in Vietnam trial measured 12 months after a 2+1 schedule, and 24% and 23%, respectively, in PNG trial measured 9 months after a 3+0 schedule) [20, 21]. The PNG trial also assessed impact on NTHi, the organism from which one of the carrier proteins in PCV10 is derived: infants were frequently co-colonized with NTHi with no significant difference between PCV10 (54%) and PCV13 (62%) immunized infants [21].

3.4 Pneumonia

Summary

- There is no systematic evidence that one product has greater impact on pneumonia outcomes than another; the range of impact was broad (-68% to -13% for clinical pneumonia and -66% to -34% for CXR-confirmed pneumonia) and variable within outcomes and product
- Cross study comparisons are confounded by substantial differences between studies in the age groups studied, the case definitions, duration of PCV use, study design, analytic approaches and the natural secular trends in pneumonia hospitalization rates.

Impact on all-cause pneumonia case definitions

- 32 studies evaluating 3-dose schedules (2+1 or 3+0) using PCV10 or PCV13 were available for review (one clinical trial [55], six case-control studies [56-61], and 28 pre/post observational studies [56, 61-86] (Appendix A, Tables 11 -14).

Impact on clinical and CXR-confirmed pneumonia:

- The review found evidence of impact from both PCV10 and PCV13 for clinical and CXR-confirmed pneumonia, both outcomes that are not specific to pneumococcus; the VE is the net effect of the proportion of cases that are due to pneumococcus and among those, the proportion that are due to vaccine types or cross-reacting types as well as serotype specific VE of each product in that population.

Impact on pneumococcal pneumonia

- Evidence of impact for pneumococcal pneumonia and all-cause empyema was only available for PCV13 use and the evidence regarding impact on empyema was mixed. . There were no studies that evaluated PCV10 use on pneumococcal pneumonia or all-cause empyema.

Regional representation of data

- The majority of studies were from Europe (EUR) (n=12) [55, 58, 60, 67, 69, 72, 73, 75, 79, 80, 83, 84] or Latin America (AMR) (n=10) [62, 63, 65, 66, 68, 74, 77, 78, 81, 82]; 8 studies were from Africa (AFR) [56, 59, 61, 64, 76, 85-87] and two studies from Oceania (WPR), both from Fiji [70, 71]. There were no studies identified from Asia (EMR, SEAR) or North America (AMR); however, the review was limited to 3-dose schedules, excluding evidence from countries using a 3+1 schedule.
- There were no studies identified from Asia (EMR, SEAR) or North America (AMR); however, the review was limited to 3-dose schedules, excluding evidence from countries using a 3+1 schedule.

Pneumonia Findings

Clinical trials

There was one RCT evaluating either PCV10 or PCV13 in a 3-dose schedule against pneumonia [55]. The Finnish study evaluated PCV10 using a 2+1 schedule and showed 28% (6% - 45%) efficacy against clinical pneumonia and 43% (19% - 61%) efficacy against chest x-ray consolidated pneumonia.

Case-control studies

All six case-control studies evaluated PCV13 [56, 58-61, 87]; there were no such studies that evaluated PCV10. Four of six studies were from Africa (Table 5). Three studies evaluated 2+1 schedules and VE ranged from 20.1% to 40.6% for ≥ 2 doses against radiologically confirmed pneumonia and 68% against bacteremic pneumococcal pneumonia; all measures of these two outcomes were statistically significant with the exception of the VE for a 2+1 schedule on radiologically-confirmed pneumonia compared to hospital controls in children in South Africa [58-60]. Three studies evaluated 3+0 schedules, all from Africa [56, 61, 87]. The VE for a 3+0 schedule ranged from 58% to 63% against radiologically confirmed pneumonia, but none were significant. The study in Togo found 80% VE for a 3+0 schedule against severe pneumonia, but this was not statistically significant [87]. The study in Rwanda showed 54% VE against severe pneumonia, which was statistically significant [61].

Pre/post observational studies, PCV10

Clinical pneumonia (Figure 4): Two studies (Iceland and Sweden) evaluated 2+1 schedules of PCV10 against clinical pneumonia in children <2 years with reductions ranging from 21% to 36% compared to the pre-PCV period [67, 83]; however, the study in Sweden showed a 3% increase in clinical pneumonia in the period after PCV7 implementation, but prior to the switch to PCV10 [67]. Three studies (two from Fiji and one from Kenya) evaluated 3+0 schedules with changes in clinical pneumonia incidence ranging from reductions of 13.3% to 32% compared to the pre-PCV period; all reductions were statistically significant [70, 71, 76].

Radiological pneumonia (Figure 6): There was one study (Kenya) using a 3+0 schedule that showed a statistically significant reduction of 48% in radiologically confirmed pneumonia.

Pneumococcal Pneumonia and empyema: No studies evaluated PCV10 against either endpoint

Pre/post observational studies, PCV13

Clinical pneumonia (Figure 4 and 5): There were 9 studies using a 2+1 schedule that evaluated a clinical pneumonia endpoint and prior PCV7 varied [63, 67, 68, 73, 74, 77, 80, 82, 84]. For children <2 years, reductions ranged from 27.3% to 68.4% compared to a pre-PCV baseline period and all reductions were statistically significant. Compared to the PCV7 period, changes in incidence in children <2 years ranged from +8% to -58%, with statistical significance varying. For children <5 years, reductions ranged from 27.8% to 49.7% compared to a pre-PCV baseline period and all reductions were statistically significant. Changes in incidence ranged from +24% to -60.5% compared to the PCV7 period and all measures were statistically significant. One study from Malawi evaluated a 3+0 schedule on clinical pneumonia and found a non-significant 47% increase in WHO-defined clinical pneumonia, but a 47% significant decrease in hypoxemic pneumonia [86]. This study compared disease incidence two years after PCV13 implementation to the first six months after PCV13 implementation with no true comparison to pre-PCV introduction, but was included due to paucity of data from Africa.

Radiological pneumonia (Figure 6 and 7): There were 7 studies using a 2+1 schedule [62, 65, 69, 72, 78, 79, 82] and one study [66] using a 3+0 schedule that evaluated a radiologically-confirmed pneumonia endpoint. For 2+1 schedules, in children <2 years, reductions ranged from 34% to 66.2% and all reductions were significant. Compared to the PCV7 period, reductions ranged from 30% to 85% and significance varied. The study from Uruguay with 85% reduction had one year of baseline data, which occurred during PCV7 use [78]. In children

<5 years, changes in incidence ranged from a 15% increase to a 53% decrease; all reductions were significant. Compared to the PCV7 period, reductions ranged from 36% to 40%; all reductions were significant. For the study that evaluated a 3+0 schedule, significant reductions (range: 26% to 33%) were seen in all age groups.

Pneumococcal pneumonia: One study evaluated pneumococcal pneumonia; the study from Argentina evaluated a 2+1 schedule and found a 72.1% reduction in disease in children <5 years compared to the pre-PCV baseline period [62].[62].

Empyema: Three studies evaluated 2+1 schedules against all-cause empyema; VE estimates and significance varied [65, 80, 84]. No studies evaluated 3+0 schedules against empyema

Pre/post observational studies, PCV7/PCV13

Clinical Pneumonia (Figure 4 and 5): There were 6 studies that evaluated the impact of PCV7 introduction followed by a switch to PCV13 use [56, 61, 64, 75, 81, 85]. Two studies evaluated PCV7/PCV13 impact using 2+1 schedules against clinical pneumonia [64, 75]; reductions ranged from 15% to 44% in children <5 years. Two studies, both from Africa, evaluated a 3+0 schedule on clinical pneumonia; one study from The Gambia showed significant reductions in hypoxic pneumonia across all age groups (range: 56% to 72%) [56]. The other study, from Rwanda, found a 70% decrease in severe pneumonia and a 7% increase in clinical pneumonia; however, this measure is only one year after PCV13 implementation and was included due to paucity of data from Africa [61].

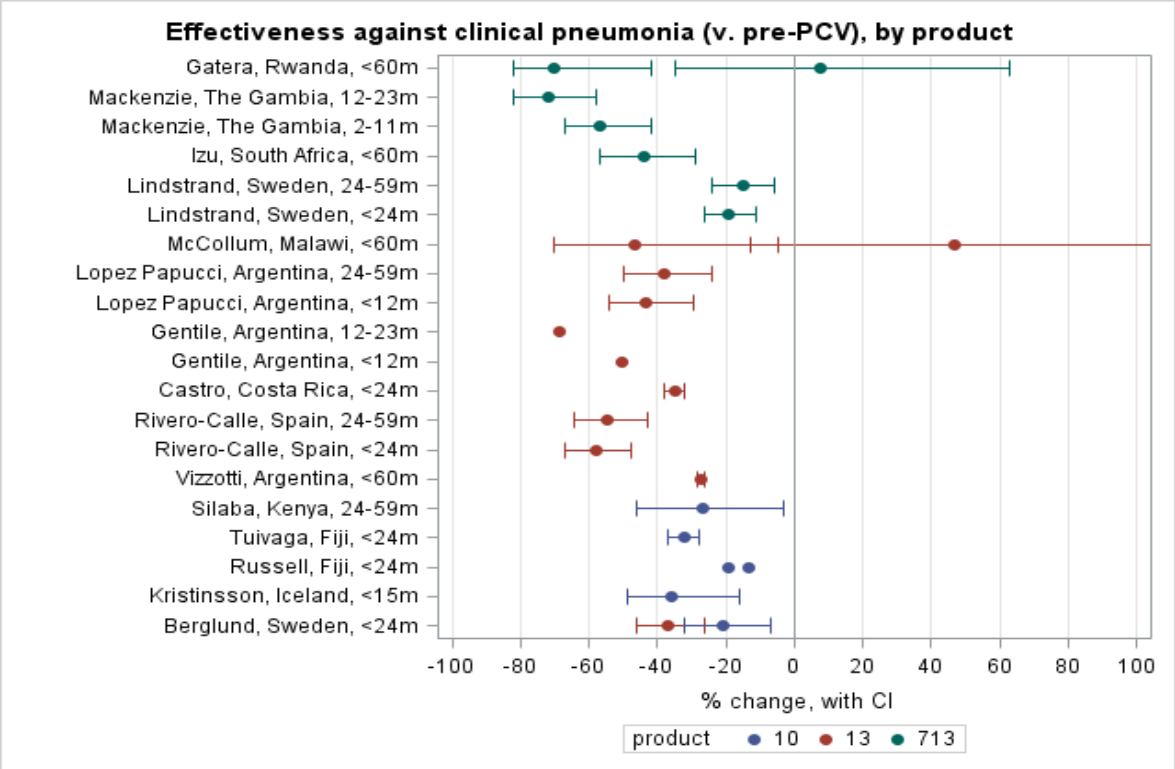
Radiological pneumonia and pneumococcal pneumonia (Figure 6 and 7): Two studies evaluated PCV7/PCV13 against radiologically-confirmed and pneumococcal pneumonia [56, 81]. The study using a 2+1 schedule found a 78% and 97% significant reduction among children <14 years for pneumococcal pneumonia and empyema, respectively [81]. The study using a 2+1 schedule found a 78% and 97% significant reduction in children <14 years for radiologically-confirmed and pneumococcal pneumonia, respectively [81]. The study evaluating a 3+0 schedule found significant reductions ranging from 22% to 29% for radiologically-confirmed pneumonia and 57% to 75% for pneumococcal pneumonia in children <5 years [56].

Empyema: Two studies evaluated PCV7/PCV13 using a 2+1 schedule against empyema [75, 85]. One study found a 50% significant reduction [85]. The other study found a 68% to 78% increase, but these were not statistically significant [75].

Serotype-specific data

This review did not identify any studies that reported the impact of PCV10 or PCV13 on serotype-specific pneumococcal pneumonia.

Figure 4. % Change in incidence of clinical pneumonia (post-PCV10, PCV13, or PCV7 and 13 v. pre-PCV), by product



*Russell study has 2 data points for 2 different indigenous groups; McCollum study is for clinical pneumonia and hypoxic pneumonia

Figure 5. % Change in incidence of clinical pneumonia (post-PCV10, PCV13, or PCV7 and 13 v. pre-PCV), by product

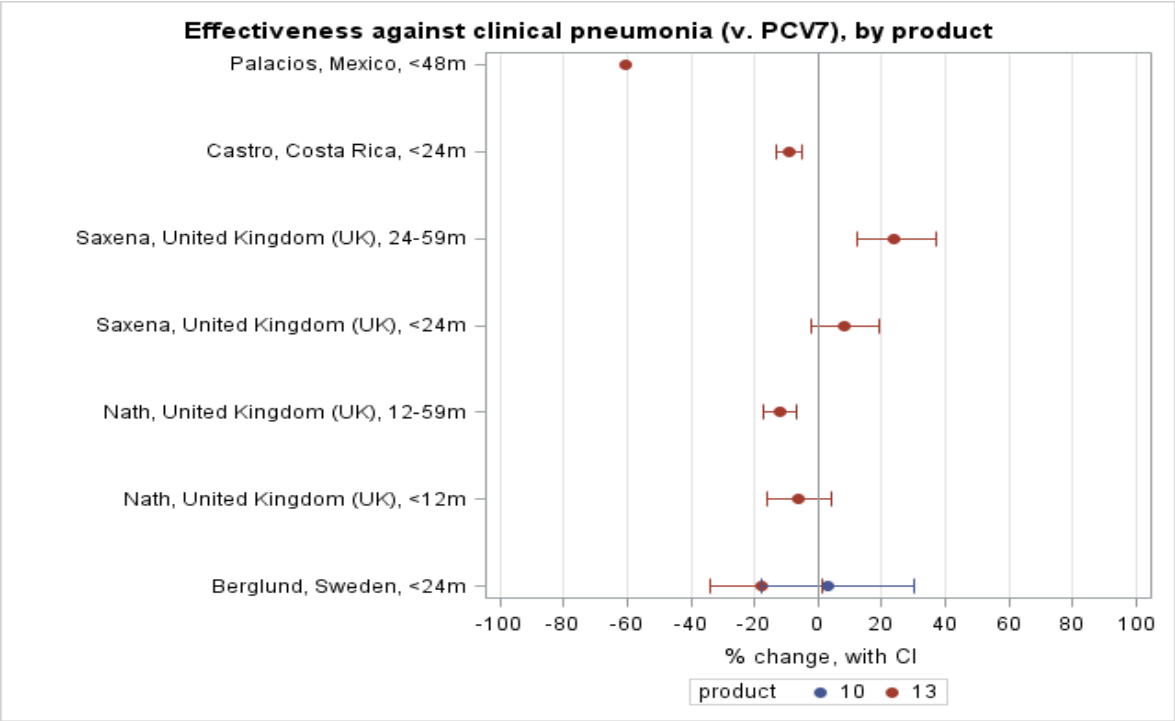


Figure 6. % Change in incidence of radiologically-confirmed pneumonia (post-PCV10 or PCV13 v. pre-PCV), by product

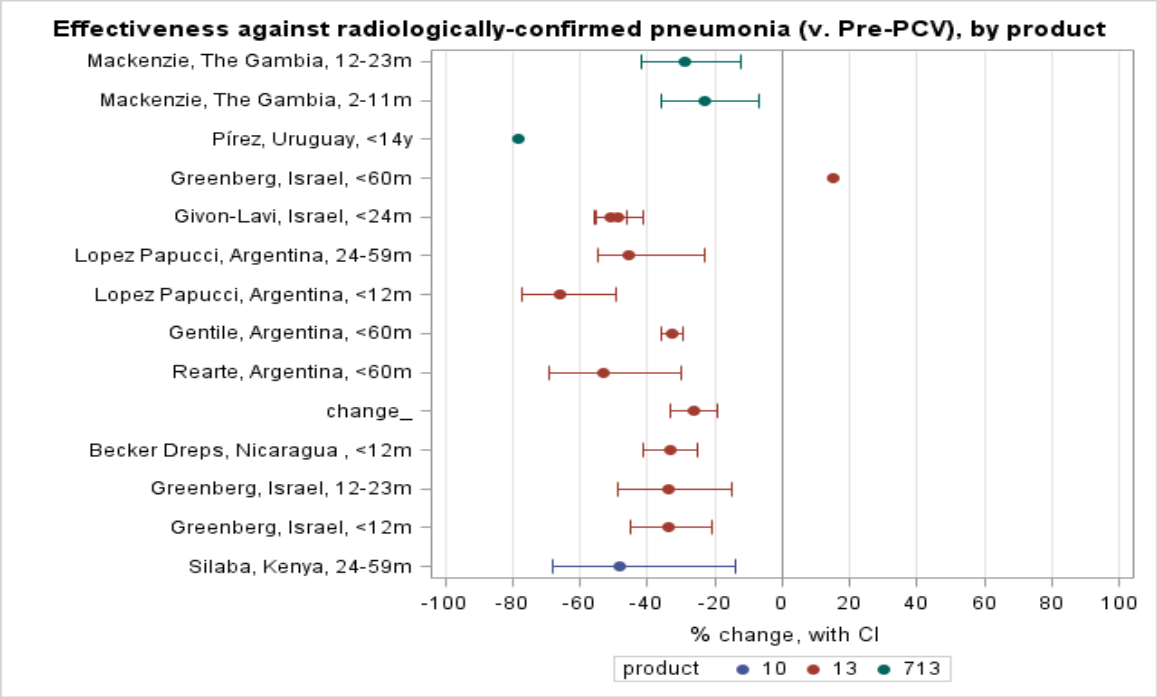
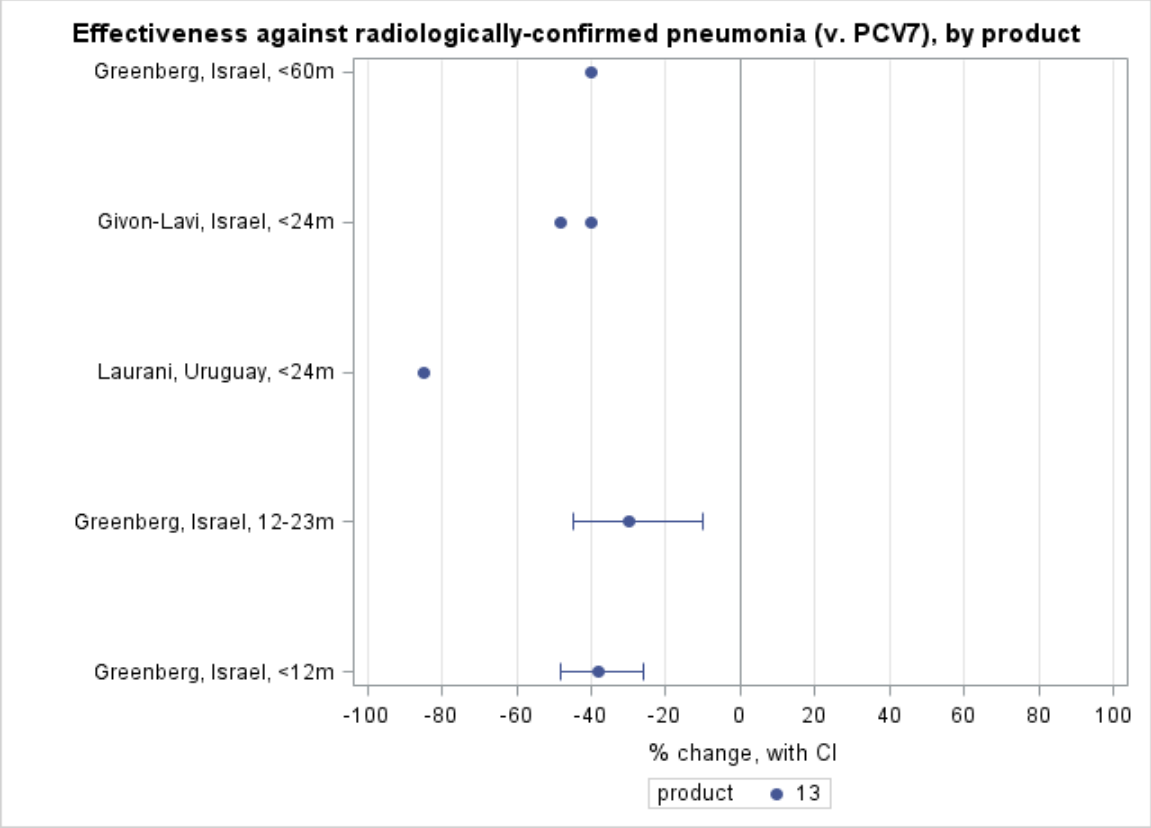


Figure 7. % Change in incidence of radiologically-confirmed pneumonia (post-PCV-10 or -13 v. PCV7 period), by product



* In the Givon-Lavi study, the 2 data points are for Jewish and Bedouin children

3.5 Invasive Pneumococcal Disease

Summary

- There are no studies with head-to-head comparisons of PCV10 and PCV13 or schedules (2+1 vs. 3+0)
- Comparison of impact of PCV10 and PCV13 on VT IPD observed across studies should be done with caution due to differences in duration of PCV7/PCV10/PCV13 use, age groups studied, vaccine coverage, and analytic methods used
- In countries that have switched products (from PCV7 to PCV10/PCV13), the magnitude of change in VT IPD should not be attributed entirely to PCV10/13

Impact on VT IPD

- Significant reduction in IPD caused by vaccine serotypes were observed following PCV10 and PCV13 introduction for both 2+1 and 3+0 schedules
- In countries that have switched from PCV7 to PCV13, PCV13/non-PCV7 type IPD declined from 57 to 100%, with reductions measured 1 to 4 years post PCV13 introduction
- Vaccine-type IPD declined from 47 to 87% in countries introducing PCV10 following, with impact measured 1 to 3 years post introduction.
- VE studies demonstrated that both PCV10 and PCV13 are highly effective in preventing VT IPD; one clinical trial demonstrated a 92% efficacy of PCV10 given on a 2+1 schedule
- There was no evidence that magnitude of reduction in VT IPD differs between products

Impact on IPD caused by ST 3, 6A, and 19A

- PCV13 is effective in reducing type 19A and 6A disease; no consistent impact on ST 3 disease has been demonstrated, with most studies showing no impact/lack of VE of PCV13 against ST 3 IPD
- Very limited data are available on PCV10 impact on IPD caused by these three serotypes
- PCV10 appears effective in reducing type 19A disease; no data on serotypes 6A and 3

Regional representation of data

- This review identified 39 studies evaluating impact of PCV10 or PCV13 on IPD cause by vaccine serotypes using 3-dose schedules (2+1 or 3+0): one clinical trial, nine case-control studies[56, 58-60, 87][56, 58-60, 87][56, 58-60, 87][56, 58-60, 87][56, 58-60, 87][56, 58-60, 87]56, 58-60, 87][56, 58-60, 87][56, 58-60, 87][56, 58-60, 87] [56, 57, 58-61, 62, 86, 87] and 29 pre/post observational studies and 29 pre/post observational studies.
- The majority of studies were from Europe (n=20), 7 from Africa, 4 from Latin America, 3 studies from each Australia/Oceania and North America, and 2 from Asia.
- Limited evidence on PCV10 compared to PCV13 was identified thus far; however, we anticipate more data on PCV10 in the coming years.
- While the review was limited to 3-dose schedules, which excluded many countries using a 3+1 schedule, due to sparse data on PCV10, we included studies conducted in setting of 3+1 PCV10 schedule if serotype-specific information was reported.

IPD Findings:

There were 42 studies available on PCV10 or PCV13 using a 3-dose schedule with an IPD outcome. The number of studies by study type, region and PCV product is provided in Appendix A Table 16.

PCV10

Clinical trials

A cluster randomized double-blind trial of PCV10 in Finland demonstrated a 92% (95%CI 58–100) efficacy for VT IPD using a 2+1 schedule among children <19 month old [88]. An extended follow up of the disease register for this trial demonstrated an 80% (95%CI 7-97) efficacy for a combined 2+1/3+1 schedule [89].

Case-control studies

Four case-control studies have been conducted in a setting of 3-dose schedule evaluated the VE of PCV10 against vaccine-type IPD. VE of PCV10 against PCV10-type IPD ranged from 77 to 97% for children receiving ≥1 dose. Three of these studies were conducted in a setting of a 2+1 national schedule (Finland, Netherland, and Canada) [90-92], and one study (Pakistan) measured the VE in a setting of a 3+0 schedule [93]. None of these case-control studies measured VE specifically for children receiving a 2+1 or 3+0 schedule. A case-control study conducted in Brazil in a setting of 3+1 schedule, estimated VE of 84% against VT IPD for children receiving up-to-date for age schedules [94].

VE against types 3, 6A, and 19A

Four case-control studies evaluated VE of PCV10 against individual STs. The VE of ≥1 dose against type 19A IPD ranged from 61 to 82%, although the estimates were not statistically significant in studies from Netherlands and Brazil (indirect cohort method) [92, 94]. The VE of PCV10 against ST 3 and 6A IPD was measured only in one study (Brazil), with non-significant VE of 8% and 15%, respectively [94].

Pre/post observational studies

Significant reductions in IPD caused by vaccine serotypes were observed following PCV10 introduction. In countries introducing PCV10 following PCV7 using a 2+1 PCV10 schedule, vaccine-type IPD declined from 77 to 96% compared to the PCV7 period, with impact measured 2 to 4 years post PCV10 introduction (Canada and Netherlands) [95, 96]. In Finland and Iceland, an 87% and 93% reduction in PCV10-type IPD was observed 3 and 5 years post PCV10 introduction using a 2+1 schedule [97-99]. A 94% reduction in PCV10 type IPD was observed in one study (Kilifi, Kenya) four years after PCV10 introduction on a 3+0 schedule [100, 101]. A 97% reduction in PCV10 type IPD was observed in Brazil following 2 years of PCV10 use on 3+1 schedule [102].

Impact on types 3, 6A, and 19A

Two studies reported reductions in IPD caused by type 19A following PCV7/PCV10 introduction: a 36% reduction was reported in Canada and a 62% reduction in Netherlands 2 and 4 years post introduction using a 2+1 schedule, respectively [95, 96]. In Finland, a 93% reduction in type 19A disease and a 100% reduction in type 6A disease was reported 5 years post PCV10 introduction [103]. Additional serotype-specific data from countries using PCV10 are pending.

PCV13

Case-control studies

Five case-control studies have been conducted in a setting of 3-dose national schedule evaluated the VE of PCV13 against vaccine-type IPD. The VE of PCV13 against PCV13-type IPD ranged from 64 to 86% for children receiving ≥1 doses in three studies with 2+1 national schedule (Dominican Republic, UK, and Canada) [90, 104-106]. A study from South Africa estimated the VE for ≥2 doses at 85% [107]. Only one study (UK) measured the VE of a 2+1 schedule (79%) [104, 105]. The same study estimated VE against PCV13/non-PCV7 serotype IPD at 73% for children receiving ≥1 or ≥2 doses. A cohort study in Australia estimated the VE of PCV13 3+0 schedule against PCV7-type IPD at 92% [108]. A case-control study conducted in Spain in a setting of 3+1 schedule estimated VE of 96% against PCV13 IPD and 95% against PCV13/non-PCV7 types for children receiving ≥1 doses [109].

VE against types 3, 6A, and 19A

Three case-control studies evaluated VE of PCV13 against individual STs. The VE of ≥1 dose against type 19A IPD was 74% (Canada) and ranged from 67 to 94% for ≥2 doses (UK and South Africa) [90, 104, 105]. One study (UK) reported no significant VE of PCV13 against type 3 IPD and 98% VE against type 6A [105].

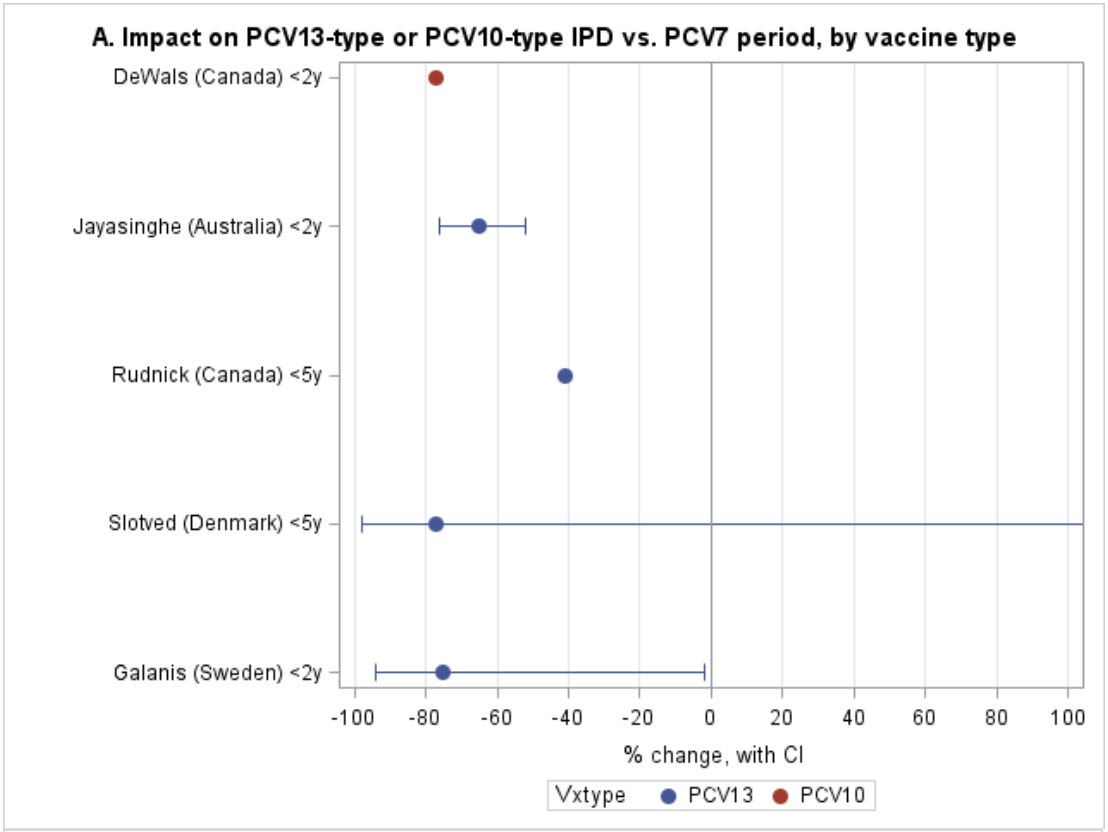
Pre/post observational studies

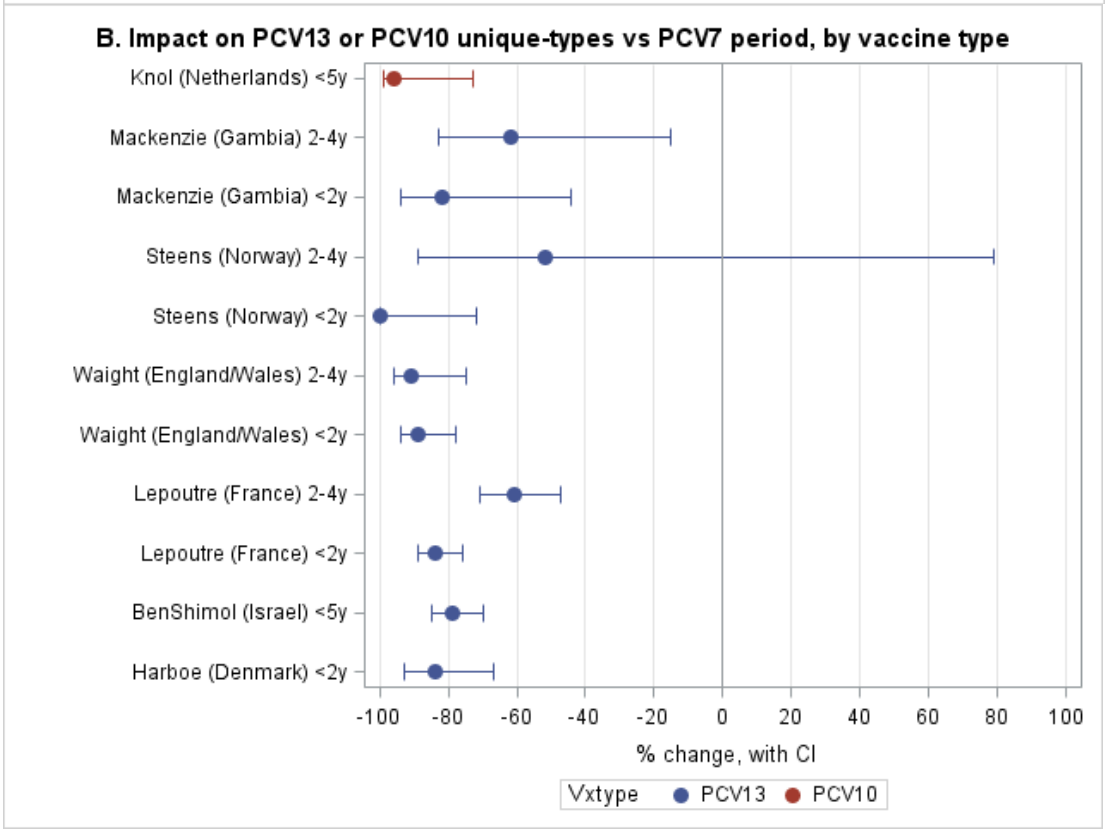
Significant reductions in IPD caused by vaccine serotypes were observed following PCV13 introduction. PCV13/non-PCV7 type IPD declined from 57 to 100% in countries introducing PCV13 following PCV7, on a 2+1 schedule, with reductions measured 1 to 4 years post PCV13 introduction (Appendix A, Table 18). In Australia, in a setting of a 3+0 PCV13 schedule, a 65% reduction in PCV13 type IPD was observed one year post-introduction [110]. In Gambia, 82% reduction in PCV13/non-PCV7 type IPD was reported 3 years post-PCV13 introduction using a 3+0 schedule [111]. Overall, reductions in PCV13/non-PCV7 type disease of greater magnitude were reported when studies reported comparisons to PCV7 period as baseline vs. when comparisons to pre-PCV7 period were made; this was due to increases in PCV13 unique serotypes reported post PCV7 introduction. There were no pre- post-observational, 3-dose studies reporting the impact of PCV13 without prior use of PCV7.

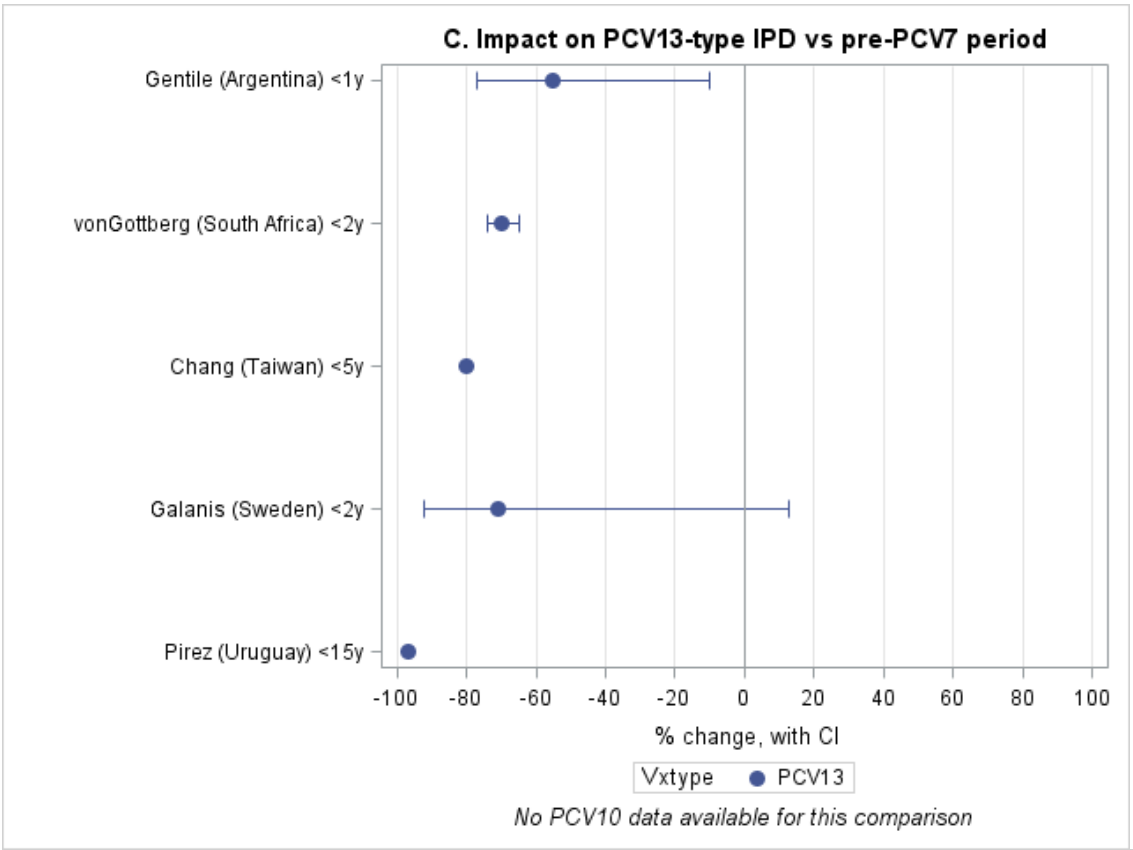
Impact on types 3, 6A, and 19A

In countries introducing PCV13 following PCV7 on a 2+1 schedule, six studies reported impact on serotype-specific IPD. Significant reductions in type 19A disease, ranging from 69 to 91% were reported in four studies (Israel, France, England, and South Africa) with 1 to 4 years post-introduction [112-115]. One study in Denmark reported no changes in type 19A disease compared to PCV7 period 3 years post PCV13 introduction, with disease incidence increasing during PCV7 period compared to pre-PCV period and then declining to pre-PCV7 levels [116]. No changes in type 3 IPD 1 to 3 years post introduction were reported in three studies (Denmark, Israel, and South Africa). Two studies reported significant reductions of 85% and 68% (France and England) in type 3 disease 1 and 4 years, respectively, post PCV13 introduction. Significant reductions in type 6A disease ranging from 85% to 100% were reported in three studies (South Africa, Israel, and England) post-PCV13 compared to pre PCV period, although most of these reductions should be attributed to PCV7 impact. Only one study (Australia) reported impact of PCV13 on type 19A disease in a setting of 3+0 schedule (77% reduction in type 19A IPD) [110].

Figure 8 (A-D). Vaccine impact in countries transitioned from PCV7 to PCV10 or PCV13






C. Impact on PCV13-type IPD vs pre-PCV7 period
Gentile (Argentina) <1y
vonGottberg (South Africa) <2y
Chang (Taiwan) <5y
Galanis (Sweden) <2y
Pirez (Uruguay) <15y
-100 -80 -60 -40 -20 0 20 40 60 80 100
% change, with CI
Vxtype PCV13
No PCV10 data available for this comparison

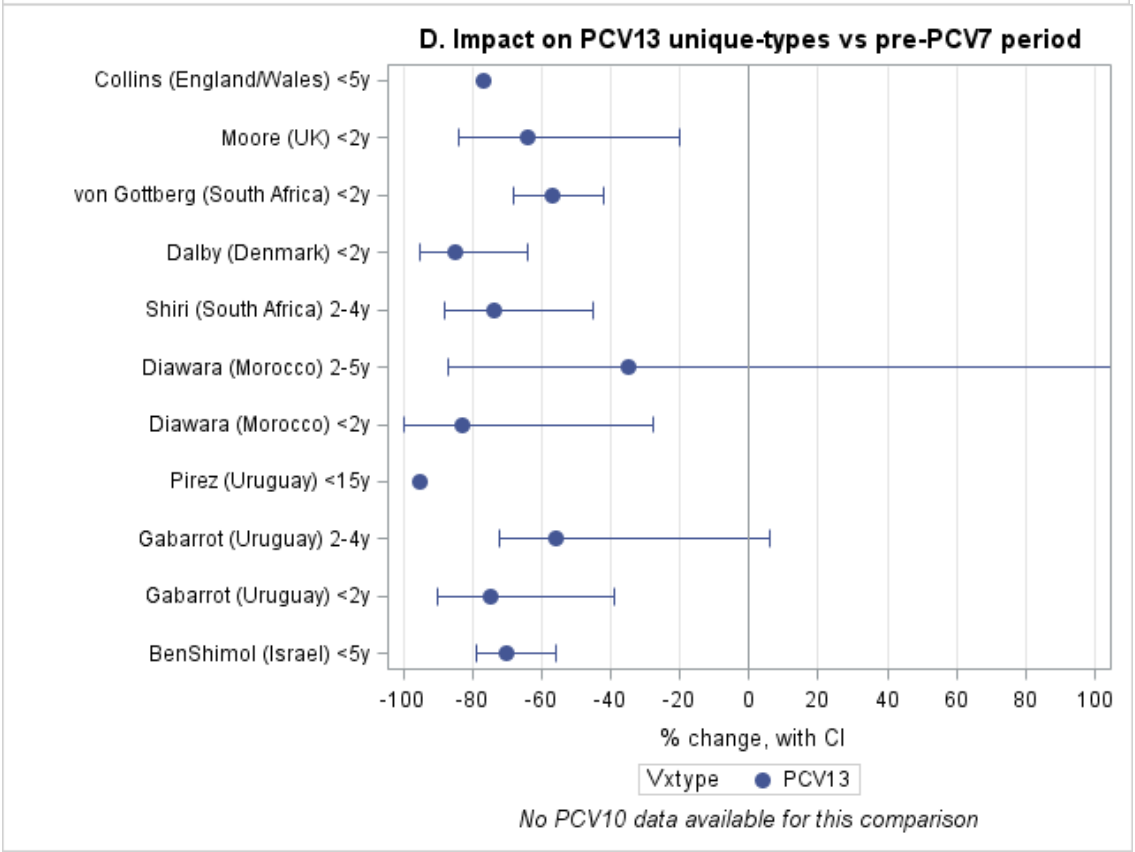
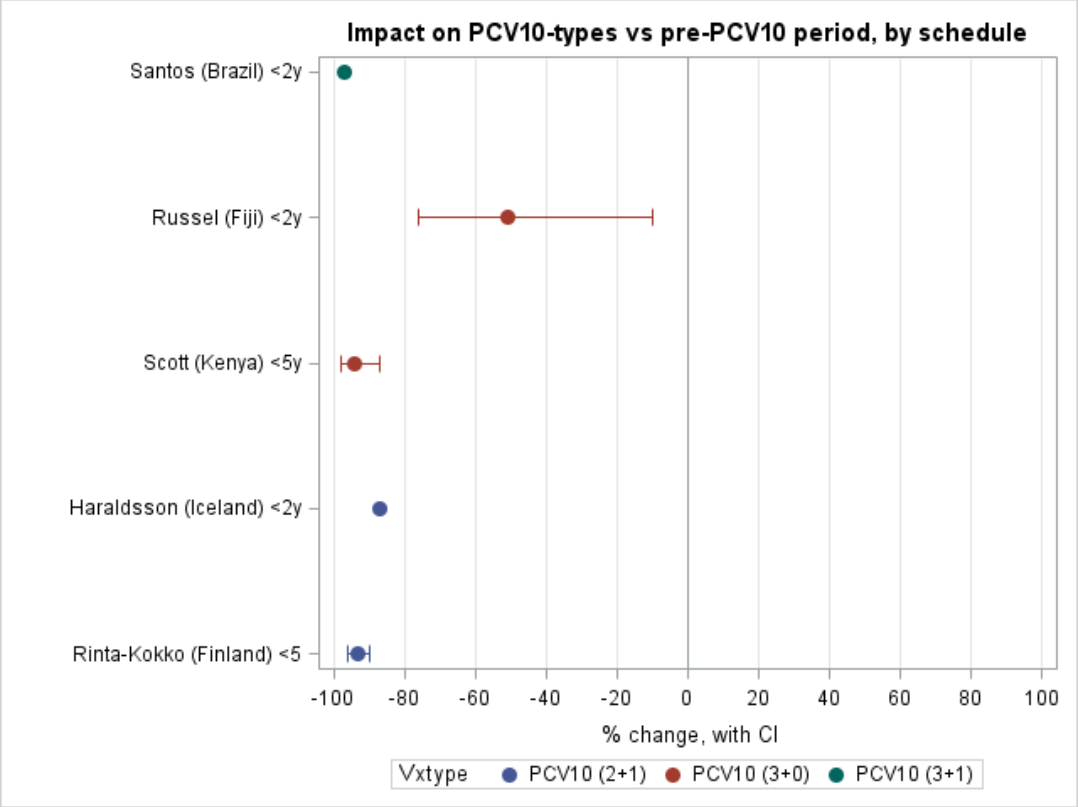

D. Impact on PCV13 unique-types vs pre-PCV7 period
Collins (England/Wales) <5y
Moore (UK) <2y
von Gottberg (South Africa) <2y
Dalby (Denmark) <2y
Shiri (South Africa) 2-4y
Diawara (Morocco) 2-5y
Diawara (Morocco) <2y
Pirez (Uruguay) <15y
Gabarrot (Uruguay) 2-4y
Gabarrot (Uruguay) <2y
BenShimol (Israel) <5y
-100 -80 -60 -40 -20 0 20 40 60 80 100
% change, with CI
Vxtype PCV13
No PCV10 data available for this comparison

Figure 9. Vaccine impact in countries introducing PCV10 without prior PCV7 use



3.6 Mortality

Summary

- Data on PCV impact on mortality following PCV10 or PCV13 introduction in a 3-dose schedule are very limited in number (9 studies) and with a few exceptions are largely from countries with low infant and child mortality
- Quantitative comparisons across studies should not be interpreted to mean there are true differences in impact on mortality; these observational studies are highly heterogeneous for factors that themselves would impact on mortality (study method, analysis approach, years of PCV use, age strata, outcome, secular trends)
- Nevertheless, most published studies demonstrate an impact of PCV on mortality in children; it is unknown how many studies have been conducted that found no impact and did not publish the findings
- No differences in impact on mortality, by product, are evident from these data

Mortality changes

- Mortality rates and absolute numbers of death are used as outcomes in studies
- The range of observed reduction, across outcomes of all-cause mortality, IPD mortality and pneumonia mortality, is from 6% - 56%

CFR changes

- Three studies reported the change in case fatality ratio for severe/very severe pneumonia [70], pneumonia hospitalizations [117], and, all-cause pneumonia [118].

- Reductions ranged from 41%-57%, which could reflect the lower fraction of bacterial disease among these cases, which are known to have a higher CFR than non-bacterial cases

Regional representativeness

- Studies are available from EUR (n=1 for each of PCV10 and PCV13), AFR (n=1 for each of PCV10 and PCV13), AMR (n=2 for each of PCV10 and PCV13) and WPR (n=1 for PCV10)
- No studies of mortality for PCV10 or PCV13 for 3-dose schedules are available from SEAR or EMR

Mortality Findings

Evaluating the impact of PCV10 and PCV13 on mortality is of high priority for policy decision-makers but are among the most technically difficult to conduct because of the relative rarity of mortal outcomes. Furthermore there are many other interventions that can affect the mortality rate absent PCV, and these confound the conclusions from mortality analyses. All studies are time-series studies looking at mortality rates, or death counts before and after PCV introduction, leaving these highly susceptible to confounding given that mortality is very non-specific for vaccine serotype pneumococcus.

The quantitative estimates of change in mortality from the observational studies should therefore be contextualized within what was observed in the course of highly controlled randomized trials, where confounding is substantially lessened through the randomization and contemporaneous evaluation of a control group. The PCV9 trial in the Gambia with 3+0 dosing schedule concluded that there was a 16% reduction in all-cause mortality for infants 3-29 months of age with the use of PCV9 [119]. This allows some benchmarking of the lower bound for changes that might be expected in other settings.

There are nine studies (n=5 PCV10; n=4 PCV13) with mortality outcome following the use of PCV10 or PCV13 in a 3-dose schedule [66, 86, 118, 120-125]. The outcomes include mortality rates, mortality cases and changes in case fatality ratio. These are assessed according to all-cause mortality, IPD mortality, and pneumonia mortality (Appendix A, Table 23). The observed reductions are not all statistically significant and their magnitude in some cases is surprisingly large, suggesting either that pneumococcus is a much greater contributor to mortality than evidenced by other work, that herd effects are contributing to the overall measured benefit, or that the studies suffer from some of the methodological issues just described.

Regardless, most published studies have demonstrated an impact on mortality following the routine use of PCV, including use of both products, in a range of high and low-income countries, across geographies.

3.7 Indirect Effects of PCVs

Summary

Most of the data on indirect effects of PCV10/13 is on IPD (n=22 studies), with limited data on NP carriage (n=3 studies) and pneumonia (n=6 studies).

VT NP Colonization

- There are limited but consistent data on the indirect effects of PCV10 (n=2 studies) or PCV13 (n=1 study) on VT NP carriage at least 3 years after vaccine introduction.
- The data indicate a reduction in VT carriage, with relative reduction ranging from 35% to 100% in persons of various ages.

Pneumonia

- Six studies report on pneumonia incidence in groups not directly vaccinated.

- In general, as the pneumonia outcomes become more specific for pneumococcal aetiology, there is a trend towards a greater observed indirect impact of PCV, but the data are spotty.
- Compared to the PCV7 period, if applicable, or the pre-PCV period--in the setting of *de novo* introduction--clinical pneumonia incidence decreased by 2% to 40% in the PCV10/13 period (n=5 studies, reaching significance in 2 studies).

VT IPD

- There has been a significant reduction in VT IPD following the introduction of PCV10 or PCV13 in various age groups studied.
- Following the transition from PCV7 to either PCV10 or PCV13, the rate of disease due to the additional serotypes included in the higher valency product has mostly decreased, though the data is more robust for PCV13 than PCV10.

Regional representativeness

- Studies are available from all regions except Asia.
- Most of the included data on indirect effects are from European countries using PCV13 in a 2+1 schedule.

Indirect Effect Findings

PCV introduction for infants has impacted the burden of pneumococcal disease in unvaccinated persons of various ages by reducing the risk of transmission from young children, the age group thought to be the reservoir for pneumococcal circulation at the community level. Young children who receive PCV are less likely to carry vaccine serotypes in their nasopharynx and thus are less likely to spread these serotypes to older, unvaccinated individuals and even infants too young to be vaccinated. With reduced exposure to vaccine serotypes, unvaccinated persons are less likely to develop disease, indirectly benefiting from PCV implementation among infants. This phenomenon is referred to as the indirect effect of PCV or herd immunity.

The evidence of PCV10 and PCV13's impact on indirect effects summarized here is based on the inclusion of studies with data prior to any PCV use and at least three years of data post PCV10/13 introduction (e.g. pre-post studies). Thirty-one studies are included, mostly representing European countries using PCV13 in a 2+1 schedule (Appendix A, Table 8). Most of the data on indirect effects is on IPD (n=22 studies), with limited data on NP carriage (n=3 studies) and pneumonia (n=6 studies). Additional data on indirect effects is available from countries using a 4-dose schedule but was not included in this summary.

VT NP Carriage—Indirect Effects

There are limited but consistent data on the indirect effects of PCV10 or PCV13's introduction on VT NP carriage in older children and adults. Data are limited mainly because most NP carriage studies do not have at least three years of post introduction data (n=19 studies excluded for this reason; see Appendix B Table 27 for exclusion reasons). Three NP carriage studies were included: one study from Israel, with data on the transition from PCV7 to PCV13, and two studies on the *de novo* use of PCV10 from Fiji and Kenya [47, 48, 126]. (Appendix A, Table 27). All three studies report reduction of VT carriage in various age groups not directly vaccinated, with the relative reduction in VT carriage ranging from 35% to 100%. In Kenya, among all persons over 5 years of age, there was a 65% reduction in PCV10 VT carriage that was significant four years after vaccine introduction [47]. More studies are needed to assess the indirect impact of PCV10 and PCV13 over time, particularly with respect to the magnitude and importance of NVT replacement carriage.

Pneumonia—Indirect Effects

Indirect effect data on pneumonia are still limited and results are more variable than for IPD and carriage, in part due to the variability in pneumonia outcomes assessed. Many studies were excluded based on having fewer than three years of post PCV10/13 use (n=9) or because they present data on an age group that included both direct and indirect effects together (n=10, Appendix A, Table 28). PCV13 studies based on a 3+1 schedule were also excluded, thus cutting out the U.S. data on this topic.

Six studies report on pneumonia incidence in groups not directly vaccinated: three studies from PCV10 countries (Finland [127] and Kenya [128, 129]), two studies from PCV13 countries (Scotland [130] with prior use of PCV7, and Argentina [131] with *de novo* PCV13 introduction), and one study from a country that switched from PCV7 to PCV13 and then to PCV10 (Appendix A, Table 28; Sweden) [132]. Five studies report on clinical pneumonia in older children (n=4 studies) and adults (n=2). The methodology of the clinical pneumonia studies varied substantially, making comparisons between studies very difficult.

- Clinical pneumonia: Two of five studies report a statistically significant reduction in clinical pneumonia, while three report no significant change. Compared to the PCV7 period, if applicable, or the pre-PCV period--in the setting of *de novo* introduction--clinical pneumonia incidence decreased by 2% to 40% in the PCV10/13 period in older children and adults.
- Radiographically confirmed pneumonia: Two studies report on CXR confirmed pneumonia in older children and found an 11% (not significant) and 44% (significant) reduction [128, 131].
- Pneumococcal pneumonia and empyema: Only one study has data on pneumococcal pneumonia, reporting a significant reduction of 94% in this outcome in persons over 18 years [129]. Another study has data on all-cause empyema in older children but found no significant decrease [130].

In general, as the pneumonia outcomes become more specific for pneumococcal etiology, there is a trend towards a greater observed indirect impact of PCV, but the data are sparse and further studies are needed to quantify these effects over time particularly in adults and the elderly.

IPD—Indirect Effects

IPD studies represent the bulk of the information that is available on the indirect effects of PCV10 and PCV13. Twenty-two studies were included, most representing European countries using PCV13 in a 2+1 schedule. One PCV10 study from the Netherlands using a 3+1 schedule was included to bolster the evidence on PCV10 and individual serotypes.[133]

Overall, there has been a reduction in all-cause IPD in the PCV10/13 period (Appendix A, Table 29A). In countries that switched from PCV7 to PCV13, this reduction continued the trend from the PCV7 period [30, 109-111, 116, 134-140]. In PCV10 using countries (Finland and the Netherlands), there is some indication there has been a small, non-significant rise in the incidence of IPD in the elderly, perhaps due to replacement with NVT disease, that warrants continued surveillance [133, 141].

With respect to VT IPD, the data are consistent in documenting a significant indirect effect of both PCV10 (n=2 studies) and PCV13 (n=6 studies) on disease in adults and the elderly. (Appendix A, Tables 29B and 29C) Specifically, following the transition from PCV7 to either PCV10 or PCV13, the rate of disease due to the additional serotypes included in the higher valency product has decreased, though the data are more robust for PCV13 than PCV10.

In ten out of 12 studies reporting on NVT IPD, there has been an increase in NVT disease from the PCV7 or pre-PCV period to the PCV13 or PCV10 period, respectively. (Data not shown.) Only four studies reported significant increases in NVT IPD between 27% and 96% in various age groups.

The observed impact of PCV10 and PCV13 use on types 3, 6A, and 19A among unimmunized age strata is described in section 3.7 below. In brief, there is evidence that PCV13 results in reductions of serotype 3 and 6A IPD compared to the PCV7 period.[114, 116, 138] (Appendix A, Table 29D) Serotype 19A IPD also decreased in the UK and Denmark after transition from PCV7 to PCV13 but increased in Ireland.[114, 116, 142] For PCV10 there are very sparse data, but they tend to show some reduction in disease due to serotype 6A (significance not reported) in unvaccinated persons, and in an increase in the rate of serotype 3 and 19A IPD. [133, 141] There is very limited data on which to draw firm conclusions one-way or the other; this is an important area of ongoing assessment.

3.8 Serotypes 3, 6A, 19A

Summary

PCV13:

- All 3 ST are highly immunogenic post PCV13.
- Carriage of ST 6A and 19A decline in the face of PCV13 vaccination. Carriage prevalence for serotype 3 is generally low precluding robust evaluation of the impact on ST 3.
- IPD: PCV13 is effective in reducing ST 19A and 6A disease; Some but not all countries demonstrate an impact on type 3 disease
- Indirect effects: PCV13 use results in reduction in 6A disease in adults. An impact on 19A has also been observed in some but not all settings while ST 3 disease has declined in the UK but not elsewhere.

PCV10:

- Some immunogenicity is seen to cross reactive ST 6A and 19A but responses are lower to those seen following PCV13. No responses to serotype 3 are seen.
- Carriage of ST 6A in PCV10 settings is difficult to assess due to the low prevalence but some reduction has been reported. No impact on 19A or 3 has been seen.
- IPD: PCV10 appears effective in reducing ST 6A and 19A disease in vaccinated children; no impact on ST 3 is seen.
- Indirect: PCV10 does not appear to impact consistently on indirect disease due to these three ST

ST 3, 6A and 19A Findings

Serotypes 3, 6A and 19A are included in PCV13 but not in PCV10. However for two of these serotypes (6A and 19A), closely related serotypes 6B and 19F are included in PCV10 raising the possibility that there may be some biological effect on 6A and 19A via cross protection following PCV10 administration. Following the use of PCV7, which contained serotype 6B but not 6A, immune responses and some direct protection against serotype 6A disease and carriage was noted. PCV7 included serotype 19F but responses to the related serotype 19A were generally poor and little consistent impact on 19A disease and carriage was seen post PCV7. The different production techniques and carrier composition of PCV10 has meant that potential cross protection to 6A and 19A following PCV10 merits investigation.

Immunogenicity

When comparing immunogenicity, post primary and pre and post booster IgG geometric mean concentrations (GMC's) to serotypes 6A and 19A were inferior post PCV10 compared with PCV13 irrespective of whether 2 or 3 primary doses were given. There was one exception to this; one study demonstrated PCV10 pre booster IgG concentrations following three primary doses that were similar to PCV13 concentrations.

When analyzing the response after the third dose in either a 3+0 or 2+1 schedule, IgG GMC's to 6A and 19A were consistently lower following PCV10 than PCV13 in the equivalent schedule. Analysis of primary, pre-boost, post-boost and post dose 3 IgG GMC's analyzed by age at first or last dose, interval between doses or region did not alter the general findings indicated above.

Analysis of proportions above correlates of efficacy (i.e. 0.35 mcg/mL or 0.22 mcg/mL, depending on the assay used) for 6A and 19A showed that proportions were consistently lower for all comparisons (schedule, doses etc.) comparing PCV10 to PCV13 immunization. However, after primary vaccination with PCV10, >50% of subjects had antibody concentrations to 6A and 19A that were above the correlate of efficacy (range 22-79% for 6A and 22-87% for 19A, based on 26 study arms). The percent responders improved to 85% after the booster dose (range 72-99% and 74-96%, respectively). Evidence of boosting of antibodies to 6A and 19A was also reflected in antibody concentrations, which increased 5-6 fold for each of the two serotypes compared to post-primary levels, based on 19 studies. A comparison of post primary percentages after 2 or 3 primary doses of PCV10 was possible and revealed 10-15% greater proportions above the threshold for efficacy following 3 compared to 2 doses.

While IgG GMC's to cross reactive serotypes 6A and 19A and proportions above the correlate of efficacy were lower following PCV10 than PCV13 this does not rule out an impact on 6A and 19A carriage and disease following PCV10 vaccination (see relevant sections below).

Only two studies measured serotype 3 IgG GMC's post PCV10 and responses were extremely low.

Carriage

a. ST 3

PCV13

N=7 studies evaluated a 3-dose PCV13 schedule on ST 3 carriage and none provided evidence of impact on ST 3, but low power due to either low baseline ST 3 carriage or insufficient time post-PCV13 introduction make conclusions uncertain at this time. N=5 studies evaluated PCV13 impact on ST 3 in countries that switched from PCV7 to PCV13 but conclusions were difficult due to low ST 3 carriage; however, mixed results (i.e., some increases and some decreases, none significant), suggest on average no impact of PCV13 on ST 3 carriage. This may be supported by a Malawi study that did not evaluate impact directly but did assess carriage under conditions that should have maximized impact (i.e., 5 years post-PCV13 introduction in PCV13-vaccinated children 3-5 years old without HIV in a setting with 85% vaccine coverage and that used a catch-up campaign in children <1 year). They found that ST 3 was the most common VT serotype carried (4%), indicating at best sustained carriage of ST 3 long after PCV13 introduction, and at worst no impact on ST 3. ST 3 carriage was also similar between children vaccinated with PCV13 (16/881 [1.8%]) compared to PCV7-vaccinated children (17/873 [1.9%]) in a clinical trial of a 3+1 schedule (i.e., after 4 doses which would be expected to have a larger impact than a 3 dose schedule), supporting the possibility that PCV13 may not reduce carriage of ST 3; but ST3 carriage was low so there was low power to assess impact.

PCV10:

Although no evidence was found that 3-dose schedules of PCV10 reduce carriage of ST 3, ability to assess impact was limited by very low ST 3 carriage. Two clinical trials observed higher ST 3 carriage in PCV10-vaccinated (1-3 isolates) compared to unvaccinated controls (0-1 isolates). In 1 study conducted in routine-use, an increase from 3.7% to 6% was observed; 3 other studies evaluated ST 3 but baseline carriage was too low to assess impact. Another study in the Netherlands of a 3+1 schedule (i.e., 4 doses) that switched from PCV7 to PCV10 found no change in ST 3 carriage at any time.

b. ST 6A

PCV13

Evidence from 9 studies suggests PCV13 reduces carriage of ST 6A. Two clinical trials showed 40% (Israel 3+0, significant) and 59% (Vietnam 2+1) reduction in carriage of ST 6A in PCV13-vaccinated children compared to PCV7-vaccinated children and unvaccinated children, respectively. In 7 studies of routine-use in countries that switched from PCV7 to PCV13, all observed continued declines from the PCV7-era to post-PCV13 (1 was statistically significant but the rest were not due to small numbers of 6A isolates). Another study in a high-risk population in Malawi (described above) assessed carriage 5 years post-PCV13 introduction and found ST 6A carriage was 2% indicating carriage was low but persisted long after PCV13 introduction.

PCV10:

Several studies suggest that PCV10 may somewhat reduce carriage of ST 6A, but none had large effects and none were statistically significant due to low ST 6A carriage. Non-significant declines of 10-20% were observed in 3 studies that evaluated impact after 2, 3 and 4 years of routine use; a 4th study after 1 year of PCV10 use observed a non-significant increase from 0.9% (7/789) to 4% (9/206). N=3 clinical trials evaluating 3-dose schedules all observed non-significant lower ST 6A carriage in PCV10-vacinated children compared to unvaccinated controls. Children who received only 2 doses also had lower carriage compared to controls pre-booster. Two studies of a 3+1 (i.e., 4 dose) schedule also suggest PCV10 may impact ST 6A carriage: a small (non-significant) reduction was observed in a clinical trial and a study in the Netherlands evaluating switching from PCV7 to PCV10 found that declines in ST 6A that were observed post-PCV7 continued to decline after the switch to PCV10.

c. ST 19A

PCV13

N=5 studies evaluated impact of a 3-dose PCV13 schedule on ST 19A carriage, several of which suggest evidence of impact, but all had inadequate sample size and/or need more time post-PCV13. N=2 clinical trials assessed impact of PCV13 on ST19A: carriage was too low to assess in one (3/184 in unvaccinated controls) but the other showed 37% lower carriage (not significant) in PCV13-vaccinated (4.5%) compared to PCV7-vaccinated controls (7%). One study in France that switched from PCV7 to PCV13 found that the significant increases in 19A that were observed following PCV7 introduction declined to baseline levels 2 years after switch to PCV13, and The Gambia is seeing a similar trend. The Cambodia study described above that assessed impact in children <5 years of age the year PCV13 was introduced (so little impact would be expected since the percent of children that actually received PCV13 would have been very low), observed carriage of ST 19A declining from 7.4% pre-PCV13 to 4.3% (42% reduction). And the Malawi study described above found ST 19A carriage was 3% 5 years post-PCV13 introduction indicating sustained carriage in high-risk populations long after PCV13 introduction.

PCV10:

There were 7 studies that evaluated the impact of PCV10 on ST 19A and overall it appears that that PCV10 has no impact. N=5 were clinical trials evaluating 3-dose schedules and conclusions were difficult due to low ST 19A carriage, but results were mixed (i.e., 3 with increases and 2 with decreases, none significant), suggesting on average no impact of PCV10 on ST 19A carriage. N=3 studies were in the context of routine PCV10 use and all observed increases in 19A carriage, generally going from 1-3% to 5-7%, one of which (Kenya) was statistically significant. One additional study in the Netherlands evaluated a 3+1 schedule (i.e., 4 doses so should have a larger effect) and after switching from PCV7 to PCV10 found that the 5-fold increases in 19A that occurred following PCV7 introduction did not return to pre-PCV7 levels after 5 years of PCV10 use, providing further evidence that PCV10 may not reduce carriage of ST 19A.

Pneumonia

This review did not identify any studies that reported the impact of PCV10 or PCV13 on serotype-specific pneumococcal pneumonia

Invasive Pneumococcal Disease

PCV13:

Three case-control studies evaluated VE of PCV13 against individual serotypes. The VE of ≥1 dose against type 19A IPD was 74% (Canada) and ranged from 67 to 94% for ≥2 doses (UK and South Africa). There was no VE of PCV13 against type 3 IPD and 98% VE against type 6A reported in one study (UK).

In countries introducing PCV13 following PCV7 on a 2+1 schedule, six studies reported impact on serotype-specific IPD. Significant reductions in type 19A disease, ranging from 69 to 91% were reported in four studies (Israel, France, England, and South Africa) with 1 to 4 years post-introduction. One study in Denmark reported no changes in type 19A disease compared to PCV7 period 3 years post introduction, with disease incidence declining to pre-PCV7 levels. No changes in type 3 IPD 1 to 3 years post introduction were reported in three studies (Denmark, Israel, and South Africa). Two studies reported significant reductions of 85% and 68% (France and England) in type 3 disease 1 and 4 years, respectively, post PCV13 introduction. Significant reductions in type 6A disease ranging from 85% to 100% were reported in three studies (South Africa, Israel, and England) post-PCV13 compared to pre PCV period, although most of these reductions should attributed to PCV7 impact. Only one study (Australia) reported impact of PCV13 on type 19A disease in a setting of 3+0 schedule (77% reduction in type 19A IPD).

PCV10:

Four case-control studies evaluated VE of PCV10 against individual serotypes. The VE of ≥1 dose against type 19A IPD ranged from 61 to 82%, although the estimates were not statistically significant in a study from Netherlands and Brazil (indirect cohort method). There was no VE of PCV10 against types 3 and 6A IPD, although measured only in one study (Brazil).

Two pre/post observational studies reported reductions in IPD caused by type 19A following PCV7/PCV10 introduction; a 36% reduction was reported in Canada and 62% reduction in Netherlands 2 and 4 years post introduction using a 2+1 schedule, respectively. In Finland, a 93% reduction in type 19A disease and a 100% reduction in type 6A disease was reported 5 years post PCV10 introduction. Additional serotype-specific data from countries using PCV10 is pending.

Indirect effects

NP

Some data is available on the indirect effects of the PCV13-non-PCV10 serotypes 3, 6A and 19A. NP carriage data from Kenya four years after PCV10 introduction has found that serotypes 3 and 6A have decreased among adults surveyed but the prevalence of 19A carriage has increased 2.5-fold, though the numbers of positive carriers are very small (0.5% to 1.4%) (Appendix A, Table 2) [143].

IPD

With respect to IPD, in Finland, there has been an 84% to 116% increase in disease caused by 3, 6A and 19A as a group in persons over 18 years, mostly driven by a large increase in serotype 3 and 19A disease in the elderly in the 5 years since PCV10 use (Appendix A, Table 4D) [141]. There has been no change in the rate of 6A IPD [141]. Serotype 6A IPD has also decreased in four other countries, one with PCV10 use and the three with PCV13 use [114, 116, 133, 138]. Serotype 3 changes have been more dependent on the PCV product in use: disease increased in the Netherlands, like Finland, in the setting of PCV10 use and decreased in the UK in the era of PCV13 use [114, 133].

Serotype 19A trends are more erratic: in three PCV13 using countries, disease has decreased in the UK and Denmark but increased in Ireland [142]. Serotype 19A IPD has increased in both of the PCV10 countries of Finland and the Netherlands in persons 5-64 years and over 65 years of age [133, 141].

IPD due to serotype 6C was also reported as increasing markedly in the Netherlands in the elderly in the PCV7 and PCV10 era [133].

Continuing surveillance of IPD and trends in serotype replacement is warranted to inform the evolving indirect impact of PCV product use in various country settings.

3.9 Mixed PCV10-PCV13 Regimens

The current WHO position paper on pneumococcal vaccines provides the following statement regarding the use of both PCV10 and PCV13 to immunize an individual (i.e. a mixed product regimen):

When primary immunization is initiated with one of these vaccines, it is recommended that remaining doses be administered with the same product. Interchangeability between PCV10 and PCV13 has not yet been documented. However, if it is not possible to complete the series with the same type of vaccine, the other PCV product should be used[1].

Since that 2012 WHO position statement three reports, from two studies, have been presented in published or abstract form on the use of PCV10 and PCV13 mixed product regimens. An immunogenicity study of PCV10 booster following PCV13 priming found lower antibody concentrations and opsonic activity as well as lack of memory B-cell induction than among those who received PCV13 booster [144, 145]. The other study assessed PCV13 booster following PCV10 or PCV13 priming and found no differences in immunogenicity of the booster dose for serotype 19A, by the product used for priming [146]. The clinical significance of these findings is not clear, reinforcing the WHO 2012 policy statement.

4. Economic and financial considerations for PCV products

Summary

- Many cost effectiveness analyses (CEA) have been conducted for PCV10 and PCV13, virtually all showing high ICER when compared to accepted standards
- Most CE studies of PCV10 and PCV13 use vaccine impact data extrapolated from PCV7 observations, assuming a differential health impact of the two products because of the marginal increase in serotype coverage of PCV13 beyond PCV10; PCV10 has lower CE generally than PCV13 because of these assumptions
- Only very few studies include the herd effects in the modelled estimates
- Together with the Eligibility and Transition policy, the co-financing policy is at the heart of Gavi's catalytic funding model. As Gavi-supported countries progress on a trajectory of increasing GNI per capita towards phasing out of Gavi support, they increasingly take on higher levels of co-financing. For more information, please refer to the latest Co-financing policy at the Gavi website: http://www.gavi.org/about/governance/programme-policies/co-financing/.
    - The Advanced Market Commitment tail price as of 2017 or PCV10 is $3.05 per dose (for 2 dose and 4 dose vials) and for PCV13 is $3.05 per dose in 4-dose vial and $3.30 in 1 dose vial. For current pricing please see: https://www.unicef.org/supply/files/PCV.pdf

4.1 Economic considerations for PCV products

Economic evaluations focus on measuring the impact of disease on the economic health of families, communities, governments and societies as a whole. A variety of health economic questions can be addressed including such questions as: How much is the prevention of pneumococcal disease costing the government and health system? How much are households spending out-of-pocket to pay for medical care related to pneumococcal disease, redirecting funds that could be used elsewhere? How much money is lost to the economy when productivity decreases because of this disease? Which intervention or program is the most cost-effective? The answers to these questions will differ by product if there are substantial differences in health impact (addressed in section 3) or in product/program costs across the available products. These health economic analyses are usually not sufficient to drive policy decisions, but they have become a necessary piece of evidence to make informed decisions on how to allocate resources in a transparent way.

Cost-effectiveness of PCV: Findings from selected studies

Measuring vaccine impact from an economic perspective has usually been done using cost-effectiveness analyses (CEAs) comparing PCV to no vaccine, comparing different PCV products, or comparing different dosing schedules. The conclusion about whether a vaccine is a cost-effective anchor on comparing the cost per disability life-year averted (cost/DALY) to some chosen threshold, often using the WHO threshold of based on the national annual GDP per capita. There is a growing body of literature on the economic evaluation of PCV in a variety of settings (Appendix A, Table 26) [147, 148] [149] [150] [151] [152] [153, 154] [155] [156, 157] [158]. Studies differ on key input variables—such as cost of vaccine, estimated vaccine effectiveness, perspective and inclusion of indirect effects—thus making direct comparisons of their results across studies ill advised. However, the vast majority of studies show incremental cost effectiveness ratios in the range considered highly cost-effective.

Studies have generally been consistent in the endpoint outcomes selected, but there is little consistency in the inclusion of indirect effects and serotype replacement. Of studies that included these, there was a wide range of parameters selected. Many studies used serotype replacement data from the U.S., which may not be applicable to settings with different serotype distributions [147, 155, 159]. Additionally, it is difficult to extrapolate results of PCV CEAs to other settings because of differences in the health system, vaccine financing (i.e., Gavi eligible vs. non-eligible), and disease epidemiology.

A 2006-2014 systematic review of CEA studies globally highlights some of the challenges in estimating the cost-effectiveness of PCV products [159]. Twenty-eight studies were included in the review based on their inclusion of PCV10 or PCV13 as one of the vaccines evaluated. The studies varied widely in vaccine cost per dose, and most studies did not perform sensitivity analyses on vaccine cost, which can be highly influential. Of the 28 studies, 17 studies were funded by industry (all the Pfizer-funded studies found PCV13 to yield favorable cost-effectiveness results, and all the GSK-funded studies preferred PCV10; some studies compared PCV13 and PCV10 directly however the comparator for cost-effectiveness in most studies was no-vaccination). This difference mainly lies in the assumptions for the model. Of the 11 studies that were not funded by the industry, all concluded that PCV13 and PCV10 were likely to perform favorably to the current situation (i.e. often PCV7) but the decision of which of these two vaccine candidates to choose from was less clear, due to uncertainties on serotype replacement and herd effects, serotype cross-protection and NTHi AOM protection. The authors concluded that cost-effectiveness was highly dependent on the price used in the models, and the weight policy makers attached to preventing IPD cases versus AOM cases through PCV use [159].

Limitations of the economic evaluation of PCV10 vs. PCV13 are important to consider. The indirect effects of PCV used were a highly influential parameter in sensitivity analyses often increasing the cost-effectiveness by several folds, but many studies did not account for herd effects or serotype replacement.

Tasslimi and colleagues provide a CEA of PCV10 and PCV13 using a 3p+0 schedule compared to no vaccine in Gavi-eligible countries [148]. The authors conclude that PCV would be highly cost effective in 69 of 73 Gavi-eligible countries based on the WHO GNI per capita thresholds. This finding was robust when assumptions regarding disease epidemiology and vaccine-related effects were varied in sensitivity analyses [148]. This study accounts for indirect effects, herd immunity and serotype replacement, and takes a 10-year societal perspective. Outcomes included in the model are: pneumococcal pneumonia, pneumococcal meningitis and non-pneumonia, non-meningitis IPD in children U5 years; and pneumococcal meningitis, pneumococcal sepsis and all-cause pneumonia in older children and adults. The authors observed a notable improvement in pooled cost effectiveness, all other variables being equal, when moving from PCV7 to PCV10, but little additional improvement from PCV10 to PCV13 (Appendix A, Table 25-26) [148].

A study of PCV cost-effectiveness in 77 middle-income countries found PCV10 and PCV13 to be cost-effective for all countries compared to no vaccine [149].

4.2 Financial considerations for PCV products

Since 2007, all countries applying to Gavi for New Vaccine Support co-finance a portion of the cost. The co-financing requirement for individual countries depends on their transition phase per the Eligibility and Transition policy. In the initial self-financing phase, the government's contribution is a flat amount: US$0.20 per dose of any Gavi-supported vaccine that is used in routine immunization programs. This contribution is intended primarily to reinforce country ownership and build procurement capacity, without discouraging new vaccine adoption. When a country enters the preparatory transition phase, the government's contribution increases by 15 percent per year. In this phase, the co-financing requirement is a percentage of the price of vaccines, and the absolute amount will thus vary from vaccine to vaccine. When a country enters accelerated transition, the government's share of vaccine costs increases from the level it had reached during the previous phase to 100% of the cost over a period of five years [149].

In 2009 the pilot Advanced Market Commitment (AMC) for PCV was established. The AMC provides an innovative finance mechanism to incentivize the scaling up of PCV production to meet developing country needs. Both GSK (the manufacturer of PCV10) and Pfizer (the manufacturer of PCV13) are AMC-eligible manufacturers. According to the terms of the AMC, the price of PCV10 and PCV13 to Gavi-supported countries will be no more than the "tail price," intended to cover the incremental production cost of vaccine [160]. **In 2017 the tail price of PCV10 2 dose vial and PCV13 4 dose vial to US$3.05 per dose and the tail price of PCV13 single dose vial is $3.30 per dose** [149]**.** 149]**.**

As of December 31, 2016, 59 out of 73 Gavi-eligible countries have been approved for AMC supported introduction of PCV, and 57 countries have introduced PCV, with 2 countries planning to introduce the vaccine with Gavi support in 2017 (India and Haiti) [149].

The AMC Terms and Conditions provide access to AMC-supply and prices for PCV to the 73 countries that were Gavi-eligible in 2003, even if they are no longer Gavi-supported. These countries will pay the tail price [161].

Other strategies for reducing vaccine cost include pooled procurement and supply-side approaches, which are mostly relevant for countries not eligible to access AMC supply and prices. Procurement of vaccine at reduced cost is made possible through the Pan American Health Organization (PAHO) revolving fund and through the UNICEF Supply Division [166]. There is also an example of a technology transfer agreement between a middle-income country and a manufacturer. Brazil has agreed to purchase US$2.2 billion of PCV10 from GlaxoSmithKline over an 8-year period in exchange for technology transfer that will eventually allow Brazil to manufacture the vaccine for itself [166].

In addition to the two PCVs that are WHO pre-qualified and have established supply agreements under the AMC, two other manufacturers have registered publically for inclusion in the AMC. These two manufacturers are Panacea Biotec Limited (India) and Serum Institute of India. Several PCV products from both multinational and developing country manufacturers are in development, and their entrance into the market will improve the balance of supply and demand and could eventually provide competitive pressures in the market. However, as PCVs are complicated products to manufacture, the prices will likely reflect costs of manufacturing that are in the same range current prices. One manufacturer, Serum Institute of India has publically stated a price of $2.00 per dose [167].

5. Programmatic considerations for available PCV products

Summary

- Both PCV10 and PCV13 will be available in 4-dose vials with preservative
    - PCV13, 4-dose vials are available in early 2017
    - PCV10, 4-dose vials are expected to be available in 2018 pending WHO pre-qualification
- The cold chain volume per dose of PCV10 4dv (2.4 cm^3) is two thirds of PCV13 4dv (3.6 cm^3).
- PCV13 will also continue to be available in 1-dose vials; PCV10 in 2-dose vials will no longer be available once PCV10 4-dose vials are available and, as the case may be, have attained local registration in countries.
- Countries may be entitled to a product switch grant up to US$0.25 per child in the birth cohort or a lump sum of US$30,000 whichever is higher, if they meet the required criteria. In order to request a product switch grant, countries should submit their request, along with a product switch budget, through the Gavi country portal at the time of the NVS renewal request. The details of the product switch policy can be found on Gavi's website at: http://www.gavi.org/about/governance/programme-policies/health-system-and-immunisation-strengthening-support-framework/.
- There is almost no information on the performance of mixed product regimens in individual children

Programmatic Findings:

Careful consideration should be given to the programmatic issues and implications around PCV product choice, and when weighing a switch between PCV products. Any change in product used will have important costs and program implications, both positive and negative:

- Retraining of health workers is required, particularly around the multi-dose vial policy to review how long the product can be kept and discuss policies regarding both wastage and avoiding missed opportunities.
- Product availability
- Operational issues – finishing out and switching supply of vaccines, cold chain space or transportation requirements
- Evidence on mixed product regimens (See Section 3.9)

As of 2017, countries may choose among one and four-dose vials for PCV13 and from 2018 will have access only to 4-dose vials for PCV10 (see Table in Section 5.3.2 below). A switch to either vaccines 4-dose vial will trigger some programmatic processes including staff retraining and planning for the switch to manage existing inventory. Currently, three presentations of PCV are available to AMC eligible countries. Future choices are expected to also be available in multi-dose vials with preservative.

5.1 Recommended PCV dosing schedules

For countries using 3 doses of PCV, WHO has recommended either of two dosing schedules – 3p+0 or, alternatively, 2p+1 – each requiring 3 doses of either available PCV product (10V or 13V) [1]. There are trade-offs in choosing between these two schedules, but the choice of schedule is not influenced by product. For this reason we do not provide an in depth discussion of product choice, by schedule in this document. Schedule preferences are under review by a SAGE PCV Working Group (WG). WHO convened the SAGE WG on PCVs in December 2016. In June 2017 the WG will review the evidence on PCV immune response, VE, and impact to inform their proposed recommendations to the WHO position on PCV use to SAGE in October 2017 (as appropriate).

5.2 Number of injections per routine immunization visit

Given that the number of doses administered of either PCV10 or PCV13 should be 3 per child and that WHO's recommended schedules for administration of these doses are the same for both products, the number of injections given at an immunization visit should not change based on the product chosen.

5.3 Current and future product packaging, presentation, cold chain and storage

Vials containing 4-doses of PCV13 are available and 4-dose PCV10 vials are expected in 2018. In some cases, Gavi-eligible countries will be required to switch presentations (PCV10 will *only* be available in a 4-dose presentation starting after PCV10 4-dose presentation has attained local registration in Gavi countries in 2018). Section 5.3.1 describes the current products available and 5.3.2 provides details on the forthcoming 4-dose presentations for both PCV10 and PCV13.

The selection of product presentation should be made by weighing the relative advantages and disadvantages of each product. For example, while single-dose presentations should minimize wastage of unused vaccine, the cold chain and storage requirements are greater. In addition, new 4-dose preservative-containing PCV10 and PCV13 products will be subject to the guidance laid out in the WHO Multidose Vial Policy [168]. Countries will need to ensure clearly articulated policies and careful training for health workers to minimize wastage of unused vaccine doses in open vials, and to maximize opportunities to vaccinate children. This is especially important in settings where immunization sessions may consist of small numbers of children and especially important for PCV10 using countries switching over from the 2-dose vial which does not contain preservative and is discarded after 6 hours.

5.3.1 Current PCV presentations

Currently, PCV10 is available in 100-vial cartons; each vial contains two-doses, corresponding to a volume of 4.8 cm^3 per dose. At present, PCV13 is available in 50-vial cartons; each vial is a single-dose, corresponding 12 cm^3 per dose, or 2.5 times the volume of PCV10. The single-dose PCV13 vial requires more space for cold chain storage and distribution, but it reduces vaccine wastage (5% estimated) compared to a two-dose vial that if opened and not used in the same day must be discarded (10% estimated wastage) (Table 3, Section 2.4). PCV13 4-dose vials are now available for use (as of 2017). PCV13 is available as a liquid vaccine in single-dose vials (Gavi and non-Gavi countries), or prefilled syringes (non-Gavi countries). The 4-dose PCV 13 is available to Gavi countries in packages of 50 vials (200 doses) [169]. Of the currently available PCV products or formulations both PCV10 and PCV13 4-dose vials contain a preservative.

PCV10 is presented in a single-dose (non-Gavi countries) or two-dose vial without preservative (Gavi countries). The WHO specifically assessed the safety of the two-dose PCV10 formulation in a Kenyan study prior to receiving full pre-qualification. In this study, the risk ratio for abscess following injection with the second vs. first vial dose of PCV10 was not significantly increased compared to another EPI vaccine (pentavalent vaccine), lending support to the feasibility of safely using this formulation in Africa and low-income settings [170].

PCV10 in a 2-dose vial presentation will no longer be available once the PCV10 4-dose presentation has been prequalified and attained local registration within your country. Countries currently supported for PCV10 2-dose vials need to submit a request to indicate to which presentation they want to switch through the Gavi country portal during the annual reporting cycle in May 2017, or if urgent through a letter to Gavi outside that date.

5.3.2 4-Dose Vial PCV presentations

PCV13 4-dose vials have become available to Gavi countries in 2017 and **PCV10 4-dose vials** are forecasted to become available in 2018 [162]. The availability of PCV10 4-dose vials is pending its prequalification by WHO, expected in late 2017, and, as the case may be, its local registration. PCV13 presentation in a 4-dose vial with a preservative has received WHO PQ and is available globally. Both 4-dose vial presentations are currently available as product options through the Gavi country portal in the May 2017 reporting cycle.

Product packaging and presentation: 4-dose vials [171]

PCV10:

Countries that currently have PCV10 2-dose vials in their routine immunization will have to switch to PCV10 4-dose vials (or to another PCV product of their preference) from 2018 onwards. If a country wishes to switch to a presentation other than PCV10 4-dose, they will need to indicate their preference through the Gavi country portal in the May 2017 reporting cycle, or if urgent through a letter to Gavi outside that date.

- 2017:
  - Single-dose vials (non-Gavi)
  - Two-dose vials: cartons of 100 vials (available to Gavi countries)
- 2018 onwards (assuming WHO PQ achieved): Instead of 1-dose vial, 4-dose vials will be available through Gavi to countries using PCV10. (Note: PCV10 2-dose will remain available until PCV10 4-dose presentation has attained local registration in Gavi countries.)
  - New 4-dose vials:
    - **Preservative:** Contains preservative (2-Phenoxyethanol)
    - **Shelf life:** 36 months
    - **Volume:** 2.4 cm^3/dose
    - Wastage rate needs to be confirmed. Current assumption is 10% as same as current 2-dose presentation†
    - EMA approval and WHO pre-qualification anticipated in fourth quarter of 2017 with product available sometime in early 2018
    - Subject to pre-established WHO Multi-dose vial policy (MDVP) for usage after opening
    - Will contain a vaccine vial monitor (VVM)

† Information provided for PCV10 4-dose vial is based on assumptions and discussions with WHO. However, final open vial policies and wastage assumptions will be reviewed and revised after WHO pre-qualification. WHO policy on the use of opened multi-dose vaccine vials (2014 Revision) can be consulted at: http://www.who.int/immunization/documents/general/WHO_IVB_14.07/en/

PCV13:

PCV13 is available in a 4-dose vial as of early 2017 and will continue to be available to Gavi countries in a single-dose vial for the foreseeable future. **The slightly lower per-dose cost of the 4-dose PCV13 product as compared the single-dose PCV13 may be offset by higher wastage compared to the slightly more expensive**

single-dose presentation and these trade-offs should be considered carefully. When considering standard wastage adjustments, the per course cost of the 1 dose vial is $9.90 compared with a cost of $9.15 for the 4-dose vial for PCV13.[172]

- 2017 onwards:
    - Single-dose vials: cartons of 50 vials
    - New 4-dose vials are also available to Gavi countries
        - **Preservative:** contains preservative (2-Phenoxyethanol)
        - **Shelf-life**: 24 months
        - **Packaging:** available in cartons of 50 vials/200 doses that are the same size as current 1d product (thus requires same storage space as current packaging of 50 single-dose vials)
        - **Volume:** 3 cm^3/dose
        - Subject to pre-established WHO Multi-dose vial policy (MDVP) for usage after opening (i.e. presentation can be used over a 28-day period following its first use, given storage at 2-8 degrees Celsius)
        - Will contain a vaccine vial monitor (VVM)

5.4 Training and supervision requirements

PCV10:

The currently available products do not contain a preservative. The 2-dose preservative-free presentation available to Gavi countries requires specific training for health workers: opened vials of this PCV product must be discarded at the end of the immunization session or six hours after opening, whichever comes first. Additional details can be found in section 3 of the WHO PCV10 Introduction Handbook [3]. Other training and administration requirements for PCV10 are similar to those for PCV13.

The forthcoming 4-dose presentation of PCV10 is expected to be pre-qualified in late 2017 and available in 2018. This is the only presentation that will be available to Gavi countries except during transition period from the current 2-dose formulation to the new 4-dose presentation for PCV10. The product will contain a preservative and will be subject to the guidance provided in WHO's MDVP. Open vials of vaccine need to be carefully managed so as to minimize wastage and must be discarded after 28 days. In addition, the policies about opening of vials for small-size immunization sessions should be carefully articulated to as to avoid inadvertent missed opportunities to vaccinate.

PCV13:

The single dose presentation does not contain a preservative. The training requirements for this presentation available to Gavi countries can be found in section 3 of the WHO PCV13 Introduction Handbook [4].

The 4-dose presentation of PCV13 is WHO pre-qualified and available as of 2017. The new 4-dose presentation contains a preservative and is subject to the guidance provided in WHO's MDVP. Open vials of vaccine need to be carefully managed so as to minimize wastage and must be discarded after 28 days. In addition, the policies about opening of vials for small-size immunization sessions should be carefully articulated to as to avoid inadvertent missed opportunities to vaccinate.

6. Supply considerations for available PCV products

Under the terms of the Advance Market Commitment (AMC), PCV is to be procured by Gavi countries through UNICEF Supply Division. This is different from procurement options for other products, which include self-procurement options and even transitioned Gavi countries must procure through UNICEF to get access to the AMC price [2, 173].

Accurate forecasting of dose procurement is also critical and countries can use the WHO Vaccine Forecasting Tool. Countries can select from one of two available prequalified products (PCV 10 2-dose vial) (PCV13, 1-dose and 4-dose vial). A 4-dose PCV 10 vial is expected to be pre-qualified in late 2017. For countries wishing to switch from the single dose presentation to the 4-dose presentation, they must indicate through the Gavi country portal during the annual reporting cycle in May [171]. Storage and logistics requirements should be considered and the 4-dose vial will reduce storage requirements significantly as described in section 5.3.2. Wastage rates for countries switching from a single dose presentation to a 4-dose presentation will also increase from 5% to 10% so that will need to be taken into account. Shelf life will be similar for both PCV products in 4-dose vials (36 months).

6.1 Supply availability & constraints

According to UNICEF, supply availability is no longer considered constrained. Both suppliers of PCV have increased production capacity, and it is sufficient to meet new approved Gavi country demand. UNICEF has a 10-year AMC supply agreements with Pfizer (740 million doses through 2023) and GSK (720 million doses through 2024). Demand reached 164 million doses in 2016 [174, 175]. India, which is planning introduction in 2017, will add an additional 8.9 million doses in 2017 on top of increases in other Gavi countries. These additional quantities will be met through the existing Supply Agreements. However, as India and other countries increase demand in future years, there could be short-term risks to the supply-demand balance prior to entry of new manufacturers.

Additionally, as the 4-dose vial from Pfizer (already prequalified) has been introduced in 2017 and the 4-dose vial from GSK is expected to be introduced in 2018 [176], demand will shift from single dose PCV to multi-dose vial (MDV) PCV. The uncertainty of country preference and demand for MDV presentations could have an impact on demand forecasts and therefore availability of preferred presentation in the future.

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Appendix A.

TABLE 1. Characteristics of included studies in NP Carriage Analysis

	PCV10				PCV13		
Characteristic N=37	2+1 N= 4 (11%)	3+0 N= 14 (38%)	3+1 N=1 (2%)	Total N= 19 (51%)	2+1 N= 13 (35%)	3+0 N=8 (22%)	Total N=21 (57%)
Study type							
Clinical trial	4	6	0	10	3	2	5
Pre/post survey	0	4	1	5	10	3	13
Post survey	0	1	0	1	0	3	3
Case-control/indirect cohort	0	3	0	3	0	0	0
Region							
Africa	0	4	0	4	2	3	5
Asia	2	3	0	5	2	1	3
Australia/Oceania	0	3	0	3	0	3	3
Europe	1	3	1	5	9	1	10
Latin America	1	1	0	2	0	0	0
North America	0	0	0	0	0	0	0
Previous Other PCV Product Use							
PCV7	0	1	1	2	10	3	13
PCV10	-	-	-	-	1	1	1

TABLE 2. Observational studies estimating percent relative reduction against **vaccine serotype** NP Carriage among the general population

Study Information							% Relative Reduction (95% Confidence Interval) Compared to	
Region	**Country (Reference)**	**Study Design**	**Dosing Schedule**	**PCV Introduction Year(s)**	**Number of Years Post Introduction Carriage Evaluated**	**Age Group (s) (Population)**	**Baseline (no PCV)**	**PCV7 Period**
PCV10								
AFR	Mozambique (Sigaque; Moiane 2016)	Pre Post Survey	3+0	PCV10: 2013	PCV10: 2	0-23 months (HIV-) 0-59 months (HIV-)	42.7% (19, 60) 30.1% (12, 44)	*PCV7 Not Used*
AFR	Kenya, Kilifi (Hammitt 2014; 2016)	Pre Post Survey	3+0	PCV10: 2011	PCV10: 4	<2 years (General) <5 years (General)	83.8% (76, 89) 97.1% (94, 99)	*PCV7 Not Used*
AFR	Kenya, Nairobi (Kim 2016; 2014)	Pre Post Survey	3+0	PCV10: 2011	PCV10: 2	<5 years (General)	51.7% (40, 61)	*PCV7 Not Used*
AFR	Ethiopia (Tsegaye 2016)	Cohort	3+0	PCV10: 2011	PCV10: 1	9 months (General)	45% (p=0.037) (17, 64)	*PCV7 Not Used*

AMR	Brazil (Andrade 2014)	Cross-Sectional	3+0	PCV10: 2010	PCV10: 1	7-11 months (General)	44.0% (14, 64)	*PCV7 Not Used*
EUR	Netherlands (Vissers 2016; Bosch 2015; 2014)	Pre Post Survey	2+1	PCV7: 2006 PCV10: 2011	PCV7: 5 PCV13: 5	<2 years (General)	88.8% (84, 92)	97.9% (72, 100)
SEAR	Pakistan (Ali; Nisar 2016)	Pre Post Survey	3+0	PCV10: 2013	PCV10: 3	<2 years (General)	30% (9, 46)	*PCV7 Not Used*
WPR	Fiji (Dunne; Russell 2016)	Pre Post Survey	3+0	PCV10: 2012	PCV10: 2	5 wk-23 months (General) 5 wk-6 years (General)	84.4% (76, 90) 95.6% (92, 97)	*PCV7 Not Used*
WPR	Australia (Leach 2016; 2016)	Post Survey	3+0	PCV7: 2001 PCV10: 2009 PCV13: 2011	PCV7: 10 PCV10:2 PCV13: 2	<6 years (Aboriginal)	*Reduction not Reported. Carriage measured in PCV10 period only (no comparison to a baseline measure).*	*Reduction not reported. Carriage measured in PCV10 period (no PCV7 period measure).*
PCV13								
AFR	Gambia (Roca 2014; 2015)	Pre Post Survey	3+0	PCV7: 2009 PCV13: 2011	PCV7: 2 PCV13: 1	6-11 months (General)	*Not Reported*	45% (28, 58)

AFR	South Africa, Soweto (Nzenze 2014; 2015)	Pre Post Survey	2+1	PCV7: 2009 PCV13: 2011	PCV7: 2 PCV13: 2	<2 years (General) ≤ 48 months (General)	8.5% (-3, 19) *Not Reported*	41.7% (32, 50) 62.0% (56, 67)
AFR	South Africa, Mpumalanga (Nzenze 2013; 2016)	Pre Post Survey	2+1	PCV7: 2009 PCV13: 2011	PCV7: 2 PCV13: 2	<2 years (General) <5 years (General)	36.3% (29, 43) 28.7% (24, 33)	55.9% (45, 65) 55.2% (47, 62)
AFR	Burkina Faso (Moisi 2016)	Pre Post Survey	3+0	PCV13: 2013	PCV13: 2	<5 years (General)	40.9% (28, 51)	*PCV7 Not Used*
AFR	Malawi (Swarthout 2016)	Post Survey	3+0	PCV13: 2011	PCV13: 5	3-5 years (General)	*Not Reported*	*PCV7 Not Used*
EMR	Cambodia (SuyKuong 2016)	Pre Post Survey	3+0	PCV13: 2015	PCV13: 0.5	0-23 months (General) <5 years (General)	28.0% (15, 39) 11.4% (0.5, 21)	*PCV7 Not Used*

EUR	Norway (Steens 2015; Vestrheim 2008; 2010)	Pre Post Survey	2+1	PCV7: 2006 PCV13: 2011	PCV7: 2 PCV13: 2	<2 years (Day Care) <59 months (Day Care)	60.3% (42, 73) 45.9% (41, 51)	73.9% (44, 88) 75.2% (67, 82)
EUR	France (Dunais 2015)	Pre Post Survey	2+1	PCV7: 2006 PCV13: 2010	PCV7: 2 PCV13: 2	3-40 months (Day Care)	72.7% (64, 80)	78.2% (59, 89)
EUR	Israel (Ben Shimol 2015; Danino 2016)	Pre Post Survey	2+1	PCV7: 2009 PCV13: 2010	PCV7: 2 PCV13: 5	7-23 months <5 years	*Not Reported* 25.3% (21,29)	56.5% (48, 64) 75.1% (70, 79)
EUR	Israel (Porat 2016)	Pre Post Survey	2+1	PCV7: 2009 PCV13: 2010	PCV7: 2 PCV13: 4	<5 years (General)	*Not Reported*	*Not Reported*
EUR	UK (Devine 2016; Jones 2016; Gladstone 2015)	Pre Post Survey	2+1	PCV7: 2006 PCV13: 2010	PCV7: 4 PCV13: 5	<4 years (General)	59% (54,63)	84.1% (44, 96)

EUR	UK (Van Hoek 2014)	Pre Post Survey	2+1	PCV7: 2006 PCV13: 2010	PCV7: 3 PCV13: 3	<5 years (General)	*Not Reported*	94.3% (78, 99)
EUR	Sweden (Galanis 2016)	Pre Post Survey	2+1	PCV7: 2007 PCV13: 2010	PCV7: 3 PCV13: 4	<6 years (General)	19.8% (NS)	46.2% (NS)
EUR	Italy (Mameli 2015; Zuccotti 2014)	Pre Post Survey	2+1	PCV7: 2006 PCV13: 2010	PCV7: 6 PCV13: 2	3-59 months (General)	2.9% (1,5)	51.6% (-6, 78)
WPR	Australia (Hoskins 2014; 2012 ; Collins 2013)	Post Survey	3+0	PCV7: 2005 PCV13: 2011	PCV7: 6 PCV13: 2	<5 years (Aboriginal)	*Not reported.*	*Not reported.*
WPR	Australia (Leach 2016; 2016)	Post Survey	3+0	PCV7: 2001 PCV10: 2009 PCV13: 2011	PCV7: 10 PCV10: 2 PCV13: 2	<6 years (Aboriginal)	*No change reported. Carriage measured in PCV10 and PCV13 periods (no baseline measure).*	*No change reported. Carriage measured in PCV10 and PCV13 periods (no PCV7 period measure).*

Studies highlighted in grey did not meet full inclusion criteria, but were included due to paucity of data.

TABLE 3. Observational studies estimating percent relative reduction against **serotype 3** NP Carriage among the general population

Study Information							% Relative Reduction (95% Confidence Interval) Compared to	
Region	**Country (Reference)**	**Study Design**	**Dosing Schedule**	**PCV Introduction Year(s)**	**Number of Years Post Introduction Carriage Evaluated**	**Age Group (s) (Population)**	**Baseline (no PCV)**	**PCV7 Period**
PCV10								
AFR	Mozambique (Sigaque; Moiane 2016)	Pre Post Survey	3+0	PCV10: 2013	PCV10: 2	0-23 months (HIV-) 0-59 months (HIV-)	*Not Reported* *Not Reported*	*PCV7 Not Used*
AFR	Kenya, Kilifi (Hammitt 2014; 2016)	Pre Post Survey	3+0	PCV10: 2011	PCV10: 4	<2 years (General) <5 years (General)	-9.1% (-403, 76) 42.3% (p=0.228)	*PCV7 Not Used*
AFR	Kenya, Nairobi (Kim 2016; 2014)	Pre Post Survey	3+0	PCV10: 2011	PCV10: 2	<5 years (General)	-62.2% (-177, 5)	*PCV7 Not Used*
AFR	Ethiopia (Tsegaye 2016)	Cohort	3+0	PCV10: 2011	PCV10: 1	9 months (General)	*Not Reported*	*PCV7 Not Used*

AMR	Brazil (Andrade 2014)	Cross-Sectional	3+0	PCV10: 2010	PCV10: 1	0-18 months (General)	*Not Reported*	*PCV7 Not Used*
EUR	Netherlands (Vissers 2016; Bosch 2015; 2014)	Pre Post Survey	2+1	PCV7: 2006 PCV10: 2011	PCV7: 5 PCV13: 5	<2 years (General)	-12.5% (-158, 51)	50% (-33, 81)
SEAR	Pakistan (Ali; Nisar 2016)	Pre Post Survey	3+0	PCV10: 2013	PCV10: 3	<2 years (General)	*Not Reported*	*PCV7 Not Used*
WPR	Fiji (Dunne; Russell 2016)	Pre Post Survey	3+0	PCV10: 2012	PCV10: 2	5 wk-23 months (General) 5 wk-6 years (General)	*Not Reported* *Not Reported*	*PCV7 Not Used*
WPR	Australia (Leach 2016; 2016)	Post Survey	3+0	PCV7: 2001 PCV10: 2009 PCV13: 2011	PCV7: 10 PCV10:2 PCV13: 2	<6 years (Aboriginal)	*Not Reported. Carriage measured in PCV10 and PCV13 periods (no baseline measure).*	*Not Reported. Carriage measured in PCV10 and PCV13 periods (no PCV7 period measure).*
PCV13								
AFR	Gambia (Roca 2014; 2015)	Pre Post Survey	3+0	PCV7: 2009 PCV13: 2011	PCV7: 2 PCV13: 1	6-11 months (General)	*Not Reported*	-200% (-23619, 100)

AFR	South Africa, Soweto (Nzenze 2014; 2015)	Pre Post Survey	2+1	PCV7: 2009 PCV13: 2011	PCV7: 2 PCV13: 2	<2 years (General) ≤ 48 months (General)	*Not Reported* *Not Reported*	-60% (-354, 44) 49.2% (-16, 78)
AFR	South Africa, Mpumalanga (Nzenze 2013; 2016)	Pre Post Survey	2+1	PCV7: 2009 PCV13: 2011	PCV7: 2 PCV13: 2	<2 years (General) <5 years (General)	*Not Reported* *Not Reported*	*Not Reported* *Not Reported*
AFR	Burkina Faso (Moisi 2016)	Pre Post Survey	3+0	PCV13: 2013	PCV13: 2	<5 years (General)	*Not Reported*	*PCV7 Not Used*
AFR	Malawi (Swarthout 2016)	Post Survey	3+0	PCV13: 2011	PCV13: 5	3-5 years (General)	*Not Reported*	*PCV7 Not Used*
EMR	Cambodia (SuyKuong 2016)	Pre Post Survey	3+0	PCV13: 2015	PCV13: 0.5	0-23 months (General) <5 years (General)	*Not Reported* 64.7% (3, 87)	*PCV7 Not Used*

EUR	Norway (Steens 2015; Vestrheim 2008; 2010)	Pre Post Survey	2+1	PCV7: 2006 PCV13: 2011	PCV7: 2 PCV13: 2	<2 years (Day Care) <59 months (Day Care)	*Not Reported* -10.3% (13, 8)	*Not Reported* 60.5% (26, 79)
EUR	France (Dunais 2015)	Pre Post Survey	2+1	PCV7: 2006 PCV13: 2010	PCV7: 2 PCV13: 2	3-40 months (Day Care)	*Not Reported*	*Not Reported*
EUR	Israel (Ben Shimol 2015; Danino 2016)	Pre Post Survey	2+1	PCV7: 2009 PCV13: 2010	PCV7: 2 PCV13: 5	7-23 months <5 years	*Not Reported* *Not Reported*	*Not Reported* *Not Reported*
EUR	Israel (Porat 2016)	Pre Post Survey	2+1	PCV7: 2009 PCV13: 2010	PCV7: 2 PCV13: 4	<5 years (General)	*Not Reported*	*Not Reported*
EUR	UK (Devine 2016; Jones 2016; Gladstone 2015)	Pre Post Survey	2+1	PCV7: 2006 PCV13: 2010	PCV7: 4 PCV13: 5	<4 years (General)	*Not Reported*	*Not Reported*

EUR	UK (Van Hoek 2014)	Pre Post Survey	2+1	PCV7: 2006 PCV13: 2010	PCV7: 3 PCV13: 3	<5 years (General)	*Not Reported*	*Not Reported*
EUR	Sweden (Galanis 2016)	Pre Post Survey	2+1	PCV7: 2007 PCV13: 2010	PCV7: 3 PCV13: 4	<6 years (General)	-54% (-133, -2)	-5% (-47, 25)
EUR	Italy (Mameli 2015; Zuccotti 2014)	Pre Post Survey	2+1	PCV7: 2006 PCV13: 2010	PCV7: 6 PCV13: 2	3-59 months (General)	*Not reported*.	-50%
WPR	Australia (Hoskins 2014; 2012 ; Collins 2013)	Post Survey	3+0	PCV7: 2005 PCV13: 2011	PCV7: 6 PCV13: 2	<5 years (Aboriginal)	*Not reported.*	*Not reported.*
WPR	Australia (Leach 2016; 2016)	Post Survey	3+0	PCV7: 2001 PCV10: 2009 PCV13: 2011	PCV7: 10 PCV10: PCV13: 2	<6 years (Aboriginal)	*No change reported. Carriage measured in PCV10 and PCV13 periods (no baseline measure).*	*No change reported. Carriage measured in PCV10 and PCV13 periods (no PCV7 period measure).*

Studies highlighted in grey did not meet full inclusion criteria, but were included due to paucity of data.

TABLE 4. Observational studies estimating percent relative reduction against **serotype 6A** NP Carriage among the general population

Study Information							% Relative Reduction (95% Confidence Interval) Compared to	
Region	**Country (Reference)**	**Study Design**	**Dosing Schedule**	**PCV Introduction Year(s)**	**Number of Years Post Introduction Carriage Evaluated**	**Age Group (s) (Population)**	**Baseline (no PCV)**	**PCV7 Period**
PCV10								
AFR	Mozambique (Sigaque; Moiane 2016)	Pre Post Survey	3+0	PCV10: 2013	PCV10: 2	0-23 months (HIV-) 0-59 months (HIV-)	*Not Reported*	*PCV7 Not Used*
AFR	Kenya, Kilifi (Hammitt 2014; 2016)	Pre Post Survey	3+0	PCV10: 2011	PCV10: 4	<2 years (General) <5 years (General)	16.5% (NS) 10.3% (NS)	*PCV7 Not Used*
AFR	Kenya, Nairobi (Kim 2016; 2014)	Pre Post Survey	3+0	PCV10: 2011	PCV10: 2	<5 years (General)	18.6% (-27, 48)	*PCV7 Not Used*
AFR	Ethiopia (Tsegaye 2016)	Cohort	3+0	PCV10: 2011	PCV10: 1	9 months (General)	*Not Reported*	*PCV7 Not Used*

AMR	Brazil (Andrade 2014)	Cross-Sectional	3+0	PCV10: 2010	PCV10: 1	0-18 months (General)	*Not Reported*	*PCV7 Not Used*
EUR	Netherlands (Vissers 2016; Bosch 2015; 2014)	Pre Post Survey	2+1	PCV7: 2006 PCV10: 2011	PCV7: 5 PCV13: 5	<2 years (General)	92.3% (86, 96)	84.4% (20, 97)
SEAR	Pakistan (Ali; Nisar 2016)	Pre Post Survey	3+0	PCV10: 2013	PCV10: 3	<2 years (General)	20.8% (-26, 50)	*PCV7 Not Used*
WPR	Fiji (Dunne; Russell 2016)	Pre Post Survey	3+0	PCV10: 2012	PCV10: 2	5 wk-23 months (General) 5 wk-6 years (General)	*Not Reported* *Not Reported*	*PCV7 Not Used*
WPR	Australia (Leach 2016; 2016)	Post Survey	3+0	PCV7: 2001 PCV10: 2009 PCV13: 2011	PCV7: 10 PCV10: PCV13: 2	<6 years (Aboriginal)	*Not Reported. Carriage measured in PCV10 and PCV13 periods (no baseline measure).*	*Not Reported. Carriage measured in PCV10 and PCV13 periods (no PCV7 period measure).*
PCV13								
AFR	Gambia (Roca 2014; 2015)	Pre Post Survey	3+0	PCV7: 2009 PCV13: 2011	PCV7: 2 PCV13: 1	6-11 months (General)	62.7% (39, 77)	*Not Reported*

AFR	South Africa, Soweto (Nzenze 2014; 2015)	Pre Post Survey	2+1	PCV7: 2009 PCV13: 2011	PCV7: 2 PCV13: 2	<2 years (General) ≤ 48 months (General)	71.8% (50, 84) *Not Reported*	*Not Reported* 67.1% (47, 80)
AFR	South Africa, Mpumalanga (Nzenze 2013; 2016)	Pre Post Survey	2+1	PCV7: 2009 PCV13: 2011	PCV7: 2 PCV13: 2	<2 years (General) <5 years (General)	*Not Reported*	*Not Reported*
AFR	Burkina Faso (Moisi 2016)	Pre Post Survey	3+0	PCV13: 2013	PCV13: 2	<5 years (General)	*Not Reported*	*PCV7 Not Used*
AFR	Malawi (Swarthout 2016)	Post Survey	3+0	PCV13: 2011	PCV13: 5	3-5 years (General)	*Not Reported*	*PCV7 Not Used*
EMR	Cambodia (SuyKuong 2016)	Pre Post Survey	3+0	PCV13: 2015	PCV13: 0.5	0-23 months (General) <5 years (General)	*Not Reported* 28.8% (5, 46)	*PCV7 Not Used*

EUR	Norway (Steens 2015; Vestrheim 2008; 2010)	Pre Post Survey	2+1	PCV7: 2006 PCV13: 2011	PCV7: 2 PCV13: 2	<2 years (Day Care) <59 months (Day Care)	*Not Reported* 44.6% (42, 47)	*Not Reported* 91.7% (70, 98)
EUR	France (Dunais 2015)	Pre Post Survey	2+1	PCV7: 2006 PCV13: 2010	PCV7: 2 PCV13: 2	3-40 months (Day Care)	*Not Reported*	*Not Reported*
EUR	Israel (Ben Shimol 2015; Danino 2016)	Pre Post Survey	2+1	PCV7: 2009 PCV13: 2010	PCV7: 2 PCV13: 5	7-23 months <5 years	*Not Reported* 13.7% (12, 16)	*Not Reported* 97.7% (93, 99)
EUR	Israel (Porat 2016)	Pre Post Survey	2+1	PCV7: 2009 PCV13: 2010	PCV7: 2 PCV13: 4	<5 years (General)	6.25% (p>0.05)	76.7% (p<0.05) (72, 81)
EUR	UK (Devine 2016; Jones 2016; Gladstone 2015)	Pre Post Survey	2+1	PCV7: 2006 PCV13: 2010	PCV7: 4 PCV13: 5	<4 years (General)	*Not Reported*	*Not Reported*

EUR	UK (Van Hoek 2014)	Pre Post Survey	2+1	PCV7: 2006 PCV13: 2010	PCV7: 3 PCV13: 3	<5 years (General)	*Not Reported*	*Not Reported*
EUR	Sweden (Galanis 2016)	Pre Post Survey	2+1	PCV7: 2007 PCV13: 2010	PCV7: 3 PCV13: 4	<6 years (General)	12% (-70, 54)	34% (-29, 66)
EUR	Italy (Mameli 2015; Zuccotti 2014)	Pre Post Survey	2+1	PCV7: 2006 PCV13: 2010	PCV7: 6 PCV13: 2	3-59 months (General)	*Not reported.*	23.5% (-325, 86)
WPR	Australia (Hoskins 2014; 2012 ; Collins 2013)	Post Survey	3+0	PCV7: 2005 PCV13: 2011	PCV7: 6 PCV13: 2	<5 years (Aboriginal)	*Not reported.*	*Not reported.*
WPR	Australia (Leach 2016; 2016)	Post Survey	3+0	PCV7: 2001 PCV10: 2009 PCV13: 2011	PCV7: 12 PCV10: 2 PCV13: 2	<6 years (Aboriginal)	*No change reported. Carriage measured in PCV10 and PCV13 periods (no baseline measure).*	*No change reported. Carriage measured in PCV10 and PCV13 periods (no PCV7 period measure).*

Studies highlighted in grey did not meet full inclusion criteria, but were included due to paucity of data.

TABLE 5. Observational studies estimating percent relative reduction against **serotype 19A** NP Carriage among the general population

Study Information							% Relative Reduction (95% Confidence Interval) Compared to	
Region	**Country (Reference)**	**Study Design**	**Dosing Schedule**	**PCV Introduction Year(s)**	**Number of Years Post Introduction Carriage Evaluated**	**Age Group (s) (Population)**	**Baseline (no PCV)**	**PCV7 Period**
PCV10								
AFR	Mozambique (Sigaque; Moiane 2016)	Pre Post Survey	3+0	PCV10: 2013	PCV10: 2	0-23 months (HIV-) 0-59 months (HIV-)	*Not Reported* *Not Reported*	*PCV7 Not Used*
AFR	Kenya, Kilifi (Hammitt 2014; 2016)	Pre Post Survey	3+0	PCV10: 2011	PCV10: 4	<2 years (General) <5 years (General)	-343.8% (p=0.005) (-1269, -44) -369.2% (p=0.001) (-1178, -72)	*PCV7 Not Used*
AFR	Kenya, Nairobi (Kim 2016; 2014)	Pre Post Survey	3+0	PCV10: 2011	PCV10: 2	<5 years (General)	-900% (-3357, -189)	*PCV7 Not Used*
AFR	Ethiopia (Tsegaye 2016)	Cohort	3+0	PCV10: 2011	PCV10: 1	9 months (General)	*Not Reported*	*PCV7 Not Used*

AMR	Brazil (Andrade 2014)	Cross-Sectional	3+0	PCV10: 2010	PCV10: 1	0-18 months (General)	*Not Reported*	*PCV7 Not Used*
EUR	Netherlands (Vissers 2016; Bosch 2015; 2014)	Pre Post Survey	2+1	PCV7: 2006 PCV10: 2011	PCV7: 5 PCV13: 5	<2 years (General)	-437.5% (-677, -272)	82.6% (75, 88)
SEAR	Pakistan (Ali; Nisar 2016)	Pre Post Survey	3+0	PCV10: 2013	PCV10: 3	<2 years (General)	*Not Reported*	*PCV7 Not Used*
WPR	Fiji (Dunne; Russell 2016)	Pre Post Survey	3+0	PCV10: 2012	PCV10: 2	5 wk-23 months (General) 5 wk-6 years (General)	*Not Reported* *Not Reported*	*PCV7 Not Used*
WPR	Australia (Leach 2016; 2016)	Post Survey	3+0	PCV7: 2001 PCV10: 2009 PCV13: 2011	PCV7: 10 PCV13: 2	<6 years (Aboriginal)	*Not Reported. Carriage measured in PCV10 and PCV13 periods (no baseline measure).*	*Not Reported. Carriage measured in PCV10 and PCV13 periods (no PCV7 period measure).*
PCV13								
AFR	Gambia (Roca 2014; 2015)	Pre Post Survey	3+0	PCV7: 2009 PCV13: 2011	PCV7: 2 PCV13: 1	6-11 months (General)	*Not Reported*	24.1% (-30, 56)

AFR	South Africa, Soweto (Nzenze 2014; 2015)	Pre Post Survey	2+1	PCV7: 2009 PCV13: 2011	PCV7: 2 PCV13: 2	<2 years (General) ≤ 48 months (General)	*Not Reported* *Not Reported*	*Not Reported* *Not Reported*
AFR	South Africa, Mpumalanga (Nzenze 2013; 2016)	Pre Post Survey	2+1	PCV7: 2009 PCV13: 2011	PCV7: 2 PCV13: 2	<2 years (General) <5 years (General)	*Not Reported*	*Not Reported*
AFR	Burkina Faso (Moisi 2016)	Pre Post Survey	3+0	PCV13: 2013	PCV13: 2	<5 years (General)	*Not Reported*	*PCV7 Not Used*
AFR	Malawi (Swarthout 2016)	Post Survey	3+0	PCV13: 2011	PCV13: 5	3-5 years (General)	*Not Reported*	*PCV7 Not Used*
EMR	Cambodia (SuyKuong 2016)	Pre Post Survey	3+0	PCV13: 2015	PCV13: 0.5	0-23 months (General) <5 years (General)	*Not Reported* -20.2% (-324, 66)	*PCV7 Not Used*

EUR	Norway (Steens 2015; Vestrheim 2008; 2010)	Pre Post Survey	2+1	PCV7: 2006 PCV13: 2011	PCV7: 2 PCV13: 2	<2 years (Day Care) <59 months (Day Care)	*Not Reported* 17.6% (16, 19)	*Not Reported* -35.7% (-209, 40)
EUR	France (Dunais 2015)	Pre Post Survey	2+1	PCV7: 2006 PCV13: 2010	PCV7: 2 PCV13: 2	3-40 months (Day Care)	-159.2% (-468, -18)	57.3% (14, 79)
EUR	Israel (Ben Shimol 2015; Danino 2016)	Pre Post Survey	2+1	PCV7: 2009 PCV13: 2010	PCV7: 2 PCV13: 5	7-23 months <5 years	*Not Reported* *Not Reported*	*Not Reported* *Not Reported*
EUR	Israel (Porat 2016)	Pre Post Survey	2+1	PCV7: 2009 PCV13: 2010	PCV7: 2 PCV13: 4	<5 years (General)	*Not Reported*	*Not Reported*
EUR	UK (Devine 2016; Jones 2016; Gladstone 2015)	Pre Post Survey	2+1	PCV7: 2006 PCV13: 2010	PCV7: 4 PCV13: 5	<4 years (General)	*Not Reported*	*Not Reported*

EUR	UK (Van Hoek 2014)	Pre Post Survey	2+1	PCV7: 2006 PCV13: 2010	PCV7: 3 PCV13: 3	<5 years (General)	*Not Reported*	*Not Reported*
EUR	Sweden (Galanis 2016)	Pre Post Survey	2+1	PCV7: 2007 PCV13: 2010	PCV7: 3 PCV13: 4	<6 years (General)	-94% (-231, -14)	33% (-4, 56)
EUR	Italy (Mameli 2015; Zuccotti 2014)	Pre Post Survey	2+1	PCV7: 2006 PCV13: 2010	PCV7: 6 PCV13: 2	3-59 months (General)	51.5% (50, 53)	52.8% (-133, 90)
WPR	Australia (Hoskins 2014; 2012 ; Collins 2013)	Post Survey	3+0	PCV7: 2005 PCV13: 2011	PCV7: 6 PCV13: 2	<5 years (Aboriginal)	*Not Reported*	*Not Reported*
WPR	Australia (Leach 2016; 2016)	Post Survey	3+0	PCV7: 2001 PCV10: 2009 PCV13: 2011	PCV7: 10 PCV10: 2 PCV13: 2	<6 years (Aboriginal)	*No change reported. Carriage measured in PCV10 and PCV13 periods (no baseline measure).*	*No change reported. Carriage measured in PCV10 and PCV13 periods (no PCV7 period measure).*

Studies highlighted in grey did not meet full inclusion criteria, but were included due to paucity of data.

TABLE 6. Observational studies estimating percent relative reduction in **PCV7-type** NP Carriage among the general population in settings where PCV7 was previously used

Study Information							% Relative Reduction (95% Confidence Interval)	
Region	**Country (Reference)**	**Study Design**	**Dosing Schedule**	**PCV Introduction Year(s)**	**Number of Years Post Introduction Carriage Evaluated**	**Age Group (s) (Population)**	**Compared to Baseline (no PCV)**	**Compared to Post-PCV7 Period**
PCV10								
EUR	Netherlands (Vissers 2016; Bosch 2015; 2014)	Pre Post Survey	2+1	PCV7: 2006 PCV10: 2011	PCV7: 5 PCV10: 5	<2 years (General)	91.4% (87, 94)	97.2% (63, 100)
WPR	Australia (Leach 2016; 2016)	Post Survey	3+0	PCV7: 2001 PCV10: 2009 PCV13: 2011	PCV7: 10 PCV10: 2	<6 years (Aboriginal)	*No data reported. Carriage measured in PCV10 and PCV13 periods (no baseline measure).*	*No data reported. Carriage measured in PCV10 and PCV13 periods (no PCV7 period measure).*
PCV13								
AFR	Gambia (Roca 2014; 2015)	Pre Post Survey	3+0	PCV7: 2009 PCV13: 2011	PCV7: 2 PCV13: 1	6-11 months (General)	47.9% (8, 71)	*Not Reported*
AFR	South Africa, Soweto (Nzenze 2014; 2015)	Pre Post Survey	2+1	PCV7: 2009 PCV13: 2011	PCV7: 2 PCV13: 2	<2 years (General) ≤ 48 months (General)	37.7% (24, 49) *Not Reported*	*Not Reported* 61.2% (53, 68)

AFR	South Africa, Mpumalanga (Nzenze 2013; 2016)	Pre Post Survey	2+1	PCV7: 2009 PCV13: 2011	PCV7: 2 PCV13: 2	<2 years (General) <5 years (General)	47.2% (30, 60) 39.1% (35, 46)	*Not Reported* 47.1% (35, 57)
EUR	Norway (Steens 2015; Vestrheim 2008; 2010)	Pre Post Survey	2+1	PCV7: 2006 PCV13: 2011	PCV7: 2 PCV13: 2	<2 years (Day Care) <59 months (Day Care)	85.7% (48, 96) 52.3% (48, 59)	*Not Reported* 88.1% (80, 93)
EUR	France (Dunais 2015)	Pre Post Survey	2+1	PCV7: 2006 PCV13: 2010	PCV7: 2 PCV13: 2	3-40 months (Day Care)	100% (-27, 100)	*Not Reported*
EUR	Israel (Ben Shimol 2015; Danino 2016)	Pre Post Survey	2+1	PCV7: 2009 PCV13: 2010	PCV7: 2 PCV13: 5	7-23 months <5 years	58.9% (46, 69) 42.9% (40, 48)	*Not Reported* 64.6% (55, 72)
EUR	Israel (Porat 2016)	Pre Post Survey	2+1	PCV7: 2009 PCV13: 2010	PCV7: 2 PCV13: 4	<5 years (General)	*Not Reported*	*Not Reported*

EUR	UK (Devine 2016; Jones 2016; Gladstone 2015)	Pre Post Survey	2+1	PCV7: 2006 PCV13: 2010	PCV7: 4 PCV13: 5	<4 years (General)	92% (88, 95)	99.4% (89, 100)
EUR	UK (Van Hoek 2014)	Pre Post Survey	2+1	PCV7: 2006 PCV13: 2010	PCV7: 3 PCV13: 3	<5 years (General)	86.8% (80, 92)	90.5% (31, 99)
EUR	Sweden (Galanis 2016)	Pre Post Survey	2+1	PCV7: 2007 PCV13: 2010	PCV7: 3 PCV13: 4	<6 years (General)	59% (50, 66)	66% (56, 74)
EUR	Italy (Mameli 2015; Zuccotti 2014)	Pre Post Survey	2+1	PCV7: 2006 PCV13: 2010	PCV7: 6 PCV13: 2	3-59 months (General)	52.8% (51, 56)	79.8% (11, 95)
WPR	Australia (Hoskins 2014; 2012 ; Collins 2013)	Post Survey	3+0	PCV7: 2005 PCV13: 2011	PCV7: 6 PCV13: 2	<5 years (Aboriginal)	*Not Reported*	*Not Reported*

WPR	Australia (Leach 2016; 2016)	Post Survey	3+0	PCV7: 2001 PCV10: 2009 PCV13: 2011	PCV7: 10 PCV10: 2 PCV13: 2	<6 years (Aboriginal)	*No change reported. Carriage measured in PCV10 and PCV13 periods.*	*No change reported. Carriage measured in PCV10 and PCV13 periods*

Studies highlighted in grey did not meet full inclusion criteria, but were included due to paucity of data.

TABLE 7. Observational studies estimating percent relative reduction against NP Carriage of the 3 additional serotypes in PCV10 or the 6 additional serotypes in PCV13 among the general population in settings where PCV7 was previously used

Study Information							% Relative Reduction (95% Confidence Interval)	
Region	**Country (Reference)**	**Study Design**	**Dosing Schedule**	**PCV Introduction Year(s)**	**Number of Years Post Introduction Carriage Evaluated**	**Age Group (s) (Population)**	**Compared to Baseline (no PCV)**	**Compared to Post-PCV7 Period**
PCV10								
EUR	Netherlands (Vissers 2016; Bosch 2015; 2014)	Pre Post Survey	2+1	PCV7: 2006 PCV10: 2011	PCV7: 5 PCV10: 5	<2 years (General)	-13.1% (-235, 62)	100% (NS)
WPR	Australia (Leach 2016; 2016)	Post Survey	3+0	PCV7: 2001 PCV10: 2009 PCV13: 2011	PCV7: 10 PCV10:2 PCV13: 2	<6 years (Aboriginal)	*No change reported. Carriage measured in PCV10 and PCV13 periods (no baseline measure).*	*No change reported. Carriage measured in PCV10 and PCV13 periods (no PCV7 period measure).*
PCV13								
AFR	Gambia (Roca 2014; 2015)	Pre Post Survey	3+0	PCV7: 2009 PCV13: 2011	PCV7: 2 PCV13: 1	6-11 months (General)	*Not Reported*	42.7% (21, 59)
AFR	South Africa, Soweto (Nzenze 2014; 2015)	Pre Post Survey	2+1	PCV7: 2009 PCV13: 2011	PCV7: 2 PCV13: 2	<2 years (General) ≤ 48 months (General)	-240.3% (-368, -147) *Not Reported*	75.3% (66, 82) 68.7% (59, 76)

AFR	South Africa, Mpumalanga (Nzenze 2013; 2016)	Pre Post Survey	2+1	PCV7: 2009 PCV13: 2011	PCV7: 2 PCV13: 2	<2 years (General) <5 years (General)	1.9% (-29, 26) 0.9% (NS)	69.7% (52, 81) 68.6% (55, 78)
EUR	Norway (Steens 2015; Vestrheim 2008; 2010)	Pre Post Survey	2+1	PCV7: 2006 PCV13: 2011	PCV7: 2 PCV13: 2	<2 years (Day Care) <59 months (Day Care)	43.8% (-21, 74) 27.9% (25, 31)	55.6% (-24, 84) 50.9% (26, 68)
EUR	France (Dunais 2015)	Pre Post Survey	2+1	PCV7: 2006 PCV13: 2010	PCV7: 2 PCV13: 2	3-40 months (Day Care)	-56.8% (-156, 4)	74.9% (52, 87)
EUR	Israel (Ben Shimol 2015; Danino 2016)	Pre Post Survey	2+1	PCV7: 2009 PCV13: 2010	PCV7: 2 PCV13: 5	7-23 months <5 years	*Not Reported* 2.3% (-1, 5)	54.3% (41, 65) 82.9% (78, 87)
EUR	Israel (Porat 2016)	Pre Post Survey	2+1	PCV7: 2009 PCV13: 2010	PCV7: 2 PCV13: 4	<5 years (General)	*Not Reported*	*Not Reported*

EUR	UK (Devine 2016; Jones 2016; Gladstone 2015)	Pre Post Survey	2+1	PCV7: 2006 PCV13: 2010	PCV7: 4 PCV13: 5	<4 years (General)	-13159% (p=0.0381)	50% (p=0.0381) (-103, 88)
EUR	UK (Van Hoek 2014)	Pre Post Survey	2+1	PCV7: 2006 PCV13: 2010	PCV7: 3 PCV13: 3	<5 years (General)	43.3% (38, 49)	96% (73, 99)
EUR	Sweden (Galanis 2016)	Pre Post Survey	2+1	PCV7: 2007 PCV13: 2010	PCV7: 3 PCV13: 4	<6 years (General)	-26% (-44, 43)	23% (17, 37)
EUR	Italy (Mameli 2015; Zuccotti 2014)	Pre Post Survey	2+1	PCV7: 2006 PCV13: 2010	PCV7: 6 PCV13: 2	3-59 months (General)	-61.8% (-63, -61)	15% (-132, 69)
WPR	Australia (Hoskins 2014; 2012 ; Collins 2013)	Post Survey	3+0	PCV7: 2005 PCV13: 2011	PCV7: 6 PCV13: 2	<5 years (Aboriginal)	*Not Reported*	18% (0.4, 33)

WPR	Australia (Leach 2016; 2016)	Post Survey	3+0	PCV7: 2001 PCV10: PCV13: 2011	PCV7: 12 PCV10: PCV13: 2	<6 years (Aboriginal)	*No change reported. Carriage measured in PCV10 and PCV13 periods.*	*No change reported. Carriage measured in PCV10 and PCV13 periods.*

Studies highlighted in grey did not meet full inclusion criteria, but were included due to paucity of data.

TABLE 8. Randomized Controlled Trials estimating percent relative reduction against NP Carriage of the **Vaccine-Type Serotypes, Serotype 3, Serotype 6A, and Serotype 19A** among the general population

Study Information			PCV10 or PCV13		Serotype 3		Serotype 6A		Serotype 19A	
Region	**Country (Reference)**	**Dosing Schedule**	**Baseline**	**% Reduction**	**Baseline**	**% Reduction**	**Baseline**	**% Reduction**	**Baseline**	**% Reduction**
PCV10										
SEAR	Nepal (Hamaluba 2015)	2+0	9	6 (118, 60)	1	-245 (-3165, 64)	6	43 (-85, 82)	3	43 (-85, 82)
SEAR	Nepal (Hamaluba 2015) * combined 2+1 and 3+0 groups for more stat power	2+0 & 3+0	9	6 (-92, 54)	1	-130 (-1932, 74)	6	43 (-49, 78)	3	71 (-54, 95)
EUR	Finland (Jokinen 2016)	2+1	13	61 (35, 76)	*Not Reported*	*Not Reported*	*Not Reported*	*Not Reported*	*Not Reported*	*Not Reported*

WPR	Vietnam (Temple 2016, Smith-Vaughan 2016)	2+1	9	51 (-1, 77)	0	-140 (-11326, 69)	7	32 (-54, 70)	2	-94 (-647, 50)
AMR	COMPAS (Borys 2012)	2+1	14	26 (NS)	*Not Reported*	*Not Reported*	*Not Reported*	*Not Reported*	*Not Reported*	*Not Reported*
SEAR	Nepal (Hamaluba 2015)	3+0	9	6 (-118, 60)	1	-15 (-1714, 93)	6	43 (-85, 82)	3	100 (NS)
WPR	Vietnam (Smith-Vaughan 2016)	3+0	9	15 (-79, 60)	*Not Reported*	*Not Reported*	7	89 (11, 99)	2	-194 (-1061, 26)
EUR	Czech Republic (Prymula 2011)	3+0	16	34 (4, 55)	*Not Reported*	*Not Reported*	*Not Reported*	*Not Reported*	*Not Reported*	*Not Reported*

EUR	Czech Republic (Prymula 2012)	3+0	16	49 (11, 70)	*Not Reported*	*Not Reported*	*Not Reported*	*Not Reported*	*Not Reported*	*Not Reported*
EUR	Netherlands (van den Bergh 2013)	3+0	*Not Reported*	*Not Reported*	*Not Reported*	*Not Reported*	*Not Reported*	*Not Reported*	7	-23 (-111, 29)
WPR	Vietnam (Smith-Vaughan 2016)	3+1	9	52 (-18, 81)	*Not Reported*	*Not Reported*	7	23 (-91, 69)	2	100 (NS)
EUR	Netherlands (van den Bergh 2013)	3+1	*Not Reported*	*Not Reported*	*Not Reported*	*Not Reported*	*Not Reported*	*Not Reported*	7	5 (-61, 45)
PCV13										
WPR	Vietnam (Temple 2016)	2+1	17	33 (-8, 59)	0	0 (NS)	7	59 (-6, 84)	2	-13 (-399, 75)

EUR	Poland (Grzesiowski 2014) **ST 19A increased from 3 to 4 cases*	2+1	16	91 (78, 96)	*Not Reported*	*Not Reported*	*Not Reported*	*Not Reported*	*Not Reported*	*Not Reported*
EUR	Israel (Dagan 2013) **Carriage measures new acquisition*	3+0	29	24 (11, 35)	*Not Reported*	*Not Reported*	5	40 (4, 63)	7	36 (5, 56)
EUR	Israel (Dagan 2013) **Carriage measures new acquisition*	3+1	57	29 (21, 35)	2	5 (-87, 52)	13	42 (22, 56)	23	45 (32, 56)

*Negative reduction indicates an increase in carriage

TABLE 9. Head to Head Randomized Controlled Trials comparing NP Carriage in PCV10 and PCV13 among the general population

Region	Country (Reference)	Dosing Schedule	Product	% Carriage					
				All Carriage	PCV10	PCV13	3, 6A, 19A		
WPR	Papau New Guinea (Pomat 2016, Orami 2016) ** Data taken from the Orami paper 9 mos group*	3+0	PCV13	89.0%	22%	30.0%	8		
			PCV10	90.0%	19%	32.0%	14		
				All Carriage	PCV10	PCV13	3	6A	19A
WPR	Vietnam (Temple 2016)	2+1	PCV10	24.0%	4.5%	14.0%	2.0%	5.0%	3.0%
			PCV13	25.0%	7.1%	12.0%	0.0%	3.0%	2.0%

TABLE 10. Characteristics 0f Studies included in Pneumonia Analysis

Characteristic	PCV10 N= 6	PCV13 N= 27	Total N= 32
Study type*			
Clinical trial	1	0	1
Case- control	0	6	6
Observational	5	23	28
Region			
Africa	1	7	8
Asia	0	0	0
Australia/Oceania	2	0	2
Europe	3	10	12
Latin America	0	10	10
North America	0	0	0
PCV dosing schedule			
2+1	3	22	24
3+0	3	5	8
Endpoint			
Clinical pneumonia (including LRTI)	6	15	20
Radiologically-confirmed pneumonia	2	13	15
Pneumococcal pneumonia	0	4	4
Empyema	0	5	5

*One study evaluates PCV10 and PCV13 (Berglund, Sweden) and has been counted in both PCV10 and PCV13 columns. Two studies (Mackenzie, Gambia; Moisi, Rwanda) evaluate PCV impact using a case-control/ indirect cohort design and a pre/post observational study design.

TABLE 11. Summary Characteristics Of Controlled Trials Evaluating A Pneumonia Endpoint, By Schedule

Country	Reference	Study design	Vaccine product	Dosing schedule	Endpoint and Case Definition	Vaccine Efficacy (95% CI)		Comments
						Intent to Treat	Per Protocol	
Finland	Kilpi ISPPD 2016	Randomized Controlled trial	PCV10	Doses >8 weeks apart; booster at >11 months	Hospital-diagnosed clinical pneumonia	28% (6 to 45)		Vaccine efficacy for a 2+1 schedule
					Consolidated pneumonia	43% (19 to 61)		

TABLE 12. Summary Characteristics And Findings Of Case-Control Studies Evaluating A Pneumonia Endpoint

Country (Reference)	Study design	Population	PCV product and dosing schedule	Endpoint	Comparison group	VE compared to no PCV (95% CI)				Comments
						2+1	3+0	≥1 dose	≥2 doses	
2+1										
Israel (Givon-Lavi, ISPPD 2014)	Case-control	2-12 months	PCV7/PCV13 (2, 4, 12 months)	CXR-confirmed pneumonia	Children with rotavirus-negative gastroenteritis				40.6 (11.1-60.3)	49.5% of doses were PCV13
Spain (Madrid) (Tagarro, J Pediatr 2016)	Case-control	2-12 months	PCV13 (2, 4, 12 months)	Bacteremic pneumonia	Children with bacterial pneumonia			86.0 (70.0-95.0) (compared to <1 doses)	68.0 (60.0-96.0) (compared to <2 doses)	
South Africa (Madhi, Thorax 2015)	Case-control	8-103 weeks	PCV13 (6, 14, 39 weeks)	CXR-confirmed pneumonia (WHO)	Hospital	20.1(-9.3-41.6) (adjusted)				
					Community	32.1 (4.6-51.6) (adjusted)				
3+0										
The Gambia (Mackenzie, unpublished)	Case-control	3-11 months	PCV13 (2, 3, 4 months)	CXR-confirmed pneumonia (WHO)	Community		63 (-8 to 70)	-8 (-83 to 37) (1 dose)	17 (-50 to 54) (2 doses)	
		≥12 months			Community		7 (-264 to 76)	-29 (-536 to 74) (1 dose)	26 (-216 to 83) (2 doses)	
Rwanda (Gatera, Vaccine 2016)	Indirect cohort	<5 years	PCV7/PCV13 (6, 10, 14 weeks)	Severe pneumonia	Mild pneumonia		54 (42 to 63)			Early post introduction
Togo (Moisi, ISPPD 2016)	Indirect cohort	<5 years	PCV13 (6, 10, 14 weeks)	CXR pneumonia	non-CXR pneumonia		58 (-100 to 99)			Early post-introduction and small sample size
				Severe pneumonia (WHO)	non-severe pneumonia		80 (-90 to 100)			
				Pneumonia with CRP >40 mg/L	pneumonia without CRP >40 mg/L		-2% (-30 to 80)			

TABLE 13. Summary Characteristics And Findings Of Pre/Post Observational Studies Evaluating A Pneumonia Endpoint, PCV10

Country	Reference	Case Definition	Study design	Dosing schedule	Age groups evaluated	Surveillance years reported*			Baseline measure (per 100,000)		% change at post-PCV introduction period compared to †¶		Comments
						Pre-PCV	Post-PCV7/Pre-PCV10	Post-PCV10	Pre-PCV	Post-PCV7/ Pre-PCV10	Pre-PCV	Post-PCV7/ Pre-PCV10	
Clinical pneumonia													
2+1													
Iceland	Kristinsson, ISPPD 2014	Not stated	Pre/post	3, 5, 12 months	<15 months	3	-	1.5	2,800		-36%¶		
Sweden	Berglund, PLoS One 2014	ICD-10 codes (J12-J18)	Pre/post	3, 5, 12 months	<2 years	11	1	2	654.7	504.4 per 100,000	-21%¶	+3%	
3+0													
Fiji	Tuivaga, ISPPD 2016	ICD- 10 codes (including bronchiolitis)	Pre/post	6, 10, 14 weeks	<2 years	5	-	2	Not reported		-18%¶		
		ICD- 10 codes (excluding bronchiolitis)							Not reported		-32%¶		
Fiji	Russell, ISPPD 2016	ICD-10 codes (iTaukei)	Pre/post	6, 10, 14 weeks	<2 years	5	-	1.5	4,250		-19%¶		% change calculated from IRs given in graph
		ICD-10 codes (FID)							1,500		-13.3%¶		
Kenya	Silaba, ISPPD 2016	WHO definition-severe/very severe	Pre/post	6, 10, 14 weeks	2-59 months	9	-	4	2,170		-27%¶		Baseline measure for 2002/2003
Radiologically-confirmed pneumonia													
3+0													
Kenya	Silaba, ISPPD 2016	WHO	Pre/post	6, 10, 14 weeks	2-59 months	9	-	4	Not reported		-48%¶		

* Years of pre- PCV data exclude the year of PCV introduction

† Negative percent change indicates a percent reduction; Positive percent change indicates a percent increase

¶Significance of $p < 0.05$

Table 14. Summary Characteristics And Findings Of Pre/Post Observational Studies Evaluating A Pneumonia Endpoint, PCV13

Country	Reference	Case Definition	Study design	Dosing schedule	Age groups evaluated	Surveillance years reported*			Baseline measure (per 100,000)		% change at post-PCV introduction period compared to †¶		Comments
						Pre-PCV	Post-PCV7/Pre-PCV13	Post-PCV13	Pre-PCV	Post-PCV7/ Pre-PCV13	Pre-PCV	Post-PCV7/ Pre-PCV13	
Clinical pneumonia													
2+1													
Argentina (Pilar)	Gentile, ISPPD 2016 (#99)	Clinical diagnosis	Pre/post	2, 4, 12 months	<12 months	3	-	2	Not reported		-50.4%¶		
					12-23 months				Not reported		-68.4%¶		
					24-59 months				Not reported		-36.1%¶		
					<5 years				Not reported		-49.7%¶		
Argentina (Rosario)	Lopez Papucci, ISPPD 2016	Not stated	Pre/post	2, 4, 12 months	<1 year	4	-	2	Not reported		0		
					1 year				Not reported		-43.2%¶		
					2-4 years				Not reported		-38.2%¶		
Argentina	Vizzotti, ISPPD 2016	Not stated (NESS data)	Pre/post	2, 4, 12 months	<1 year	2	-	3	3,295		-27.3%¶		
					<5 years				5,545		-27.8%¶		
Costa Rica	Castro, ISPPD 2016	Not stated	Pre/post	2, 4, 15 months	≤2 years	4	2	2	1,180	850	-35.0%¶	-9%¶	
Mexico	Palacios ISPPD 2016	ICD-10 codes	Pre/post	2, 4, 12 months	≤ 4 years	0	6	4		2,443		-60.5%	PCV10 used for 8 months in 2010 and changed to PCV13; significance unknown

Spain (Galicia)	Rivero-Calle, ISPPD 2016	ICD-9 codes (480-486, 487)	Pre/post	2, 4, 12 months	<2 years	6	5	2	Not reported	-23.1%¶		-58.0%¶	Not clear in abstract if Post-PCV13 % change is compared to pre-vaccine or post-PCV7
					2-4 years				Not reported	-9.7%		-54.8%¶	
Sweden	Berglund, PLoS One 2014	ICD-10 codes (J12-J18)	Pre/post	3, 5, 12 months	<2 years	11	1	2	654.7	504.4	-37%¶	-18%	PCV13 v. PCV7 % change borderline significant
UK	Saxena, J Infect 2015	ICD-10 codes (J12-J18)	Pre/post	2, 3, 13 months	<2 years	5	4	4		-20%¶		+8%	Post-PCV periods include year of introduction
					2-4 years					-12%¶		+24%¶	
UK (Scotland)	Nath, Arch Dis Child, 2015	ICD-10 codes (J12-J18)	Pre/post	2, 3, 13 months	<1 year	24	4	4	Baseline measure only available for <14 years	-13%¶		-6%	Post-PCV periods include year of introduction
					1-4 years					+1%		-12%¶	
3+0													
Malawi	McCollum, PLoS One, 2017	WHO clinical pneumonia	Post	6, 10, 14 weeks	<5 years	0	-	2.5	1,067 (hospital, 2012)		+47		Post-PCV compared to early post-PCV
		WHO clinical pneumonia + hypoxemia							119 (hospital, 2012)		-46.8¶		
Radiologicallly-confirmed pneumonia													
2+1													
Argentina	Gentile, ISPPD 2016 (#100)	Not stated	Pre/post	2, 4, 12 months	<5 years	5	-	2	Not reported		-32.9%¶		

Argentina (Rosario)	Lopez Papucci, ISPPD 2016	Culture-negative plus pneumococcal consolidate pneumonia	Pre/post	2, 4, 12 months	1 year	4	-	2	Not reported		-66.2%¶		
					2-4 years				Not reported		-45.5%¶		
Argentina (Concordia)	Rearte, ISPPD 2016	Chest radiograph	Pre/post	2, 4, 12 months	<5 years	4	-	2	732		-53.3%¶		
Israel	Givon-Lavi ISPPD 2016	Not stated	Pre/post	2, 4, 12 months	<2 years Bedouin	4	2	2	2,840	2,660	-51%¶	-48%	PCV7 period includes PCV13 year of introduction; PCV13 v. PostPCV7 % change calculated
					<2 years Jewish				1,650	1,410	-49%¶	-40%	
Israel	Greenberg, Vaccine 2015	WHO	Pre/post	2, 4, 12 months	<12 months	7	2	2	1,870	2,020	-34%¶	-38%¶	PCV7 period includes PCV13 year of introduction
					12-23 months				990	930	-34%¶	-30%¶	
					24-59 months				390	730	-27%¶	-36%¶	
Israel	Greenberg ISPPD 2016	Not stated	Pre/post	2, 4, 12 months	<5 years	4	2	2	Not reported	Not reported	+15%¶	-40%¶	Related to Greenberg, Vaccine 2015 article; PCV7 period includes PCV13 year of introduction
Uruguay	Laurani, ISPPD 2014	WHO	Cohort	2, 4, 12 months	<2 years		1	4		-69.3% among children vaccinated with 3 doses		-85% among children vaccinated with 3 doses	Significance unknown; time period for % change unknown; PCV13 period

													includes year of introduction; only 1 year of baseline data
3+0													
Nicaragua	Becker-Dreps, PIDJ 2014	Physician diagnosis	Pre/post	2, 4, 6 months	<12 months	3	-	2	6,400		-33%¶		
					12-23 months				2,500		-26%¶		
Pneumococcal pneumonia													
2+1													
Argentina	Gentile, ISPPD 2016 (#100)	Not stated	Pre/post	2, 4, 12 months	<5 years	5	-	2	Not reported		-72.1%¶		
Empyema													
2+1													
Argentina (Concordia)	Rearte, ISPPD 2016	pleural effusion	Pre/post	2, 4, 12 months	<5 years	4	-	2	103		-84.5%¶		
UK (Scotland)	Nath, Arch Dis Child, 2015	ICD codes (J86.9 and A156-165)	Pre/post	2, 3, 13 months	<1 year	24	4	4	Baseline measure only available for <14 years	+72%		-53%	Post-PCV periods include year of introduction
					1-4 years					+126%¶		-8%	
UK	Saxena, J Infect 2015	ICD-10 codes (J86.0, J86.9)	Pre/post	2, 3, 13 months	<2 years	5	4	4		-41%¶		-42%¶	Post-PCV periods include year of introduction
					2-4 years					-20%		+22%	

* Years of pre- and post-PCV data exclude the year of PCV introduction, unless stated otherwise

† Negative percent change indicates a percent reduction; Positive percent change indicates a percent increase

¶Significance of $p < 0.05$

Studies highlighted in grey did not meet full inclusion criteria, but were included due to paucity of data.

TABLE 15. Summary Characteristics and Findings of Pre/Post Observational Studies Evaluating a Pneumonia Endpoint, PCV7/13

Country	Reference	Case Definition	Study design	Dosing schedule	Age groups evaluated	Surveillance years reported*			Baseline measure (per 100,000)		% change at post-PCV introduction period compared to [†¶]		Comments
						Pre-PCV	Post-PCV7/Pre-PCV13	Post-PCV13	Pre-PCV	Post-PCV7/ Pre-PCV13	Pre-PCV	Post-PCV7/ Pre-PCV13	
Clinical pneumonia													
2+1													
South Africa	Izu ISPPD 2016	Not stated	Pre/post	6, 14 weeks; 9 months;	<5 years, HIV-uninfected	3	2	4	Not stated		-44%[¶]		Significant reductions in 0-3m, 3-12m, 2-5y, not 1-2y; PCV13 period includes year of introduction
Sweden	Lindstrand, Pediatr 2014	ICD-10 codes (J13-J18)	Pre/post	3, 5, 12 months	<2 years	4	2	3	450		-19%[¶]		PCV13 period includes year of introduction
					2 - <5 years				250		-15%[¶]		
3+0													
The Gambia	MacKenzie, unpublished	Hypoxic pneumonia	Pre/post	2, 3, 4 months	2-11 months	1	1	2	1,310		-57%[¶]		Only 1 year of baseline data
					12-23 months				680		-72%[¶]		
					24-59 months				130		-56%[¶]		
Rwanda	Gatera, Vaccine 2016	Severe pneumonia	Pre/post	6, 10, 14 weeks	<5 years	7	1	1		67.1	-70.3%[¶]		Change is for latest year; only 1 year post-PCV13 introduction
		Mild pneumonia								331.5	+7.6%[¶]		
Radiologicallly-confirmed pneumonia													
2+1													

Uruguay	Pirez, PIDJ 2014	Clinical signs + radiograph (clinical reading)	Pre/post	2, 4, 12 months	<14 years	5	2	2	8,791		-78.1%¶		Change is for latest year; % Post-PCV7 periods includes PCV13 year of introduction
3+0													
The Gambia	MacKenzie, unpublished	WHO	Pre/post	2, 3, 4 months	2-11 months	1	1	2	2,100		-23%¶		Only 1 year of baseline data
					12-23 months				1,600		-29%¶		
					24-59 months				500		-22%¶		
Pneumococcal pneumonia													
2+1													
Uruguay	Pirez, PIDJ 2014	Isolation of pneumococcus from blood or pleural fluid	Pre/post	2, 4, 12 months	<14 years	5	2	2	662	608 (PCV13 add. 6 st)	-90.4%¶	-97.1%¶ for PCV13 add. 6 st	Change is for latest year; Post-PCV7 periods includes PCV13 year of introduction
3+0													
The Gambia	MacKenzie, unpublished	pneumococcal pneumonia	Pre/post	2, 3, 4 months	2-11 months	1	1	2	290		-58%¶		Only 1 year of baseline data
					12-23 months				260		-75%¶		
					24-59 months				110		-57%¶		
Empyema													
2+1													
South Africa	Zampoli, PIDJ 2015	pleural effusion with purulent or turbid pleural tap	Pre/post	6, 14 weeks; 9 months;	<12 years	2	2	3	1,040 pneumonia admissions (2007-2011; PCV7 introduced in 2009)		-50%¶		92% of children in "pre" cohort unimmunized with full series
Sweden	Lindstrand, Pediatr 2014	ICD-10 codes (J86)	Pre/post	3, 5, 12 months	<2 years	4	2	3	2.5		+78%		PCV13 period includes year of

					2 - <5 years				1.8		+68%		introduction

* Years of pre- and post-PCV data exclude the year of PCV introduction, unless stated otherwise

† Negative percent change indicates a percent reduction; Positive percent change indicates a percent increase

¶Significance of $p < 0.05$

Studies highlighted in grey did not meet full inclusion criteria, but were included due to paucity of data.

TABLE 16. Characteristics of included studies in IPD Analysis

Characteristic	2+1 N= (%)	3+0 N= (%)	Total N= (%)
Study type			
Clinical trial	1	0	1
Pre/post surveillance	25	4	30*
Case- control/indirect cohort	7	2	11*
Region			
Africa	5	2	7
Asia	1	1	2
Australia/Oceania		3	3
Europe	20		21*
Latin America	4		6*
North America	3		3
PCV product			
PCV10	9	3	12*
PCV13	24	3	30*
Endpoint			
VT IPD	30	6	39*
VT Meningitis	2	0	2
VT Bacteremic Pneumonia	1	0	1

*Two case-control studies and one pre-post study conducted in a setting of a 3+1 schedule included

Clinical trials summary:

A cluster randomized double-blind trial of PCV10 in Finland demonstrated a 92% (95%CI 58–100) efficacy for 2+1 schedule among children <19 month old (Palmu et al. Lancet 2013). An extended follow up of the disease register for this trial demonstrated an 80% (95%CI 7-97) efficacy for a combined 2+1/3+1 schedule (Palmu et al ISPPD 2016).

TABLE 17. Observational studies estimating vaccine effectiveness against VT-IPD by schedule

Study				VE compared to no vaccine (95%CI)				
Country (Reference)	**Study Design**	**Population age**	**PCV product (Country Schedule)**	**VT group**	**2+1**	**3+0**	**≥1 dose**	**≥2 doses**
PCV13								
United Kingdom (Miller et al., 2011) (Andrews et al., 2014)	Indirect cohort	2.5-<24 months	PCV13 (2+1)	PCV13+6C PCV13/non-PCV7 PCV7	79% (25-94%)		69% (37-85%) 73% (57-83%) 83% (35-96%)	73% (55-84%)[1] 90% (34-98%)[1]
Canada (Deceuninck et al., 2015)	Case-control	2-59 months	PCV13 (2+1), catch up for <5 years	PCV13			86% (62-95%)	
South Africa (Von Gottberg et al. ISPPD 2016)	Case-control	6 weeks-9 months	PCV13 (2+1)	PCV13				85% (37-96%)
Dominican Republic (Tomczyk et al. ISPPD	Case-control		PCV13 (2+1)	PCV13			64% (-47-94%)	

2016)								
Australia (Gidding et al. ISPPD 2016)	Cohort	<2 months	PCV7/PCV13 (3+0)	PCV7		92% (86-93%)		
Spain (Guevara et al., 2016)	Case-control	2-13.5 months	PCV13 (3+1)	PCV13 PCV13/non-PCV7			96% (43-100%) 95% (30-100%)	
PCV10								
Finland (Auranen et al. ISPPD 2014) Rinta-Kokko et al. ISPPD 2016)	Indirect cohort Indirect cohort Case-control Cohort	≥3 months, PCV10 eligible < 5 years	PCV10 (2+1)	PCV10			 95% (42-100%) 78% (17-94%) 93% (76-98%)	95% (47-99%)
Netherlands (Knol et al. ISPPD 2016)	Indirect cohort	2-54 months	PCV10 (2+1)	PCV10			89% (41-98%)	
Canada (Deceuninck et al., 2015)	Case-control	2-59 months	PCV10 (2+1)	PCV10+6A			97% (84-99%)	
Pakistan (Ali et al. Unpublished)	Case-control	<5 years	PCV10 (3+0)	PCV10			76.5% (NS)	80.3 (NS)
Brazil (Domingues et al	Case-control	<5 years	PCV10 (3+1), catch	PCV10			84% (66-92%)[2]	

2014) (Verani et al 2015)	Indirect cohort		up for 12-23 months				74% (42-88%)[2]	

[1]VE for at least 2 doses before age 12 months or one dose on or after age 12 months

[2]VE for up to date for age number of doses

TABLE 18. Observational studies documenting impact of PCV introduction on all IPD, VT-IPD, meningitis or bacteremia among young children before and after vaccine introduction, by PCV dosing schedule

Reference	Outcome, age groups	Country	PCV product(s)	Surveillance years reported			Baseline incidence (cases/100,000)			Percent change at maximum years post-introduction compared to	
				PrePCV	Post-PCV7/pre-PCV10/13	Post-PCV10/13	VT group	PrePCV	Post-PCV7/pre-PCV10/13	Pre-PCV	Post-PCV7/pre-PCV10/13
PCV7-PCV10 (2+1)											
De Wals et al. Vaccine 2014	VT IPD, <2 years	Canada (Quebec)	PCV7, PCV10	4	5	2	PCV7 PCV10	57.0	 5.6	-98	 -77
Knol et al, EID 2015	VT IPD, <5 years	Netherlands	PCV7, PCV10	3	5	4	PCV10/non-PCV7				-96 (-99,–73)
PCV7-PCV13 (2+1)											
Harboe et al. CID 2014	VT IPD, <2 years	Denmark	PCV7, PCV13	7	3	3	PCV7 PCV13/non	36.4 (32.9–40.3)	 14.4 (11.1–	-99	 -84 (-67,-93)

							-PCV7		18.7)		
Ben-Shimol et al Vaccine 2014	VT- IPD, <5 years	Israel	PCV7, PCV13	4	1	1	PCV7 PCV13/non-PCV7	30.5 14.8	3.2 21.7	-95 (-91, -97) -70 (-56, -79)	-53 (-7,-77) -79 (-70, -85)
Ben-Shimol et al PIDJ 2015	VT- Bacteremic Pneumonia (BP) vs other IPD (non-BP IPD), <5 years	Israel	PCV7, PCV13	4	1	1	PCV7 PCV13/non-PCV7	9.6 (BP) 20.9 (non-BP IPD) 6.8 (BP) 8.0 (non-BP IPD)	0.9 (BP) 2.5 (non-BP IPD) 13 (BP) 8.4 (non-BP IPD)	-96 (-88,-99) -95 (-90,-97) -62 (-37,-77) -75 (-56,-86)	-59 (+59,-89) -55 (0, -79) -80 (-69,-88) -77 (-60,-77)
Gabarrot et al, PLosOne 2014	VT IPD, <2 years, 2-4 years	Uruguay	PCV7, PCV13	5	2	3	PCV7 PCV13/non-PCV7	38.0 (<2) 7.0 (2-4) 24.8 (<2) 16.1 (2-4)		-92 (-74, -97) -83 (-86, -98) -75(-39, -90) -56 (-72, +6)	
Pirez et al. PIDJ 2014	VT CAP, <15 years	Uruguay	PCV7, PCV13	5	2	3	PCV7	30.4 per 10,000 discharges		-91	

							PCV13/non -PCV7 PCV13	36.4 60.8		-95 -97	
Lepoutre et al, Vaccine 2015	VT IPD, <2 years, 2-4 years	France	PCV7, PCV13	2	2	1	PCV7 PCV13/non PCV7	20.8 (<2) 5.3 (2-4) 15.5 (<2) 7.6 (2-4)		-95 (-91,-87) -91 (-96,-82)	-84 (-89,-76) -61 (-71,-47)
Galanis et al. Eur Respir J 2016	VT IPD, <2 years	Sweden	PCV7, PCV13	2	1	3	PCV7 PCV13	22.71 4.42	5.22	-92(-68,-98) -71(-92,13)	-75(-94,-2)
Slotved et al. Vaccine 2016	VT IPD, <5years	Denmark	PCV7, PCV13	8	2	3	PCV7 PCV13	2.34	0.99	-80(-96,-14)	-77(-98,193)
Diawara et al. Int J Infect Dis 2015	VT IPD, ≤2 years, >2-5 years	Morocco	PCV13 replaced by PCV10	3		3	PCV7 PCV10/non - PCV7	18.0 (≤2) 0.6 (3-5) 5.7 (≤2) 0.3 (3-5)		-74 (-100,-41) -54 (-82, 128) -78 (-94, -22) -4 (-81, 128)	

							PCV13/non - PCV10	5.7 (≤2) 0.2 (3-5)		-83 (-100,-28) -35(-87,585)	
Rudnick et al. Vaccine 2013	VT IPD, <5 years	Canada (Ontario)	PCV7 (3+1), PCV10 (3+1), PCV13 (2+1)		1	1	PCV13		11.6		-41 (p=0.07)
Waight et al. Lancet Inf Dis 2015	VT-IPD; <2 years 2-4 years	England and Wales	PCV7, PCV13	5	4	4	PCV7 PCV13/non -PCV7		1.58 (<2) 0.78 (2-4) 12.67 (<2) 4.98 (2-4)		-76 (-7,-94) -80 (-96,+12) -89 (-78,-94) -91 (-75,-96)
Shiri et al, ISPPD 2014	VT IPD, <2 years	South Africa	PCV7, PCV13	4	2	1	PCV7 PCV13/non -PCV7	149 32.1		-90 (-83,-94) -74 (-45,-88)	
Dalby et al, ISPPD 2014	VT IPD, <2 years	Denmark	PCV7, PCV13	7	3	2	PCV13/non -PCV7	N/A	N/A	-85 (-64,-95)	
Chang et al, Value in Health 2014	VT IPD, <5 years	Taiwan	PCV7, PCV13	3	6	2	PCV7 PCV13	-	-	-71 (p=0.012) -80 (p=0.001)	

Steens et al, Vaccine 2013	VT IPD, <2 years, 2-4 years	Norway	PCV7, PCV13	2	5	1	PCV7 PCV13/non PCV7	64 (<2) 15 (2-4)	10 (<2) 6 (2-4)	-77 (-87,-61) -45 (-74,+11)	-100 (-100,-72) -52 (-89,+79)
Von Gottberg et al, NEJM 2014	VT IPD, <2 years	South Africa	PCV7, PCV13	4	2	2	PCV7 PCV13/non PCV7	32.1 7.5		-89 (-92,-86) -57 (-68,-42)	
Moore et al, JID 2014	VT IPD, <2 years	UK	PCV7, PCV13	9	4	3	PCV7 PCV13/non PCV7	33.4-46.5 8.3-9.9		-76 (-86,-59) -64 (-84,-20)	
von Gottberg et al., ISPPD-10 2016	VT IPD, <2 years	South Africa	PCV7 PCV13	3		4	PCV7 PCV13	33.6 14.4		-97 (-96, -98) -70 (-65, -74)	
Gentile et al., ISPPD-	Meningitis, <1 year	Argentina	PCV13	4		1	PCV13	1.2		-55 (-10,-77)	

10 2016											
Collins et al., ISPPD-10 2016	Meningitis, <5 years	UK (England, Wales)	PCV7 PCV13	6	2	4	PCV7 PCV13/non-PCV7	3.4	 1.5	-99 -77	
PCV7-PCV13 (3+0)											
Jayasinghe et al., ISPPD-10 2016	VT IPD, <2 years	Australia	PCV7 PCV13	2	3	1	PCV7 PCV13			-96 (-94,-98)	-65 (-52,-76)
Mackenzie et al., Lancet Inf. Dis 2016	VT IPD, <2 years, 2-4 years	Gambia	PCV7, PCV13	N/R	2	3	PCV7 PCV13/non-PCV7		122 (<2) 44 (2-4) 78 (<2) 58 (2-4)		-83 (-93,-57) -74 (-91,-26) -82 (-94,-44) -62 (-83,-15)
PCV10 (2+1)											
Jokinen et al, ISPPD 2012	VT-IPD, <1 years	Finland	PCV10	5		1	PCV10		33.8		-46.7
Rinta-	VT-IPD, 3-	Finland	PCV10	5		5	PCV10		38.8		-93 (-90,-96)

Kokko et al. ISPPD 2016	66 months										
Haraldsson et al, ISPPD 2014	VT IPD, <2 years	Iceland	PCV10	3		3	PCV10		51.8		-87 (p<0.001)
PCV10 (3+0)											
Scott et al, ISPPD 2012	VT-IPD, <5 years	Kenya	PCV10	7		<1	PCV10	50.8		-70 (-91, -30)	
Russell et al., ISPPD-10 2016	IPD (overall IPD?), <2 years	Fiji	PCV10	3		1	?			-51 (-10,-76)	
PCV10 (3+1)											
Santos et al., Vaccine 2013	VT IPD, <2 years	Brazil	PCV10	4		2	PCV10	16.5		-97 (p=0.0002)	

TABLE 19. Observational studies estimating vaccine effectiveness against IPD by serotype and by schedule

Study				VE compared to no vaccine (95%CI)		
Country (Reference)	**Study Design**	**Population age**	**PCV product (Country Schedule)**	**Serotype**	**≥1 dose**	**≥2 doses**
PCV13						
United Kingdom (Andrews et al., 2014)	Indirect cohort	2.5-<24 months	PCV13 (2+1)	1 3 6A 7F 19A		84% (54-95%)[1] 26% (–69-68%)[1] 98% (64-99%)[1] 91% (70 to 98)[1] 67% (33 to 84)[1]
Canada (Deceuninck et al., 2015)	Case-control	2-59 months	PCV13 (2+1)	19A	74% (11-94%)	
South Africa (Von Gottberg et al. ISPPD 2016)	Case-control	6 weeks-9 months	PCV13 (2+1)	19A		94% (44-100%)
PCV10						
Finland (Auranen et al. ISPPD 2014)	Indirect cohort	≥3 months, PCV10 eligible	PCV10 (2+1)	19A		29% (-631-93%)

Netherlands (Knol et al. ISPPD 2016)	Indirect cohort	2-54 months	PCV10 (2+1)	19A 7F	61% (-79- 92%) 87% (13 to 98)	
Canada (Deceuninck et al., 2015)	Case-control	2-59 months	PCV10 (2+1)	19A 7F	71% (24–89%) 93% (23–99%)	
Brazil (Domingues et al 2014)	Case-control	<5 years	PCV10 (3+1), catch up for 12-23 months	3 6A 19A	7·8% (–272-77%)[2] 15% (–312-82%)[2] 82% (11- 96%)[2]	
(Verani et al 2015)	Indirect cohort			6A 19A	62% (−42- 89.9%) [2] 63% (−17- 88.6%) [2]	51% (−52- 84%) 71% (17- 90%)

[1]VE for at least 2 doses before age 12 months or one dose on or after age 12 months

[2]VE for up to date for age number of doses

TABLE 20. Observational studies documenting impact of PCV introduction on all IPD, meningitis or bacteremia among young children before and after vaccine introduction, by PCV dosing schedule and by serotype

Reference	Outcome, age groups	Country	PCV product(s)	Surveillance years reported			Baseline incidence (cases/100,000)			Percent change at maximum years post-introduction compared to	
				PrePCV	Post-PCV7/pre-PCV10/13	Post-PCV10/13	Serotype	PrePCV	Post-PCV7/pre-PCV10/13	Pre-PCV	Post-PCV7/pre-PCV10/13
PCV7-PCV10 (2+1)											
De Wals et al. Vaccine 2014	VT IPD, <2 years	Canada (Quebec)	PCV7, PCV10	4	5	2	19A		21.1		-36
Knol et al, EID 2015	VT IPD, <5 years	Netherlands	PCV7, PCV10	3	5	4	19A				-62 (-81,–23)
PCV7-PCV13 (2+1)											
Harboe et al. CID 2014	VT IPD, <2 years	Denmark	PCV7, PCV13	7	3	3	1 3 19A		1.3 1.3 3.8		No change No change Decreased to

											pre-PCV7 level
Ben-Shimol et al Vaccine 2014	VT- IPD, <5 years	Israel	PCV7, PCV13	4	1	1	1 3 19A	3.8 0.3 5.1	5.2 0.8 5.0	-88 (-95, -71) +13 (-62, +237) -68 (-83,–41)	-84 (-94,–58) +145 (-36, +130) -69 (-84,–42)
Lepoutre et al, Vaccine 2015	VT IPD, <2 years, 2-4 years	France	PCV7, PCV13	2	2	1	19A 7F 1 3				-83 (-72,- 90) -77 (-59, -87) -96 (-73,-100) -85 (-36, -96)
Porat et al. Vaccine 2016	VT IPD, <2 years	Israel	PCV7, PCV13	8	2	3	6A 6B	7.1 7.1		-86(9,-98) -86(9,-98)	-36(-96,921) -36(-96,921)
Waight et al. Lancet Inf Dis 2015	VT-IPD; <2 years 2-4 years	England and Wales	PCV7, PCV13	5	4	4	1 3 6A 7F 19A				-91 (-98,–68) -68 (-89,–6) -100 (-100,–62) -91 (-97,–74) -91 (-97,–75)
Von Gottberg et al, NEJM	VT IPD, <2 years	South Africa	PCV7, PCV13	4	2	2	6A 1 3	6.3 1.5 0.6		-85 (-91,-76) -57 (-79,-16) -41 (-79,+54)	

2014							5 7F 19A	0.7 0.2 4.5		+22 (-60,+63) -100 (-100, +132) -70 (-81 to -55)	
PCV7-PCV13 (3+0)											
Jayasinghe et al., ISPPD-10 2016	VT IPD	Australia, <2 years	PCV7 PCV13	2	3	1	19A				-77 (-87,-65)
PCV10 (3+0)											
PCV10 (2+1)											
Rinta-Kokko et al. ISPPD 2016	VT-IPD, <2 years	Finland	PCV7, PCV10	N/R	5	5	19A 6A 3		6.8 2.8 0.4		-93 (-90,-96) -100(-68,-100) +192 (NS)

TABLE 21. Summary of included Immunogenicity study arms in Analyses

	PCV10 (n=44)		PCV13 (n=18)	
	2 dose	3 dose	2 dose	3 dose
	(n=10)	(n=34)	(n=11)	(n=7)
Region				
Africa	0	2	0	0
Asia	6	10	2	0
Europe	4	18	9	3
N America	0	1	0	2
Oceania	0	2	0	2
S America	0	1	0	0
Concomitant DTaP				
DTaP	9	18	4	3
No DTaP	1	16	7	4
Age dose 1				
1m	0	2	0	2
1.5-1.75m	2	7	0	0
2m	5	21	8	5
3m	3	4	3	0

Dose 1-2 interval				
0.5m	0	0	0	0
1m	2	25	1	4
1.25-1.5m	0	1	0	0
2m	7	8	10	3
4m	1	0	0	0
Dose 2-3 interval				
1m	NA	23	NA	4
2m	NA	10	NA	3
3m	NA	1	NA	0
Age at last dose				
3-3.5m	4	8	1	2
4-4.5m	2	11	7	2
5m	3	6	3	0
6m	1	9	0	3
Age at booster				
None	2	13	0	3
9m	4	1	2	0
11-14m	4	12	9	4

15-24m	0	8	0	0

TABLE 22. Characteristics of included Mortality studies included in Analysis

Characteristic	PCV10 N=5 (56%)	PCV13 N=4 (44%)
Study type		
Clinical trial	0	0
Pre/post surveillance	5 (100%)	4 (100%)
Case-control/indirect cohort	0	0
Region		
Africa	1 (20%)	1 (25%)
Asia	0	0
Australia/Oceania	1 (20%)	0
Europe	1 (20%)	1 (25%)
Latin America	2 (40%)	12(50%)
North America	0	0
Dosing Schedule		
2+1	2 (40%)	2 (50%)
3+0	2 (40%)	2 (50%)
3+1*	1 (20%)	0
Endpoint		
CFR	2 (40%)	1 (25%)
Mortality Rate or Cases	3 (60%)	3 (75%)

*Included due to paucity of data on mortality

TABLE 23. Studies Reporting on Mortality Pre and Post PCV Introduction

Country (Reference)	Endpoint	Age Group	% Relative Reduction (95% CI)
PCV10			
Finland **(Palmu 2015)**	All IPD/sepsis	 3-42m	51% (-94, 93) 35% (-181, 90)
Colombia **(Carrasquilla 2016)**	Pneumonia All Cause	 <5y	Bogota: 56.80% (49.2, 63.3) Nationwide: 33.4% (27.6-38.8) Bogota: 22.1% (19.4-24.7) Nationwide: 25.3% (23.8-26.8)
Brazil **(Simonsen 2016)**	 Pneumonia	 3-24m	 6%
Kenya **(Verani 2016)**	Pneumonia related CFR	 <5y	 43% (0, 68)
Fiji **(Tuigava 2016)**	Severe/very severe pneumonia CFR CXR Pneumonia CFR	 <2y	50% 57%
PCV13			
Denmark **(Harboe 2014)**	IPD related 30-day mortality	 All	 28% (18, 37)
Nicaragua **(Becker-Dreps 2014)**	 All cause	 <1y	 33% (20, 43)
Costa Rica **(Castro 2016)**	 Pneumonia	 <2y	 34.9%
Malawi (McCollum **2017)**	Pneumonia Hospitalizations CFR	 <5y	 41% (21, 63)

CFR=Case Fatality Rate

TABLE 24. ICER (US$/DALY averted) by U5 mortality strata in Gavi-eligible countries (23)

Under five mortality strata	<25 deaths/1000 live births	25-99 deaths/1000 live births	100-149 deaths/1000 live births	>=150 deaths/1000 live births
PCV7	$1078	$283	$103	$65
PCV10	$582	$152	$66	$41
PCV13	$471	$125	$60	$37

TABLE 25. Summary of selected CEAs of PCV

Vaccine	Country/region	Vaccine price per dose	Number of doses	Vaccine efficacy	Perspective	ICER	Notes
PCV7	GAVI-eligible countries (n=72)	AMC price + $1 administration cost per dose	3	85%	Societal	2005 US$146/DALY averted	Includes indirect effects and serotype replacement, discounting 3%
PCV10	GAVI-eligible countries (n=72)	AMC price + $1 administration cost per dose	3	85%	Societal	2005 US$88/DALY averted	Includes indirect effects and serotype replacement
PCV13	GAVI-eligible countries (n=72)	AMC price + $1 administration cost per dose	3	85%	Societal	2005 US$77/DALY averted	Includes indirect effects and serotype replacement
PCV7	Middle-income countries (n=77)	$10 or $20 +$5 administration cost per dose	3	85%	Societal	2005 US$1,600/DALY averted	Includes indirect effects and serotype replacement, discounting 3%
PCV7	Lower middle-income countries (n=35)	$10+$5 administration cost per dose	3	85%	Societal	2005 US$1,500/DALY averted	Includes indirect effects and serotype replacement
PCV7	Upper middle-income countries (n=42)	$20+$5 administration cost per dose	3	85%	Societal	2005 US$1,900/DALY averted	Includes indirect effects and serotype replacement
PCV10	Middle-income countries (n=77)	$10 or $20 +$5 administration cost per dose	3	85%	Societal	2005 US$1,000/DALY averted	Includes indirect effects and serotype replacement
PCV10	Lower middle-income	$10+$5 administration	3	85%	Societal	2005 US$920/DALY averted	Includes indirect effects and serotype replacement

	countries (n=35)	cost per dose					
PCV10	Upper middle-income countries (n=42)	$20+$5 administration cost per dose	3	85%	Societal	2005 US$1,300/DALY averted	Includes indirect effects and serotype replacement
PCV13	Middle-income countries (n=77)	$10 or $20 +$5 administration cost per dose	3	85%	Societal	2005 US$900/DALY averted	Includes indirect effects and serotype replacement
PCV13	Lower middle-income countries (n=35)	$10+$5 administration cost per dose	3	85%	Societal	2005 US$800/DALY averted	Includes indirect effects and serotype replacement
PCV13	Upper middle-income countries (n=42)	$20+$5 administration cost per dose	3	85%	Societal	2005 US$1,100/DALY averted	Includes indirect effects and serotype replacement
PCV7	Latin America and Caribbean countries (n=45)	$20	3	97%	Societal	2005 US$1,747/DALY averted	Does not include indirect effects
PCV7	Latin America and Caribbean countries (n=45)	$20	3	97%	Societal	2005 US$59,000/life saved	Does not include indirect effects
PCV7	The Gambia	$3.50	3	26% against all-cause pneumonia, 16% against Spn meningitis/sepsis	Societal	2005 US$910/DALY averted	Direct effects only in base case scenario, adding indirect effects reduced ICER to $830/DALY averted
PCV10	The Gambia	$3.50	3	35% against all-cause pneumonia, 22% against Spn meningitis/sepsis	Societal	2005 US$670/DALY averted	Direct effects only in base case scenario, adding indirect effects reduced ICER to $550/DALY averted
PCV13	The Gambia	$3.50	3	41% against all-cause pneumonia, 26% against Spn meningitis/sepsis	Societal	2005 US$570/DALY averted	Direct effects only in base case scenario, adding indirect effects reduced ICER to $480/DALY averted

PCV9	The Gambia	$5	3	35-37% against pneumonia, 77% against VT-IPD and 16% against all-cause mortality	Public healthcare	$30/DALY averted	Direct effects only, costs of illness and VE from PCV9 clinical trial in The Gambia (26)
PCV10	Kenya	$3.50	3	77% against pneumonia, 92% against sepsis and meningitis	Societal	2010 US$59/DALY averted	Inclusion of indirect effects reduced ICER to $32/DALY averted
PCV10	Kenya	$3.50	3	77% against pneumonia, 92% against sepsis and meningitis	Societal	2010 US$1,958/life saved	Inclusion of indirect effects reduced ICER to $1158/life saved
PCV13	Kenya	$3.50	3	77% against pneumonia, 92% against sepsis and meningitis	Societal	2010 US$47/DALY averted	Inclusion of indirect effects reduced ICER to $25/DALY averted
PCV13	Kenya	$3.50	3	77% against pneumonia, 92% against sepsis and meningitis	Societal	2010 US$1,558/life saved	Inclusion of indirect effects reduced ICER to $888/life saved
PCV10	Uganda	$3.50 program cost per dose	3	85% in HIV-negative children	Public healthcare	US$38.50/DALY averted	Only direct effects and direct medical costs included. PCV10 would be cost-saving at co-financing cost of $0.15 per dose
PCV10	Thailand	$61.90	3	89% against IPD, 6% against pneumonia, 6% against AOM	Societal	2013 US$45,183 per QALY gained	PCV10 vs. no vaccination without inclusion of herd effects
PCV10	Thailand	$61.90	3	89% against IPD, 6% against pneumonia, 6% against AOM	Societal	2013 US$17,173 per QALY gained	PCV10 vs. no vaccination with herd effects: 40% against IPD in 20-39 year olds, 14% against IPD in 40-64 year olds, and 29% against IPD in >65 year olds
PCV13	Thailand	$46.20	3	89% against IPD, 6% against pneumonia, 6%	Societal	2013 US$49,220 per QALY gained	PCV13 vs. no vaccination without inclusion of herd effects

				against AOM			
PCV13	Thailand	$46.20	3	89% against IPD, 6% against pneumonia, 6% against AOM	Societal	2013 US$17,437 per QALY gained	PCV13 vs. no vaccination with herd effects: 40% against IPD in 20-39 year olds, 14% against IPD in 40-64 year olds, and 29% against IPD in >65 year olds
PCV10	Brazil	$19.60	4	94% against IPD in 0-5 year olds, 87.5% against VT pneumonia in 0-2 year olds, 57.5% against VT AOM in 0-2 year olds	Healthcare, societal	2013 US$11,815 per DALY averted	Universal PCV10 vaccination vs. high-risk PCV10 vaccination
PCV10	Colombia	$16.20	3	74% against Spn meningitis, 21% against CXR pneumonia, 34% against AOM	Societal	2013 US$1,892 per LYG gained	PCV10 vs. no vaccination
PCV13	Colombia	$17.90	3	83% against Spn meningitis, 24% against CXR pneumonia, 9% against AOM	Societal	2013 US$9,801 per LYG gained	PCV13 vs. no vaccination
PCV10	Peru	$14.24	3	13% against AOM, 81% against IPD multiplied by serotype coverage of 71%	Government	2011 US$1,605 per DALY averted	PCV10 vs. no vaccination, highly cost-effective
PCV13	Peru	$16.34	3	8% against AOM, 81% against IPD multiplied by serotype coverage of 81%	Government	2011 US$1,304 per DALY averted	PCV13 vs. no vaccination, highly cost-effective
PCV10	Paraguay	$14.85	3	34% against AOM, 6% against all-cause pneumonia, 80% against IPD	Government, societal	2009 US$3,851 per DALY averted (gov't), US$1,920 per DALY averted (societal)	PCV10 vs. no vaccination, cost-effective from government perspective and highly cost-effective from societal perspective

				multiplied by 80% VT coverage			
PCV13	Paraguay	$20	3	6% against AOM, 6% against all-cause pneumonia, 80% against IPD multiplied by 85% VT coverage	Government, societal	2009 US$4,901 per DALY averted (gov't), US$3,657 per DALY averted (societal)	PCV13 vs. no vaccination, cost-effective from both government and societal perspective

TABLE 26. Characteristics Of Indirect Effects Studies

Characteristic	PCV10 N= (%)	PCV13 N= (%)	Total N=31
Region			
Africa	3	3	6
Asia	0	0	0
Australia/Oceania	1	3	4
Europe[1]	5	14	18
Latin America	0	2	2
North America[2]	1	1	1
PCV dosing schedule			
2+1[1,2]	5	19	22
3+0	4	4	8
3+1	1	0 (not included)	1
Outcome			
NP Carriage	2	1	3
Pneumonia[1]	4	3	6
IPD[2]	4	19	22

[1]One pneumonia article reports on both PCV13 and 10 used sequentially in Sweden.

[2]One IPD article reports on both PCV13 and PCV10 in Canada.

TABLE 27: Indirect Effects On Np Carriage Prevalence

Reference	Age group	Country	PCV product(s)	Number of years			Prevalence			Percent change at maximum years post-PCV10/13 introduction compared to	
				Pre PCV surveillance	PCV7 use	PCV10/ PCV13	Pre PCV (dates)	PCV7 (dates)	PCV10/13 (dates)	Pre-PCV	PCV7
PCV7 VT											
Ben-Shimol Hum Vacc Immunother 2016	7-59 mo, unvaccinated	Israel	PCV7, PCV13 2+1	--	5	4	--	16.7% (2009-Jun 2011)	9.0% (Jul 2011-2014)	--	-46%
PCV13-nonPCV7 VT (1, 3, 5, 6A, 7F, 19A)											
Ben-Shimol Hum Vacc Immunother 2016	7-59 mo, unvaccinated	Israel	PCV7, PCV13 2+1	--	5	4	--	13.4% (2009-Jun 2011)	4.5% (Jul 2011-2014)	--	-66%
PCV10 VT											
Dunne ISPPD10 2016	5-8 wks	Fiji	PCV10 3+0	1	--	3	9.4% (2012)	--	0% (2015)	-100%	--
Dunne ISPPD10 2016	Adults	Fiji	PCV10 3+0	1	--	3	2.2% (2012)	--	0% (2015)	-100%	--
Hammitt ISPPD10 2016	≥ 5 yrs	Kenya	PCV10 3+0	2	--	4	8% (2009-2010)	--	3% (2011-2015)	-65% (sig)	--
Hammitt ISPPD10 2016	5-9 yrs	Kenya	PCV10 3+0	2	--	4	16.9% (2010)	--	9.1% (2015)	-46%	--
Hammitt ISPPD10 2016	10-14 yrs	Kenya	PCV10 3+0	2	--	4	9.5% (2010)	--	4.6% (2015)	-52%	--
Hammitt ISPPD10 2016	15-19 yrs	Kenya	PCV10 3+0	2	--	4	15.4% (2010)	--	0% (2015)	-100%	--
Hammitt ISPPD10 2016	20-39 yrs	Kenya	PCV10 3+0	2	--	4	5.1% (2010)	--	3.3% (2015)	-35%	--
Hammitt	40-49	Kenya	PCV10	2	--	4	5.2%	--	0%	-100%	--

ISPPD10 2016	yrs		3+0				(2010)		(2015)		
Hammitt ISPPD10 2016	50-59 yrs	Kenya	PCV10 3+0	2	--	4	9.8% (2010)	--	0% (2015)	-100%	--
Hammitt ISPPD10 2016	≥ 60 yrs	Kenya	PCV10 3+0	2	--	4	5.3% (2010)	--	0% (2015)	-100%	--
Serotype 3											
Hammitt, personal communication 2016	≥18 yrs	Kenya	PCV10 3+0	2	--	4	1.3% (2010)	--	0.5% (2015)	-62%	
Serotype 6A											
Hammitt, personal communication 2016	≥18 yrs	Kenya	PCV10 3+0	2	--	4	1.8% (2010)	--	0.9% (2015)	-50%	
Serotype 19A											
Hammitt, personal communication 2016	≥18 yrs	Kenya	PCV10 3+0	2	--	4	0.4% (2010)	--	1.4% (2015)	250%	

TABLE 28: Indirect Effects On Pneumonia Incidence

Country	Ref	Case Definition	Age groups evaluated	Number of years			Baseline measure (per year)[1]		% change at post-PCV10/13 introduction period compared to		Comments
				Pre-PCV surveillance	PCV7 use	PCV10/PCV13 use	Pre-PCV	Post-PCV7/ Pre-PCV10/13	Pre-PCV	PCV7	
Clinical pneumonia											
PCV 10 2+1											
Finland	Okasha ISPPD10 2016	All-cause pneumonia hospitalizations	≥18 yrs	6.5	--	4	548	--	-5.3% (sig)		% change in expected vs. observed rate in 2014 based on interrupted time series analysis. Pneumonia trend had been increasing pre-PCV.
Finland	Okasha ISPPD10 2016	All-cause pneumonia hospitalizations	50-64 yrs	6.5	--	4	NR	--	-21% (sig)		
Finland	Okasha ISPPD10 2016	All-cause pneumonia hospitalizations	≥ 65 yrs	6.5	--	4	1752	--	-7.3% (sig)		
PCV10 3+0											
Kenya	Silaba ISPPD10 2016	Severe or very severe pneumonia hospitalizations	5-12 yrs	9	--	4	NR	--	-5% (not sig)		IRR=0.95 (95% CI 0.56, 1.59)
PCV13 2+1											
UK (Scotland)	Nath Arch Dis Child 2015	Pneumonia hospitalizations by ICD codes	10-14 yrs	6	4	3	NR	NR	NR	-2% (not sig)	IRR=0.98 (95% CI 0.87, 1.11)

Argentina	Lopez Papucci ISPPD10 2016	Clinical pneumonia hospitalizations	5-12 yrs	4	--	4	499 per 10,000 hospital discharges	--	-40% (sig)		Data from 1 hospital
PCV13→PCV10 2+1											
Sweden	Kostenniemi ISPPD10 2016	Clinical pneumonia hospitalizations by ICD codes	6-17 yrs	4	1	4	418	600	+7%	-25%	Vasterbotten County: introduced PCV7 in 2009, PCV13 in 2010 and then PCV10 in 2011
Sweden	Kostenniemi ISPPD10 2016	Clinical pneumonia hospitalizations by ICD codes	18-64 yrs	4	1	4	825	1,004	+8%	-12%	
Sweden	Kostenniemi ISPPD10 2016	Clinical pneumonia hospitalizations by ICD codes	≥65 yrs	4	1	4	4,010	4,141	-3%	-6%	
CXR pneumonia											
PCV10 3+0											
Kenya	Silabla ISPPD10 2016	CXR pneumonia hospitalizations	5-12 yrs	5	--	3	NR	--	-11% (not sig)		IRR=0.89 (95% CI 0.47, 1.69)
PCV13 2+1											
Argentina	Lopez Papucci ISPPD10 2016	CXR pneumonia hospitalizations	5-12 yrs	4	--	4	261 per 10,000 hospital discharges	--	-44% (sig)		Data from 1 hospital
Pneumococcal pneumonia											
PCV10 3+0											
Kenya	Bigogo ISPDD10	Pneumococcal	≥18 yrs, gen pop	3	--	3	112	--	-94% (sig)		Based on blood or urine antigen

	2016	pneumonia surveillance									testing of ARI cases. More severe illness was less likely to be tested.
Kenya	Bigogo ISPDD10 2016	Pneumococcal pneumonia surveillance	≥18 yrs, HIV neg	3	--	3	59	--	-100%		
Empyema											
PCV13 2+1											
UK (Scotland)	Nath Arch Dis Child 2015	Empyema hospitalizations by ICD codes	10-14 yrs	6	4	3	NR	NR	NR	-37% (not sig)	IRR=0.63 (95% CI 0.34, 1.12)

[1] unless otherwise noted the denominator is rate per 100,000

NR = not reported

TABLE 29: Indirect Effects On IPD Incidence

29A: All –cause IPD											
Reference	Age group	Country	PCV product(s)	Number of years			Baseline incidence (cases/100,000)			Percent change at maximum years post-PCV10/13 introduction compared to	
				Pre PCV surveillance	PCV7 use	PCV10/ PCV13 use	Pre PCV (dates)	PCV7 (dates)	PCV10/ PCV13 (dates)	Pre-PCV	PCV7
All Pneumococcal Serotypes											
PCV10 2+1											
Nuorti ISPPD10 2016	18-49 yrs	Finland	PCV10	5	--	5	8 (2005-2008) 10.1 (2008)	--	6.56 (2012-2015) 6.8 (2015)	-18% (sig) -33%	
Nuorti ISPPD10 2016	50-64 yrs	Finland	PCV10	5	--	5	17.63 (2005-2008) 22.1 (2008)	--	17.29 (2012-2015) 18.1 (2015)	-2% -18%	
Nuorti ISPPD10 2016	≥65 yrs	Finland	PCV10	5	--	5	31.17 (2005-2008) 36.8 (2008)	--	33.64 (2012-2015) 38 (2015)	8% 3%	
Nuorti ISPPD10 2016	≥18 yrs	Finland	PCV10	5	--	5	15.9 (2005-2008)	--	16.1 (2012-2015)	1% (not sig)	
PCV10 3+1 → 2+1											
Knol ISPPD10 2016	5-64 yrs	Netherlands	PCV7, PCV10	NR 2	5	5	NR 7.2 (2005-2006)	NR (2009-2011) 7.9 (2010-2011)	NR (2014-2016) 7.2 (2015-2016)	 0%	-8% (not sig) -9%
Knol ISPPD10	≥65 yrs	Netherlands	PCV7, PCV10	--	5	5	NR	NR (2009-2011)	NR (2014-2016)		4% (not sig)

2016							63 (2005-2006)	50.9 (2010-2011)	51.3 (2015-2016)	-19%	1%
PCV13 2+1											
Steens Epidemics 2015	≥65 yrs	Norway	PCV7, PCV13	2	5	3	73	54	34	-53%	-37%
Harboe CID 2014	5-17 yrs	Denmark	PCV7, PCV13	8	3	3	2.5 (2000-2007)	1.9 (2008-2010)	2.4 (2011-2013)	-5% (not sig)	29% (not sig)
Harboe CID 2014	18-49 yrs	Denmark	PCV7, PCV13	8	3	3	7.1 (2000-2007)	6.8 (2008-2010)	5.7 (2011-2013)	-20% (sig)	-16% (sig)
Harboe CID 2014	50-64 yrs	Denmark	PCV7, PCV13	8	3	3	23.6 (2000-2007)	21.6 (2008-2010)	19 (2011-2013)	-20% (sig)	-12% (sig)
Harboe CID 2014	≥65 yrs	Denmark	PCV7, PCV13	8	3	3	66.5 (2000-2007)	60.0 (2008-2010)	49.4 (2011-2013)	-25% (sig)	-18% (sig)
Galanis Eur Resp J 2016	18-65 yrs	Sweden	PCV7, PCV13	3	2	4	11.72 (2005-2007) 9.9 (2007)	8.47 (2009-2010) 8.2 (2009)	7.22 (2011-2014) 4.9 (2014)	-38% (sig) -51%	-25% (not sig) -40%
Galanis Eur Resp J 2016	≥65 yrs	Sweden	PCV7, PCV13	3	2	4	38.0 (2005-2007) 35.6 (2007)	37.6 (2009-2010) 37.4 (2009)	34.2 (2011-2014) 35.4 (2014)	-10% (not sig) -1%	-9% (not sig) -5%
Guevara Euro Surv 2016	75 days-59 mo	Spain	PCV7, PCV13	4	3	4	75 (2001-2004)	41 (2008-2010)	16 (2011-2014)	-79%	-61%
Collins ISPPD10 2016	15-44 yrs	UK	PCV7, PCV13	6	4	5	7.8 (2005/2006)	4.3 (2009/2010)	2.9 (2014/2015)	-63%	-33%
Collins ISPPD10 2016	45-64 yrs	UK	PCV7, PCV13	6	4	5	17.7 (2005/2006)	9.7 (2009/2010)	9.3 (2014/2015)	-47%	-4%
Collins ISPPD10 2016	≥65 yrs	UK	PCV7, PCV13	6	4	5	32.2 (2005/2006)	26.1 (2009/2010)	25.2 (2014/2015)	-22%	-3%
Ricketson ISPPD10	≥15 yrs	Canada (Toronto)	PCV7, PCV10,	4	4	5	11.2 (1998-2001)	8.4 (2002-2010)	6.7 (2011-2015)	-40%	-20%

2016			PCV13								
Ricketson ISPPD10 2016	≥15 yrs	Canada (Calgary)	PCV7, PCV13	4	8	5	10.4 (1998-2001)	11.3 (2002-2010)	8.8 (2011-2015)	-15%	-22%
Villalobos ISPPD10 2016	Adults	Costa Rica	PCV7, PCV13	1	NR	5	3.9	--	2.3	-41%	
Villalobos ISPPD10 2016	Adults < 65 yrs	Costa Rica	PCV7, PCV13	1	NR	5	1.8 (2007)	--	0.93 (2015)	-48%	
Villalobos ISPPD10 2016	≥65 yrs	Costa Rica	PCV7, PCV13	1	NR	5	23.6 (2007)	--	10.3 (2015)	-56%	
Von Gottberg ISPPD10 2016	10-14 yrs	South Africa	PCV7, PCV13	4	2	4	2.6 (2008)	2.1 (2010)	1.0 (2015)	-62%	-52%
Von Gottberg ISPPD10 2016	15-24 yrs	South Africa	PCV7, PCV13	4	2	4	3.2 (2008)	3.1 (2010)	1.5 (2015)	-53%	-52%
Von Gottberg ISPPD10 2016	25-44 yrs	South Africa	PCV7, PCV13	4	2	4	12.3 (2008)	11.2 (2010)	6.2 (2015)	-50%	-45%
Von Gottberg ISPPD10 2016	45-64 yrs	South Africa	PCV7, PCV13	4	2	4	8.9 (2008)	9.4 (2010)	6.7 (2015)	-25%	-29%
Von Gottberg ISPPD10 2016	≥64 yrs	South Africa	PCV7, PCV13	4	2	4	6.3 (2008)	6.9 (2010)	6.4 (2015)	2%	-7%
du Plessis ISPPD10 2016	≥25 yrs	South Africa	PCV7, PCV13	4	2	4	28 (2005-2008)	NR	19 (2012-2015)	-33% (sig)	
PCV13 3+0											
Jayasinghe ISPPD10 2016	15-49 yrs	Australia	PCV7, PCV13	3	6	3.5	4.9 (2002-2004)	--	2.8 (2014)	-45% (sig)	--

Jayasinghe ISPPD10 2016	50-64 yrs	Australia	PCV7, PCV13	3	6	3.5	9.5 (2002-2004)	--	7.6 (2014)	-19% (sig)	
Jayasinghe ISPPD10 2016	≥65 yrs	Australia	PCV7, PCV13	3	6	3.5	25.1 (2002-2004) 25 (2004)	-- 15.9 (2010	15 (2014) 12.4 (2015)	-40% (sig) -50%	 -22%
Moberley ISPPD10 2016	15-24 yrs Non-indigenous	Australia	PCV7, PCV13	5	6	3	2.6 (2002-2006)	1.7 (2007-2010)	1.5 (2011-2014)	-42%	-12%
Moberley ISPPD10 2016	25-34 yrs Non-indigenous	Australia	PCV7, PCV13	5	6	3	4.3 (2002-2006)	2.9 (2007-2010)	2.7 (2011-2014)	-37%	-7%
Moberley ISPPD10 2016	35-49 yrs Non-indigenous	Australia	PCV7, PCV13	5	6	3	5.4 (2002-2006)	4.4 (2007-2010)	4.8 (2011-2014)	-11%	9%
Moberley ISPPD10 2016	50-64 yrs Non-indigenous	Australia	PCV7, PCV13	5	6	3	8.9 (2002-2006)	7.7 (2007-2010)	7.6 (2011-2014)	-15%	-1%
Moberley ISPPD10 2016	≥65 yrs Non-indigenous	Australia	PCV7, PCV13	5	6	3	22.6 (2002-2006)	17 (2007-2010)	16.8 (2011-2014)	-26%	-1%
Mackenzie Lancet ID 2016	5-14 yrs	The Gambia	PCV7, PCV13	1	2	3	12 (2008-2010)	8.6 (2011)	10 (2013-2014)	-16% (not sig)	16%
Mackenzie Lancet ID 2016	≥15 yrs	The Gambia	PCV7, PCV13	1	2	3	9 (2008-2010)	11.7 (2011)	4 (2013-2014)	-59% (not sig)	-66%

29B: VT-IPD in PCV10 countries											
Reference	Age group	Country	PCV product(s)	Number of years			Baseline incidence (cases/100,000)			Percent change at maximum years post-PCV10 introduction compared to	
				Pre PCV surveillance	PCV7 use	PCV10	Pre PCV (dates)	PCV7 (dates)	PCV10 (dates)	Pre-PCV	PCV7
PCV10 VT											
Nuorti ISPPD10 2016	18-49 yrs	Finland	PCV10	5	--	5	5.62 (2005-2008) 6.9 (2008)	--	2.81 (2012-2015) 1.7 (2015)	-51% (sig) -75%	--
Nuorti ISPPD10 2016	50-64 yrs	Finland	PCV10	5	--	5	10.7 (2005-2008) 11.6 (2008)	--	6.3 (2012-2015) 4.0 (2015)	-41% (sig) -66%	--
Nuorti ISPPD10 2016	≥65 yrs	Finland	PCV10	5	--	5	19.2 (2005-2008) 22.2 (2008)	--	10.1 (2012-2015) 6.7 (2015)	-47% (sig) -70%	--
PCV7 VT											
Knol ISPPD10 2016	5-64 yrs	Netherlands	PCV7, PCV10	2	5	5	3.2 (2005-2006)	1.9 (2010-2011)	0.7 (2015-2016)	-78%	-63%
Knol ISPPD10 2016	≥65 yrs	Netherlands	PCV7, PCV10	2	5	5	29.6 (2005-2006)	7.6 (2010-2011)	3.2 (2015-2016)	-89%	-58%
PCV10-non PCV7 VT (1, 5, 7F)											
Knol ISPPD10 2016	5-64 yrs	Netherlands	PCV7, PCV10	2	5	5	1.5 (2005-2006)	2.7 (2010-2011)	1.3 (2015-2016)	-13%	-52%
Knol ISPPD10 2016	≥65 yrs	Netherlands	PCV7, PCV10	2	5	5	9.5 (2005-2006)	9.1 (2010-2011)	4.8 (2015-2016)	-49%	-47%

29C: VT-IPD in PCV13 countries											
Reference	Age group	Country	PCV product(s)	Number of years			Baseline incidence (cases/100,000)			Percent change at maximum years post-PCV13 introductio compared to	
				Pre PCV surveillance	PCV7 use	PCV13	Pre PCV (dates)	PCV7 (dates)	PCV13 (dates)	Pre-PCV	PCV7
PCV7 VT											
Harboe CID 2014	≥65 yrs	Denmark	PCV7, PCV13	8	3	3	29.2 (2007)	14 (2009)	2.4 (2013)	-92%	-83%
Collins ISPPD10 2016	15-44 yrs	UK	PCV7, PCV13	6	4	5	2.5 (2005/2006)	0.3 (2009/2010)	0.1 (2014/2015)	-96%	-67%
Collins ISPPD10 2016	45-64 yrs	UK	PCV7, PCV13	6	4	5	7.1 (2005/2006)	1.0 (2009/2010)	0.2 (2014/2015)	-97%	-80%
Collins ISPPD10 2016	≥65 yrs	UK	PCV7, PCV13	6	4	5	15.9 (2005/2006)	3.2 (2009/2010)	0.9 (2014/2015)	-94%	-72%
Galanis Eur Resp J 2016	18-65 yrs	Sweden	PCV7, PCV13	3	2	4	6.1 (2005-2007) 4.7 (2007)	2.6 (2009-2010) 2.9 (2009)	0.94 (2011-2014) 0.4 (2014)	-84% (sig) -91%	-63% (sig) -86%
Galanis Eur Resp J 2016	≥65 yrs	Sweden	PCV7, PCV13	3	2	4	22.3 (2005-2007) 18.4 (2007)	10.1 (2009-2010) 12.1 (2009)	3.24 (2011-2014) 2.4 (2014)	-85% (sig) -87%	-68% (sig) -80%
von Gottberg ISPPD10 2016	10-14 yrs	South Africa	PCV7, PCV13	4	2	4	1.0 (2008)	0.5 (2010)	0.2 (2015)	-80%	-60%
von Gottberg ISPPD10 2016	15-24 yrs	South Africa	PCV7, PCV13	4	2	4	0.9 (2008)	0.7 (2010)	0.2 (2015)	-78%	-71%
von Gottberg ISPPD10 2016	25-44 yrs	South Africa	PCV7, PCV13	4	2	4	4.3 (2008)	3.2 (2010)	0.7 (2015)	-84%	-78%

von Gottberg ISPPD10 2016	45-64 yrs	South Africa	PCV7, PCV13	4	2	4	3.3 (2008)	2.8 (2010)	0.9 (2015)	-73%	-68%
von Gottberg ISPPD10 2016	≥64 yrs	South Africa	PCV7, PCV13	4	2	4	2.1 (2008)	2.2 (2010)	0.7 (2015)	-67%	-68%
Mackenzie Lancet ID 2016	5-14 yrs	The Gambia	PCV7, PCV13	1	2	3	--	2.1 (2011)	1.0 (2013-2014)	--	-52%
Mackenzie Lancet ID 2016	≥15 yrs	The Gambia	PCV7, PCV13	1	2	3	1.0 (2008-2010)	1.35 (2011)	--	--	--
Jayasinghe ISPPD10 2016	5-64 yrs	Australia	PCV7, PCV13	3	6	4	4.1 (2004)	0.5 (2010)	0.3 (2015)	-93%	-40%
Jayasinghe ISPPD10 2016	≥65 yrs	Australia	PCV7, PCV13	3	6	4	17.3 (2004)	1.9 (2010)	1.1 (2015)	-94%	-42%
PCV13 VT											
Steens Epidemics 2015	≥65 yrs	Norway	PCV7, PCV13	2	5	3	58 (2004-2006)	27.5 (2010/2011)	8.8 (2013/2014)	-85%	-68%
Slotved Vaccine 2016	5-64 yrs	Denmark	PCV7, PCV13	9	3	4	NR	0.46 (2008-2010)	0.29 (2011-2014)	--	-38% (not sig
Slotved Vaccine 2016	≥65 yrs	Denmark	PCV7, PCV13	9	3	4	NR	2.7 (2008-2010)	1.41 (2011-2014)	--	-48% (not sig
Mackenzie Lancet ID 2016	5-14 yrs	The Gambia	PCV7, PCV13	1	2	3	10 (2008-2010)	--	10 (2013-2014)	5% (not sig)	--
Mackenzie Lancet ID 2016	≥15 yrs	The Gambia	PCV7, PCV13	1	2	3	7.0 (2008-2010)	--	4.0 (2013-2014)	-50% (not sig)	--
PCV13-nonPCV7 VT (1, 3, 5, 6A, 7F, 19A)											
Harboe CID 2014	≥65 yrs	Denmark	PCV7, PCV13	8	3	3	17.6 (2007)	20/7 (2009)	11.4 (2013)	-35%	-45%

Collins ISPPD10 2016	15-44 yrs	UK	PCV7, PCV13	6	4	5	3.4 (2005/2006)	2.4 (2009/2010)	0.7 (2014/2015)	-79%	-71%
Collins ISPPD10 2016	45-64 yrs	UK	PCV7, PCV13	6	4	5	5.8 (2005/2006)	4.4 (2009/2010)	1.7 (2014/2015)	-71%	-61%
Collins ISPPD10 2016	≥65 yrs	UK	PCV7, PCV13	6	4	5	8.6 (2005/2006)	10.4 (2009/2010)	5.1 (2014/2015)	-41%	-51%
Galanis Eur Resp J 2016	18-65 yrs	Sweden	PCV7, PCV13	3	2	4	2.96 (2005-2007) 3.2 (2007)	3.25 (2009-2010) 3.2 (2009)	2.52 (2011-2014) 1.4 (2014)	-15% (not sig) -56%	-22% (not sig -56%
Galanis Eur Resp J 2016	≥65 yrs	Sweden	PCV7, PCV13	3	2	4	7.75 (2005-2007) 7.4 (2007)	12.1 (2009-2010) 13.4 (2009)	9.65 (2011-2014) 8.6 (2014)	25% (not sig) 16%	-20% (not sig -36%
von Gottberg ISPPD10 2016	10-14 yrs	South Africa	PCV7, PCV13	4	2	4	1.2 (2008)	1.0 (2010)	0.3 (2015)	-75%	-70%
von Gottberg ISPPD10 2016	15-24 yrs	South Africa	PCV7, PCV13	4	2	4	1.4 (2008)	1.4 (2010)	0.3 (2015)	-79%	-79%
von Gottberg ISPPD10 2016	25-44 yrs	South Africa	PCV7, PCV13	4	2	4	4.1 (2008)	4.4 (2010)	1.3 (2015)	-68%	-70%
von Gottberg ISPPD10 2016	45-64 yrs	South Africa	PCV7, PCV13	4	2	4	3.3 (2008)	3.7 (2010)	1.5 (2015)	-55%	-59%
von Gottberg ISPPD10 2016	≥64 yrs	South Africa	PCV7, PCV13	4	2	4	1.8 (2008)	2.6 (2010)	0.9 (2015)	-50%	-65%
Mackenzie	5-14 yrs	The	PCV7,	1	2	3	10 (2008-	6.4 (2011)	9.0 (2013-	-5% (not sig)	41%

Lancet ID 2016		Gambia	PCV13				2010)		2014)		
Mackenzie Lancet ID 2016	≥15 yrs	The Gambia	PCV7, PCV13	1	2	3	7.0 (2008-2010)	7.3 (2011)	4.0 (2013-2014)	-48% (not sig)	-45%
Jayasinghe ISPPD10 2016	5-64 yrs	Australia	PCV7, PCV13	3	6	4	0.7 (2004)	2.1 (2010)	0.8 (2015)	14%	-62%
Jayasinghe ISPPD10 2016	≥65 yrs	Australia	PCV7, PCV13	3	6	4	3.6 (2004)	5.7 (2010)	2.2 (2015)	-39%	-61%

29D: Serotype 3, 6A, 6C and/or 19A IPD											
Reference	Age group	Country	PCV product(s)	Number of years			Baseline incidence (cases/100,000)			Percent change at maximum years post-PCV10/13 introduction compared to	
				Pre PCV surveillance	PCV7 use	PCV10/ PCV13	Pre PCV (dates)	PCV7 (dates)	PCV10/ PCV13 (dates)	Pre-PCV	PCV7
3, 6A, 19A											
PCV10											
Nuorti ISPPD10 2016	>18 yrs	Finland	PCV10	5	--	5	2.05 (2005-2008)	--	4.43 (2012-2015)	116%	--
Nuorti ISPPD10 2016	18-49 yrs	Finland	PCV10	5	--	5	0.93 (2005-2008)	--	1.79 (2012-2015)	92%	--
Nuorti ISPPD10 2016	50-64 yrs	Finland	PCV10	5	--	5	2.46 (2005-2008)	--	4.52 (2012-2015)	84%	--
Nuorti ISPPD10 2016	≥65 yrs	Finland	PCV10	5	--	5	4.68 (2005-2008)	--	9.71 (2012-2015)	107%	--
Serotype 3											
PCV10											
Nuorti ISPPD10 2016	≥65 yrs	Finland	PCV10	5	--	5	1.36 (2005-2008)	--	4.94 (2012-2015)	263%	--
Knol ISPPD10 2016	5-64 yrs	Netherlands	PCV10	2	5	5	0.37 (2005-2006)	0.37 (2010-2011)	0.39 (2015-2016)	5%	5%
Knol ISPPD10 2016	≥65 yrs	Netherlands	PCV10	2	5	5	3.24 (2005-2006)	4.16 (2010-2011)	4.81 (2015-2016)	48%	16%
PCV13											
Waight Lancet	15-44 yrs	UK	PCV7, PCV13	6	4	4	0.18 (2005/200	0.13 (2009-2010)	0.07 (2013-2014)	-61%	-46%

2015							6)				
Waight Lancet 2015	45-64 yrs	UK	PCV7, PCV13	6	4	4	0.85 (2005/2006)	0.8 (2009-2010)	0.33 (2013-2014)	-61%	-59%
Waight Lancet 2015	≥65 yrs	UK	PCV7, PCV13	6	4	4	2.7 (2005/2006)	2.8 (2009-2010)	1.6 (2013-2014)	-41%	-43%
Harboe CID 2014	≥65 yrs	Denmark	PCV7, PCV13	8	3	3	4.2 (2000-2007)	4.4 (2008-2010)	4.5 (2011-2013)	7%	2%
Serotype 6A											
PCV10											
Nuorti ISPPD10 2016	≥65 yrs	Finland	PCV10	5	--	5	2.22 (2005-2008)	--	1.96 (2012-2015)	-12%	--
Knol ISPPD10 2016	5-64 yrs	Netherlands	PCV7, PCV10	2	5	5	0.13 (2005-2006)	0 (2010-2011)	0 (2015-2016)	-100%	--
Knol ISPPD10 2016	≥65 yrs	Netherlands	PCV7, PCV10	2	5	5	1.6 (2005-2006)	0.66 (2010-2011)	0.17 (2015-2016)	-89%	-74%
PCV13											
Waight Lancet 2015	15-44 yrs	UK	PCV7, PCV13	6	4	4	0.07 (2005/2006)	0.05 (2009-2010)	0 (2013-2014)	-100%	-100%
Waight Lancet 2015	45-64 yrs	UK	PCV7, PCV13	6	4	4	0.22 (2005/2006)	0.15 (2009-2010)	0 (2013-2014)	-100%	-100%
Waight Lancet 2015	≥65 yrs	UK	PCV7, PCV13	6	4	4	1.1 (2005/2006)	0.77 (2009-2010)	0.03 (2013-2014)	-97%	-96%
Harboe CID 2014	≥65 yrs	Denmark	PCV7, PCV13	8	3	3	2.0 (2000-2007)	1.5 (2008-2010)	0.3 (2011-2013)	-85%	-80%
von Gottberg ISPPD10 2016	10-14 yrs	South Africa	PCV7, PCV13	4	2	4	0.2 (2008)	0.1 (2010)	0. 1 (2015)	-50%	0%
von Gottberg	15-24 yrs	South Africa	PCV7, PCV13	4	2	4	0.2 (2008)	0.2 (2010)	0 (2015)	-100%	-100%

ISPPD10 2016											
von Gottberg ISPPD10 2016	25-44 yrs	South Africa	PCV7, PCV13	4	2	4	0.6 (2008)	0.7 (2010)	0.1 (2015)	-83%	-86%
von Gottberg ISPPD10 2016	45-64 yrs	South Africa	PCV7, PCV13	4	2	4	0.7 (2008)	0.9 (2010)	0.2 (2015)	-71%	-78%
von Gottberg ISPPD10 2016	≥64 yrs	South Africa	PCV7, PCV13	4	2	4	0.2 (2008)	0.2 (2010)	0.1 (2015)	-50%	-50%
Serotype 6C											
PCV10											
Knol ISPPD10 2016	5-64 yrs	Netherlands	PCV7, PCV10	2	5	5	0 (2005-2006)	0 (2010-2011)	0.21 (2015-2016)	--	--
Knol ISPPD10 2016	≥65 yrs	Netherlands	PCV7, PCV10	2	5	5	0.11 (2005-2006)	0.42 (2010-2011)	1.26 (2015-2016)	1045%	200%
Serotype 19A											
PCV10											
Nuorti ISPPD10 2016	≥65 yrs	Finland	PCV10	5	--	5	1.1 (2005-2008)	--	2.9 (2012-2015)	164%	
Knol ISPPD10 2016	5-64 yrs	Netherlands	PCV7, PCV10	2	5	5	0.58 (2005-2006)	1.09 (2010-2011)	1.33 (2015-2016)	129%	22%
Knol ISPPD10 2016	≥65 yrs	Netherlands	PCV7, PCV10	2	5	5	2.11 (2005-2006)	4.72 (2010-2011)	4.98 (2015-2016)	136%	6%
PCV13											
Corcoran ISPPD10	≥65 yrs	Ireland	PCV7, PCv13	1	3	5	1.12 (2007)	1.85 (2010)	3.28 (2015)	193%	77%

2016											
Waight Lancet 2015	15-44 yrs	UK	PCV7, PCV13	6	4	4	0.13 (2005/2006)	0.4 (2009-2010)	0.17 (2013-2014)	31%	-58%
Waight Lancet 2015	45-64 yrs	UK	PCV7, PCV13	6	4	4	0.49 (2005/2006)	1.1 (2009-2010)	0.41 (2013-2014)	-16%	-63%
Waight Lancet 2015	≥65 yrs	UK	PCV7, PCV13	6	4	4	1.5 (2005/2006)	3.6 (2009-2010)	1.1 (2013-2014)	-27%	-63%
Harboe CID 2014	≥65 yrs	Denmark	PCV7, PCV13	8	3	3	1.6 (2000-2007)	3.3 (2008-2010)	2.9 (2011-2013)	81%	-12%

Appendix B.

Table 1. Excluded studies

Study Characteristics				
Country, Reference	**Study Design**	**Population age**	**PCV product and Country Schedule**	**Exclusion Reason**
NP Carriage				
Australia, Leach, Journal of Paediatrics and Child Health, 2011	Post survey	children	PCV7, PCV10, 3+0	Only reports all carriage, no serotyping done
Germany, Linden, Eur J Pediatr, 2015	Post survey	children	PCV7, PCV10, PCV13, 3+1, 2+1	Reports PCV10 and PCV13 together, cannot distinguish data by product received
Italy, Camili, PLoS ONE, 2013	Post survey	children	PCV7, PCV13, 2+1	Reports PCV10 and PCV13 together, cannot distinguish data by product received
Italy, Martinelli, ISPPD-10, 2016	Post survey	Seniors	PCV7, PCV13, 2+1	Only reports on ages over 65
France, Cohen, Pediatric Infectious Disease Journal, 2012	Post survey	children	PCV7, PCV13, 2+1	NP Carriage surveyed only among AOM cases
France, Cohen, Vaccine, 2015	Pre/Post survey	children	PCV7, PCV13, 3+1, 2+1	NP Carriage surveyed only among AOM cases
France, Angoulvant, BMC Infectious Diseases, 2015	Post survey	children	PCV7, PCV13, 2+1	NP Carriage surveyed only among AOM cases
Isreal, Greenberg,	Pre/Post survey	children	PCV7, PCV13, 2+1	NP Carriage surveyed only among AOM cases

ISPPD-10, 2016				
Colombia, Morales, ISPPD-10, 2016	Post survey	children	PCV10, 2+1	No dates provided for survey and only estimates for prevalence given
Tanzania , Ndossa, Journal of Health Research, 2015	Cohort	children	PCV10, 3+0	Only reports on all pneumococcal carriage
Iceland, Quirk, ISPPD-10, 2016	Pre/Post survey	children	PCV10, 2+1	Ages of children sampled was not reported
Iceland, Sigurðsson, ISPPD-10, 2016	Pre/Post survey	children	PCV10, 2+1	Only reports on all pneumococcal carriage
Ethiopia, Assefa, Pediatrics and Neonatology	Post survey	children	PCV10, 3+0	Only reports on all pneumococcal carriage
Malawi, Kamng'ona, BMC Infectious Diseases	Pre/Post survey	children	PCV13, 3+1	Does not distinguish between Pre and Post-Introduction periods or vaccinated and unvaccinated groups
Togo, Tall, ISPPD-10, 2016	Pre/Post survey	Both	PCV10, 3+0	NP Carriage surveyed only among pneumonia cases
Australia, Beissbarth, ISPPD-10, 2016	RCT	children	PCV10, PCV13, 3+1, 3+0	Does not distinguish between schedules
Pakistan, Kerai, ISPPD-10, 2016	Post survey	children	PCV10, 3+0	Low coverage in study population and reports carriage 6A and 19A together. Uses the same data as Tsegaye 2016, which will be included
Fiji, Russell, ISPPD-10, 2016	Pre/Post survey	Both	PCV10, 3+0	Only reports on all pneumococcal carriage
Portugal, Rodrigues, ISPPD-10, 2016	Post survey	children	PCV7, PCV10, PCV13, 2+1	Does not distinguish between schedules
Fiji, Russell, ISPPD-10, 2016	Pre/Post survey	Both	PCV10, 3+0	Only reports on all pneumococcal carriage

USA, Shea, ISPPD-10, 2016	Pre/Post survey	children	PCV7, PCV13, 3+1	Only reports all pneumococcal carriage
Korea, Ahn, Infectious Diseases	Pre/Post survey	children	PCV7, PCV10, PCV13, 2+1	Reports among patients with respiratory infections, including pneumonia, not representative of general population
Iceland, Erlendsdottir, ISPPD-9, 2014	Post survey	children	PCV10 2+1	No impact assessment, children reported on unlikely to be vaccinated
Pneumonia				
Israel, Ben Shimol, PIDJ 2015	Pre/Post observation	children	PCV13, 2+1	Insufficient number of years post-introduction (1 year)
Uruguay, Gabarrot, PLoS ONE 2014	Pre/Post observation	all ages	PCV13, 2+1	Main outcome IPD with proportion of IPD cases that were pneumonia
Italy, Martinelli,Human Vac & Immuno 2014	Pre/Post observation	children	PCV13, 2+1	Insufficient number of years post-introduction (1 year)
Morocco, Jroundi,J Trop Ped 2014	Post-only observation	children	PCV10, 2+1	Only post- data
United Kingdom (UK), Moore, JID 2014	Pre/Post observation	all ages	PCV13, 2+1	Paper mentions proportion of IPD cases that were pneumonia or bacteremia, but overall rates are for IPD in general
Israel, Weinberger, EID 2013	Pre/Post observation	children	PCV13, 2+1	Insufficient number of years post-introduction (1.5 years)
United Kingdom (UK), Elemraid, Diag Micro & Infect Dis 2013	Post-only observation	all ages	PCV13, 2+1	Insufficient number of years post-introduction (1.5 years); study is on diagnostics, not impact
Brazil, Afonso, EID 2013	Pre/Post observation	children	PCV10, 3+0	Insufficient number of years post-introduction (1 year)
Uruguay, Hortal, ISPPD 2012	Pre/Post observation	children	PCV13, 2+1	Duplicate data
Argentina, Bakir, ISPPD 2014	Pre/Post observation	children	PCV13, 2+1	Insufficient number of years post-introduction (1 year); no pre-PCV data, only year of intro
Argentina, Bakir,	Pre/Post	children	PCV13, 2+1	Insufficient number of years post-introduction (1 year)

ISPPD 2014	observation			
Argentina, Rearte, ISPPD 2014	Pre/Post observation	children	PCV13, 2+1	Insufficient number of years post-introduction (1 year)
Argentina, Ranca, ISPPD 2014	Pre/Post observation	children	PCV13, 2+1	Insufficient number of years post-introduction (1 year)
Gambia, Ikumapayi, ISPPD 2014	Pre/Post observation	all ages	PCV13, 3+0	Case data only; etiology of pna cases
Gambia, Ebruke, ISPPD 2014	case control	children	PCV13, 3+0	No pneumonia outcome
Uruguay, Giachetto, ISPPD 2014	Pre/Post observation	children	PCV13, 2+1	Insufficient number of years post-introduction (1 year)
Madagascar, Rabezanahary, ISPPD 2014	case control	children	PCV10, 3+0	Pre-PCV data only
Ireland, O'Connell, ISPPD 2014	Pre/Post observation	children	PCV13, 2+1	Main outcome of interest is IPD; states reduction in incidence of complicated pneumonia, but no data shown
Argentina, Badano, ISPPD 2014	Pre/Post observation	children	PCV13, 2+1	Insufficient number of years post-introduction (1 year)
Multiple Countries (Please Specify), PERCH Study Group, ISPPD 2014	case control	children	PCV10/PCV13, 2+1, 3+0	Etiology of pneumonia, not impact
Brazil, Oliveira, Vaccine 2016	cohort	children	PCV10, 2+1	No relevant outcome of interest- study focuses on complications of ARIs and risk factors for ARI
France, Noel, J Pediatr Infect Dis Soc 2016	Pre/Post observation	children	PCV13, 2+1	ED visits only; all other data presented in report is for hospitalized cases
South Africa, Zar, Lancet Respir Med 2016	case control	children	PCV13, 2+1	Study on etiology, not PCV impact
Sweden, Johansson Kostenniemi, ISPPD 2016	Pre/Post observation	all ages	PCV10/PCV13, 2+1	Only qualitative data

Multiple Countries, Tregnaghi, ISPPD 2016	Randomized Controlled Trial	children	PCV10, 3+0	3+1 schedule
Iceland, Sigurðsson, ISPPD 2016	Pre/Post observation	children	PCV10, 2+1	No pneumonia data
Italy, Martinelli, ISPPD 2016	Post-only observation	all ages	PCV13, 2+1	No pneumonia data; only post data
Venezuela, del Nogal, ISPPD 2016	case control	children	PCV13, 2+1	Cross-sectional study nested in cohort study; no incidence
Togo, Tall, ISPPD 2016	Pre/Post observation	all ages	PCV13, 3+0	No pneumonia data
Argentina, Rearte, ISPPD 2016	Pre/Post observation	children	PCV13, 2+1	Case series
Argentina, Rearte, ISPPD 2016	Pre/Post observation	children	PCV13, 2+1	Duplicate
Fiji, Russell, ISPPD 2016	Pre/Post observation	all ages	PCV10, 3+0	Duplicate
Multiple Countries , Tregnaghi, ISPPD 2016	Randomized Controlled Trial	children	PCV10, 3+0	3+1 schedule
Mortality				
Sweden, Luthander, Acta Paediatrica	Pre/Post observation	all ages	PCV7, PCV10, 2+1	Aetiology study that breaks down deaths into pre/post periods, however there was another intervention in PCV time period
United Kingdom, Slack, ISPPD, 2012	Indirect Cohort	children	PCV7, PCV10, 2+1	No pre/post comparison just a complete serotype distribution of the deaths occurred over study period
Iceland, Haraldsson, ISPPD, 2014	Pre/Post observation	all ages	PCV10, 2+1	Only case numbers (not incidence or reduction); Too small sample size
Australia, Kluyver	Pre/Post observation	all ages	PCV7, PCV13, 3+1	Number of deaths in reported period of surveillance, but no pre/post comparison possible; Too small sample size
South Africa, Zar,	case control	children	PCV13, 2+1	Drakenstein Child Health study. No comparison of PCV vs.

Lancet of Respiratory Medicine, 2016				no PCV group
Argentina, Gentile, ISPPD, 2016	Pre/Post observation	children	PCV13, 2+1	Only case numbers (not incidence)
United Kingdom, Collins, ISPPD, 2016	Pre/Post observation	children	PCV7, PCV10, 2+1	Post only measure of deaths, by ST group, no comparison pre and post able to be made
Czech Republic, Stock, PLoS ONE, 2015	Pre/Post observation	all ages	PCV10, PCV13, 3+1	Case fatality rate for all IPD only
Brazil, Grando, Cadernos de saude publica, 2015	Pre/Post observation	children	PCV13, 3+1	Case fatality rate for pneumococcal meningitis only
Canda, Rudnick, Vaccine, 2013	Pre/Post observation	all ages	PCV7, PCV10, PCV13, 2+1, 3+1	Case fatality rate for adults only

Table 2: Indirect Effects Studies Excluded from Review

Study Characteristics				
Country, Reference	**Study Design**	**Population age**	**PCV product and Country Schedule**	**Exclusion Reason**
NPC				
Italy Ansaldi Hum Vac Immunother 2013	Post survey	>60 yrs	PCV13 2+1	Less than 3 years post data No pre-PCV comparison period
Italy Azzari Hum Vac Immunother 2016	Post survey	<5 yrs	PCV13 2+1	Excluded based on age group, mostly direct effects
Australia Beissbarth ISPPD10 2016	RCT	<1 yr	PCV10, PCV13 3+0, 4+0	No comparison period for post PCV10/13 Exclude based on study design
Netherlands Bosch Vaccine 2016	Pre post survey	Adults	PCV10 3+1	Less than 3 years post data
Italy Camilli PLoS One 2013	Post survey	<5 yrs	PCV13 2+1	Less than 3 years post data
South Africa Dube ISPPD10 2016	Post survey	<5 yrs	PCV13 2+1	Exclude based on age group, mostly direct effects
Italy Durando ISPPD9 2014	Post survey	>60 yrs	PCV13 2+1	Only data on all pneumococcal carriage Less than 3 years post data
Iceland Erlendsdottir	Pre post survey	2-6 yrs	PCV13 2+1	Only data on all pneumococcal carriage Less than 3 years post data

ISPPD9 2014				
Sweden Galanis Eur Resp J 2016	Pre post survey	<6 yrs	PCV13 2+1	Excluded based on age groups, mixed direct effects
UK Hamaluba Arch Dis Child 2012	Post survey	Adults >65 yrs	PCV13 2+1	Less than 3 years post data
Kenya Hammitt Lancet Global Health 2014	Pre post survey	>5 yrs	PCV10 3+0	Less than 3 years post data
Australia Hoskins ISPPD9 2014	Post survey	>5 yrs	PCV13 3+0	Less than 3 years post data
Finland Jokinen ISPPD10 2016	RCT	5-9 yrs	PCV10 2+1, 3+1	Exclude based on study design
Finland Jokinen ISPPD9 2014	RCT	3-7 yrs	PCV10 2+1, 3+1	Exclude based on study design
Kenya Kim ISPPD10 2016	Pre post survey	Adults, HIV+	PCV10 3+0	Less than 3 years post data HIV+ high risk group
Netherlands Krone PloS One 2015	Post survey	>60 yrs	PCV10 3+1	Less than 3 years post data
Italy Martinelli ISPPD10 2016	Post survey	>65 yrs	PCV13 2+1	No comparison period for post PCV13
Burkina Faso Moisi ISPPD10 2016	Pre post survey	>5 yrs	PCV13 3+0	Less than 3 years post data

South Africa Nzenze ISPPD9 2014	Pre post survey	15-45 yrs	PCV13 2+1	Less than 3 years post data
South Africa Nzenze ISPPD10 2016	Post survey	>5 yrs	PCV13 2+1	Less than 3 years post data
Italy Pasinato Vaccine 2014	Post survey	<5 yrs	PCV13 2+1	Less than 3 years post data
Italy Principi J Med Micro 2014	Post survey	15-19 yrs	PCV13 2+1	Less than 3 years post data
Fiji Russell ISPPD10 2016	Pre post survey	Adults	PCV10 3+0	Only report data on all pneumococcal carriage
Fiji Russell ISPPD10 2016	Pre post survey	Adults	PCV10 3+0	Only report data on all pneumococcal carriage
Mozambique Sigauque ISPPD10 2016	Pre post survey	<5 yrs	PCV10 3+0	Less than 3 years post data
Iceland Sigurosson ISPPD10 2016	Pre post survey	<4 yrs	PCV10 2+1	Exclude based on age group
Norway Steens PIDJ 2015	Pre post survey	>5 yrs	PCV13 2+1	Less than 3 years post data
Togo Tall ISPPD10 2016	Pre post survey	>5 yrs	PCV13 3+0	Less than 3 years post data
UK van Hoek Vaccine 2014	Pre post survey	>5 yrs	PCV13 2+1	Less than 3 years post data
Netherlands Vissers ISPPD10	Pre post survey	Adults	PCV10 3+1	All pneumococcal carriage data only

2016				
IPD				
France Alexandre Acta Paediatrica 2010	Pre post inc	2-18 yrs	PCV13 2+1	Post PCV7 data only
Uruguay Algorta ISPPD10 2016	Pre post inc	Adults	PCV13 2+1	PCV7 and PCV13 data reported together
Brazil Azevedo ISPPD9 2014	Pre post inc	>50 yrs	PCV10 3+1	Only all Spn incidence, 3+1 schedule
Brazil Caierao PLoS One 2014	Pre Post cases	>6 yrs	PCV10 3+1	Excluded based on study design
Spain Camara ISPPD10 2016	Pre post inc	>18 yrs	PCV13 2+1	Low coverage of PCV13 in private market
Taiwan Chang Value in Health 2014	Pre post inc	<18 yrs	PCV10, PCV13	Exclude based on age groups, mixed direct effects
Australia De Kluyver CDI 2015	Post case series	>5 yrs	PCV13 3+0	Excluded based on study design
Canada De Wals Vaccine 2014	Pre post inc	>5 yrs	PCV10, PCV13 2+1	Less than 3 years post data
Morocco Diawara ISPPD9 2014	Pre post inc	General population	PCV13, PCV10 2+1	Age group with mixed direct effects, no incidence data Less than 3 years post data
Brazil dos Santos	Pre post inc	>15 yrs	PCV13 3+1	Less than 3 years post data, 3+1 schedule

Vaccine 2013				
Spain Ercibengoa ISPPD10 2016	Pre post cases	>5 yrs	PCV13 2+1	Excluded based on study design
Iceland Erlendsdottir ISPPD9 2014	Pre post inc	>2 yrs	PCV10 2+1	Less than 3 years post data
Uruguay Gabarrot PLoS One 2014	Pre post inc	>5 yrs	PCV13 2+1	Less than 3 years post data
Uruguay Gabarrot ISPPD9 2014	Pre post inc	>5 yrs	PCV13 2+1	Less than 3 years post data
Argentina Gentile ISPPD10 2-16	Pre post inc	5-15 yrs	PCV13 2+1	Less than 3 years post data
Denmark Harboe ISPPD9 2014	Pre post inc	Gen pop	PCV13 2+1	Excluded based on age groups, mixed direct effects
Canada Helferty Int J Circumpolar Health 2013	Pre post inc	>2 yrs	PCV10, PCV13 2+1	Less than 3 years post data
France Janoir PLoS One 2014	Pre post cases	>16 yrs	PCV13 2+1	Excluded based on study design
Netherlands Knol Emerging Inf Dis 2015	Pre post inc	>18 yrs	PCV10 3+1	Data covered in Knol ISPPD10 2016
France Lepoutre Vaccine 2015	Pre post inc	>5 yrs	PCV13 2+1	Less than 3 years post data

UK Martin Lancet 2014	Pre post inc	>65 yrs	PCV13 2+1	Less than 3 years post data
Switzerland Meichtry Vaccine 2014	Case series	>16 yrs	PCV13 2+1	Cases only for PCV13 period
UK Moore ISPPD9 2014	Pre post inc	General pop	PCV13 2+1	Excluded based on age groups, mixed direct effects
South Africa Nzenze ISPPD9 2014	Pre post inc	15-45 yrs	PCV13 2+1	Less than 3 years post data
Finland Palmu ISPPD9 2014	Clinical trial	>5 yrs	PCV10 2+1	Excluded based on study design
Finland Palmu ISPPD10 2016	Pre post inc	<7 yrs	PCV10 2+1	Historical control, age group for direct effects
Spain Picazo PIDJ 2013	Post inc	>5 yrs	PCV13 2+1	Exclude based on study design, post only
Uruguay Pirez PIDJ 2014	Pre post inc	<15 yrs	PCV13 2+1	Excluded based on age group, mixed direct effects Less than 3 years post data
Finland Polkowska ISPPD10 2016	Pre post inc	>5 yrs	PCV10 2+1	Dates not reported for comparison period pre and post PCV
Costa Rica Ramirez ISPPD10 2016	Pre post inc	>65 yrs	PCV13 2+1	Mixed outcome of IPD and pneumonia reported together
Israel Regev-Yochay ISPPD10 2016	Post inc	>18 yrs	PCV13 2+1	Started in year of PCV7 introduction, so post only
Canada Ricketson ISPPD9 2014	Pre post inc	>5 yrs	PCV13 2+1	Less than 3 years post data

Canada Rudnick Vaccine 2013	Pre post inc	>5 yrs	PCV10, PCV13 2+1	Less than 3 years post data
Fiji Russell ISPPD10 2016	Pre post inc	<4 yrs	PCV10 3+0	Excluded based on age groups
Canada Sahni Can J Public Health 2012	Pre post inc	>5 yrs	PCV13 2+1	Less than 3 years post data
Denmark Slotved ISPPD9 2014	Pre post inc	<90 days	PCV13 2+1	PCV7 and PCV13 data reported together
Norway Steens Vaccine 2013	Pre post inc	>5 yrs	PCV13 2+1	Less than 3 years post data
Norway Steens BMC Inf Dis 2014	Pre post inc	>5 yrs	PCV13 2+1	Post PCV7 data only
Finland, USA Suaya ISPPD10 2016	Pre post inc	>5 yrs	PCV10, PCV13 2+1	Same data as reported in Nuorti ISPPD10 2016
Germany van der Linden PLoS One 2015	Pre post cases	>5 yrs	PCV13 2+1	Excluded based on study design
Germany van der Linden ISPPD10 2016	Pre post cases	>16 yrs	PCV13 2+1	Excluded based on study design
South Africa von Gottberg NEJM 2014	Pre post inc	>5 yrs	PCV13 2+1	Less than 3 years post data
Netherlands Wagenvoort ISPPD10 2016	Pre post inc	>5 yrs	PCV10 3+1, 2+1	Males and females reported separately

Pneumonia				
Nicaragua Becker-Dreps PIDJ 2014	Pre post inc	5-14 yrs	PCV13 3+0	Less than 3 years post data
Nicaragua Becker-Dreps Vaccine 2015	Pre post inc	>50 yrs	PCV13 3+0	Less than 3 years post data
Venezuela del Nogal ISPPD10 2016	Pre post cases	<10 yrs	PCV13 2+1	Excluded based on study design and age group
Argentina Gentile ISPPD9 2014	Pre post inc	<18 yrs	PCV13 2+1	Excluded because of age groups, mixed direct effects
Argentina Gentile ISPPD10 2016	Pre post inc	5-15 yrs	PCV13 2+1	Less than 3 years post data
Israel Greenberg Vaccine 2015	Pre post inc	<18 yrs	PCV13 2+1	Excluded because of age groups, mixed direct effects
Sweden Lindstrand Pediatrics 2014	Pre post inc	5-18 yrs	PCV13 2+1	Less than 3 years post data
Italy Martinelli ISPPD10 2016	Post cases	>65 yrs	PCV13 2+1	Excluded based on study design
UK McDonald Diabetic Med 2013	Pre post inc	>65 yrs	PCV13 2+1	Excluded because high risk group only: diabetic patients
Poland Patrzalek Curr Med Res Opin 2016	Pre post inc	>30 yrs	PCV13 2+1	Less than 3 years post data

Uruguay Pirez PIDJ 2014	Pre post inc	<15 yrs	PCV13 2+1	Excluded because of age groups, mixed direct effects Less than 3 years post data
Uruguay Pirez ISPPD9 2014	Pre post inc	<14 yrs	PCV13 2+1	Excluded because of age groups, mixed direct effects Less than 3 years post data
Spain Rivero-Calle ISPPD10 2016	Pre post inc	>5 yrs	PCV13 2+1	Less than 3 years post data
Fiji Russell ISPPD10 2016	Pre post inc	<2 yrs	PCV10 3+0	Excluded based on age groups
Fiji Russell ISPPD10 2016	Pre post inc	<2 yrs	PCV10 3+0	Excluded based on age groups
UK Saxena J Inf 2015	Pre post inc	<16 yrs	PCV13 2+1	Excluded because of age groups, mixed direct effects
Togo Tall ISPPD10 2016	Pre post inc	<4 yrs	PCV13 3+0	Excluded based on age groups, mixed direct effects
Spain Tagarro J Peds 2015	Case control	<14 yrs	PCV13 2+1	Excluded based on study design
Israel Verani ISPPD9 2014	Case control	<5 yrs	PCV13 2+1	Excluded based on study design
South Africa Zampoli PIDJ 2015	Pre post inc	<12 yrs	PCV13 2+1	Excluded based on age groups, mixed direct effects

Appendix C.

Search Strategy:

Librarians at the Johns Hopkins Medical Institutes, Welch Library, will work with the PRIME coordinator to refresh the literature search strategy developed for the PCV dosing landscape in 2010. Electronic searches were conducted in EMBASE, PubMed, Biological Abstracts (BA), Pascal Biomed, Global Health, BioAbst/Reports, Reviews, Meetings, Cochrane Library, African Index Medicus (AIM), Western Region Index Medicus (WPRIM), Index Medicus for Eastern Med. Region (IMEMR), Index Medicus for South-East Asia Region (IMSEAR), Latin America and Caribbean Health Sciences Info. (LILACS), Pan-American Health Org. (PAHO), and, IndiaMed (IndMed).

The terms listed in Appendix 1 will be used to identify all potentially relevant articles for this review. Each article must include a minimum of one "narrow vaccine term" and one "Pneumococcal term" to be identified in the search. Terms may be listed as Medical Subject Headings (MeSH) or other categories specific to each database. Only studies published in the English language will be considered for review because of the low likelihood that such studies have been published in non-English journals[1]. It is our assessment that the vast majority of reports will be reported in English, and the effort required to search in other languages will yield little if any additional data.

Other resources will also be considered: "Gray literature" (national surveillance data, congress and conference proceedings and annals (especially the international symposium of pneumococcus and pneumococcal disease (ISPPD)); hand-searching from reference lists of included studies; contact with authors of included studies and with experts, vaccine manufacturers and associations related to the topic

Search terms

Pneumococal Terms:	**Narrow Vaccine Terms:**
1. Pathogen terms	
"Streptococcus pneumoniae"[mesh]	"Vaccines, conjugate"[mesh]
("Diplococcus"[all fields] AND "pneumoniae"[all fields])	"Pneumococcal Vaccines"[mesh]
("micrococcus"[all fields] AND "pneumoniae"[all fields])	"streptococcal vaccines"[mesh]
"Pneumococcus"[all fields]	
"pneumococcal"[all fields]	(("conjugate" OR "conjugated" OR "pneumococcal"[all fields]
"s. pneumoniae"[all fields]	OR "streptococcal"[all fields])
"pneumococci"[all fields]	AND
Pneumococc*[all fields]	("vaccine"[tiab] OR "vaccines"[tiab] OR "vaccination"[tiab]
"Streptococcus" [mesh]	OR "vaccinated"[tiab] OR "immunization"[tiab] OR
"Streptococcal"[mesh]	"immunisation"[tiab] OR "immunized"[tiab] OR
	"immunised"[tiab]))
2. Outcome-related terms	
"Pneumonia, Pneumococcal"[mesh]	(("Pneumococcal"[all fields] OR "pneumococcus"[all fields]
"Meningitis, Pneumococcal"[mesh]	OR "capsular"[all fields])
"Meningitis, Streptococcal"[mesh]	AND

[1] Articles that have been translated into English will be included.

“Pneumococcal Infections”[mesh] “Streptococcal Infections”[mesh] “Otitis Media”[mesh] (“lobar”[all fields] AND “pneumonia”[all fields]) (“Nasopharyngeal”[all fields] AND “carriage”[all fields]) (“Nasopharyngeal”[all fields]AND “colonization”[all fields]) (“ nasopharyngeal”[all fields] AND “colonisation”[all fields]) (“Community acquired”[all fields] AND “pneumonia”[all fields]) (“community acquired”[all fields] AND “pneumonias”[all fields]) (“Bacteraemic”[all fields] AND “pneumonia”[all fields]) (“bacteraemic”[all fields] AND “pneumonias”[all fields]) (“Bacteremic”[all fields] AND “pneumonia”[all fields]) (“bacteremic”[all fields] AND “pneumonias”[all fields]) “Anti-pneumococcal”[all fields] “antipneumococcal”[all fields] (“lower respiratory tract infection”[all fields]) (“lower respiratory tract infections”[all fields]) (“Invasive disease” [all fields]) (“invasive pneumococcal disease” [all fields]) (“invasive bacterial disease” [all fields]) (“Bacterial pneumonia”[all fields]) (“Bacterial pneumonias”[all fields]) (“Otitis Media”[all fields]) (“inner ear infection”[all fields]) (“inner ear infections”[all fields])	(“polysaccharide”[all fields]) AND (“vaccine”[tiab] OR “vaccines”[tiab] OR “vaccination”[tiab] OR “vaccinated”[tiab] OR “immunization”[tiab] OR “immunisation”[tiab] OR “immunized”[tiab] OR “immunised”[tiab])) “PncCRM197”[all fields] “PCV”[all fields] “Pneumovax”[all fields] “Pnu-Imune” [all fields] “Pnu Imune”[all fields] “PnuImune”[all fields] “pneu immune”[all fields] “pnu immune”[all fields] “pneumo 23”[all fields] “pneumopur”[all fields] “streptopur”[all fields] “streptorix”[all fields] “PncOMPC vaccine” [Substance Name] “PncOMPC”[all fields] (“Pneumococcal”[all fields] AND “polysaccharide”[all fields] AND “meningococcal”[all fields] AND “outer”[all fields] AND “membrane”[all fields] AND “protein”[all fields] AND “complex”[all fields]) “five-valent pneumococcal conjugate vaccine” [Substance Name] “five-valent”[all fields] “5-valent”[all fields] “PCV5”[all fields] “PCV-5”[all fields] “heptavalent pneumococcal conjugate vaccine” [Substance Name] “heptavalent”[all fields] “PNCRM7”[all fields] “PNCRM-7”[all fields] “PCV7”[all fields] “PCV-7”[all fields] “seven-valent”[all fields] ” 7-valent”[all fields] “Prevenar”[all fields] “Prevnar”[all fields] “10-valent pneumococcal vaccine” [Substance Name] “Ten-valent”[all fields] “10-valent”[all fields] “PCV10”[all fields] “PCV-10”[all fields] “13-valent pneumococcal vaccine” [Substance Name] “Thirteen-valent”[all fields] “13-valent”[all fields] “PCV13”[all fields] “PCV-13”[all fields] “nine-valent”[all fields] “9-valent”[all fields] “PCV9”[all fields] “PCV-9”[all fields]

	"two-valent"[all fields] "2-valent"[all fields] "PCV2"[all fields] "PCV-2"[all fields] "three-valent"[all fields] "3-valent"[all fields] "PCV3"[all fields] "PCV-3"[all fields] "four-valent"[all fields] "4-valent"[all fields] "PCV4"[all fields] "PCV-4"[all fields] "six-valent"[all fields] "6-valent"[all fields] "PCV6"[all fields] "PCV-6"[all fields] "7vPnC"[all fields] "7vCRM"[all fields] "PHiD-CV"[all fields] (("23-valent"[all fields] "23vPPV"[all fields] "PPV23"[all fields] "PPSV23"[all fields] "23-valent pneumococcal capsular polysaccharide vaccine"[substance name] "pneumococcal surface protein" [all fields] "pneumococcal surface proteins"[all fields] "pneumococcal protein"[all fields] "pneumococcal proteins"[all fields] "streptococcal surface protein"[all fields] "streptococcal surface proteins"[all fields] "streptococcal protein"[all fields] "streptococcal proteins"[all fields]
Additional search elements: Additional controlled vocabulary used in EMBASE (pathogen/outcome terms): • 'streptococcus pneumonia'[EMTREE term] • 'lower respiratory tract infection' [EMTREE term] • 'bacterial pneumonia' [EMTREE term] • 'lobar pneumonia' [EMTREE term] • 'community acquired pneumonia' [EMTREE term] Additional controlled vocabulary in EMBASE (vaccine terms): • 'Pneumococcus vaccine' [EMTREE term] • 'Streptococcus vaccine' [EMTREE term] • 'Pneumococcus polysaccharide' [EMTREE term] Adjacency Searching (near 5) used in: EMBASE Global Health Biological Abstracts Biological Abstracts/RRM	

Pascal BioMed Cochrane Library <u>Animal Limits used in:</u> PubMed EMBASE Biological Abstracts Biological Abstracts/RRM <u>Other limits:</u> English language Date: 1994 – December 31, 2016 <u>Not needed – pneumococcal/streptococcal finds that did not yield additional material:</u> *Pneumococcal Pneumonia* *Pneumococcal Pneumonias* *Pneumococcal Meningitis* *Pneumococcal Infection* *Pneumococcal Infections* *Pneumococcal mortality* *Pneumococcal mortalities* *Streptococcal infection* *Streptococcal infections*	