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The relative importance of *S. pneumoniae* serotypes causing invasive pneumococcal disease in young children after the introduction of conjugate vaccines

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Declaration

I, Evelyn Balsells, hereby declare that this thesis, presented for the degree of Doctor of Philosophy of Population Health Sciences, has been composed solely by myself and that it has not been submitted, in whole or in part, in any previous application for a degree or professional qualification. Except where states otherwise by reference or acknowledgement, the work presented is entirely my own.

Date: 1st of February 2021

Evelyn Balsells

Abstract

Introduction: Pneumococcal diseases include a range of infections caused by *S. pneumoniae*, which is a common cause of morbidity and mortality globally. Even though pneumococcal conjugate vaccines (PCVs) are available, invasive pneumococcal disease (IPD) remains a global public health issue in young children. Given the large diversity of pneumococcal serotypes and differences in their prevalence geographically, it is important to assess and quantify their burden in a comprehensive way to inform global health interventions.

Aims and objectives: This thesis aims to characterise the relative burden of *S. pneumoniae* serotypes in childhood in IPD in settings where PCVs have been implemented, with a focus on serotypes not included in current formulations, to inform research and future prevention strategies.

Methods: I conducted two systematic reviews to answer questions related to the change in the incidence of IPD in young children, the proportional contribution of serotypes to IPD, and the relative invasive disease potential of circulating serotypes after the introduction of PCVs. Data on the first two outcomes were identified from published literature, complemented by grey literature and they were pooled through meta-analysis. Serotype data from carriage and IPD studies to estimate the relative invasive disease potential were obtained through a systematic review and from collaborators who provided re-analysed or an extension of published data. Then, data were pooled using meta-analysis. To examine the impact of PCVs on the incidence of IPD, by serotype categories, among young children in Latin America I extracted and pooled data from annual SIREVA-II reports using meta-analysis.

Results: The introduction of highly valent PCVs (PCV13 and/or PCV10) has resulted in a consistent reduction of IPD incidence among young children. The decreases in the incidence of IPD have been driven by declines of cases due to vaccine-targeted serotypes. Less consistently, there is evidence of a potential lag between PCV introduction and increases of non-PCV13 serotypes. Based on data from varying years after the implementation of highly

valent PCVs, a pooled analysis indicated that less than half of childhood IPD cases were found to be associated with non-PCV13 serotypes, with differences by region. Due to the high heterogeneity, these estimates should be interpreted with caution. The estimates of invasive disease potential of non-PCV13 serotypes were usually lower than that of 19A or other vaccine types. However, there is evidence to support that some non-PCV13 serotypes are more invasive than other serotypes not included in PCVs. When focusing on the Latin American region, a large, yet variable, protective effect of highly valent PCVs has been identified on childhood IPD in seven countries. Regional estimates for the different serotype categories are difficult to interpret due to heterogeneity but the average incidence of IPD associated with PCV7 and PCV10non7 has declined by over 70% after three years of highly valent PCV use when compared to the year before their introduction. The moderate heterogeneity in the estimates of these reductions (I^2 0-49%) offer support for the protective effects of PCVs against targeted serotypes.

Conclusion: Incidence data of childhood IPD provide evidence for serotype replacement post-highly valent PCVs, which has not yet been sufficient to offset the protective effect of the vaccines. As vaccination programmes mature, the relative contribution of serotypes to childhood IPD is changing, with non-PCV13 serotypes accounting for a third (or more) of IPD cases in some settings with over five years of use. Estimates of invasive disease potential for non-PCV13 serotypes show that most have a low invasive disease potential. In Latin America region there is evidence of reductions in IPD due to vaccine-targeted serotypes by the third year of highly valent PCVs use. The estimates presented in this thesis show there is a need to monitor the role of non-PCV13 serotypes in IPD closely. It is not possible, as of yet, to know which, if any, of these serotype(s) could emerge as the leading serotype in IPD or have an impact that would mitigate PCVs' high protective effects. Globally, PCV programmes need to be introduced, sustained and expanded where possible to reduce the burden of pneumococcal disease. Close attention to the diversity of serotypes that are associated with IPD in different

world regions is warranted to inform the development and implementation of future pneumococcal disease vaccines.

Lay summary

The bacterium *Streptococcus pneumoniae* causes invasive pneumococcal disease (IPD), including infections of the membranes of the brain, the blood or the lungs. It usually lives in the nose of humans and most commonly causes disease in young children (under five years of age) or the elderly. With the introduction of pneumococcal conjugate vaccines (PCV), episodes of IPD among children began to be prevented. However, there are two challenges from a global public health perspective. First, vaccines are not designed to prevent all pneumococcal disease because available vaccines are designed to offer protection for a limited number of the 90 varieties, or serotypes, of the bacteria. The first vaccine offered protection for seven serotypes, second-generation of PCVs offer currently in use include ten to thirteen serotypes (PCV10 and PCV13). Second, the vaccines were initially designed to protect against those varieties of the bacteria that cause disease in high-income countries, which differs from the leading varieties in resource-limited settings. In this thesis, I aimed to quantify various metrics that describe or are related to understanding the amount of disease associated with each serotype in IPD at a global level to inform prevention strategies, including new vaccines.

I used data from studies from different countries to quantify the amount of IPD in different settings. My analyses show that since the introduction of PCVs there have been consistent reductions of IPD in young children, mainly because the burden of disease due to the serotypes contained in the vaccine has decreased. However, IPD due to the serotypes not included in the vaccines has increased in relative, not absolute, terms. This means, the increase has not been enough to return to the pre-vaccine period, at least after the fourth year since the vaccine's introduction. Globally, I estimated that around four out of ten childhood IPD cases were related to one of the serotypes not included in PCV10 or PCV13. However, there is large variability in this estimate, and it should be interpreted with caution.

Serotypes not included in the vaccines currently available vary in their ability to cause IPD in children. Though the varieties of the bacteria that are not included in the vaccines are less likely to cause disease than the varieties in the vaccine, this thesis shows that some non-PCV13 serotypes are more invasive than others.

In one of the chapters, I focus on PCV use in Latin America. In this world region, all countries have introduced PCVs. I found a large yet variable, protective effect in seven countries in the region. Evidence on the varieties that are causing the disease are lacking from several countries, most of them middle-income, for which surveillance efforts need to be strengthened.

Together, all findings show that PCV programmes need to be introduced, sustained and expanded where possible to reduce the burden of pneumococcal disease. Close attention to the diversity of serotypes, through surveillance, is needed to evaluate how effective available PCVs are in prevention of IPD in children. It is hoped that the findings of this thesis on the relative importance of individual serotypes also contribute to the development and monitoring of future pneumococcal disease vaccines.

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Abbreviations

ABCs	Active Bacterial Core surveillance
AFRO	African Regional Office
AME	Americas
aOR	Adjusted odds ratio
CBP	Choline-binding proteins
CC	Clonal complex
CDC	Centers for Disease Control and Prevention
CI	Confidence intervals
CSF	Cerebrospinal fluid
EMRO	Eastern Mediterranean Regional Office
HIC	High-income country
HIV	Human immunodeficiency viruses
I^2	I-square
IPD	Invasive pneumococcal disease
IRR	Incidence rate ratios
IR	Incidence rate
IVAC	International Vaccine Access Center
JBI	Joanna Briggs Institute
LAT	Latex agglutination test
LIC	Low-income countries
LILACS	Acronym for: Literature in the Health Sciences in Latin America and the Caribbean in Portuguese language [Literatura Latino-Americana e do Caribe em Ciências da Saúde]
LMIC	Lower middle-income countries
MIC	Minimum inhibitory concentrations
NAAT	Nucleic acid amplification tests
NIP	National Immunisation Programme
OR	Odds ratio
PAHO	Pan-American Health Organization
PCR	Polymerase chain reaction
PCV	Pneumococcal conjugate vaccine
PPSV	Pneumococcal polysaccharide vaccines
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SEARO	South-East Asia Regional Office
SIREVA-II	Acronym for Network of surveillance systems for agents responsible for pneumonia and bacterial meningitis in Spanish [Sistema de Redes de Vigilancia de los Agentes Responsables de Neumonias y Meningitis Bacterianas]
SSI	Statens Serum Institute
UK	United Kingdom
UMIC	Upper middle-income countries
UNICEF	United Nations Children's Fund
UR	Uncertainty range
USA	United States of America
WHO	World Health Organization
WCV	Whole-cell vaccine
WPRO	Western Pacific Regional Office

1 Introduction

1.1 General overview

1.1.1 Global burden of childhood pneumococcal disease

Pneumococcal diseases include a range of infections caused by *Streptococcus pneumoniae (S. pneumoniae)*, a common cause of morbidity and mortality in young children. The most concerning and severe type of infections caused by *S. pneumoniae* are pneumonia and invasive pneumococcal disease (IPD) (see section 1.1.2), which occur when the bacteria infect the lungs or normally sterile sites, respectively.

Before pneumococcal conjugate vaccines (PCVs), i.e., the vaccines effective against childhood IPD (see section 1.1.5), 14.5 million cases of serious pneumococcal disease were estimated globally among children under five years of age in 2000 (uncertainty range [UR]: 11.1–18.0 million) (O'Brien et al., 2009). Among these cases, researchers estimated that 826,000 deaths occurred (UR: 582,000–926,000). Together with other studies focused on different regions, these global estimates evidence the high and uneven burden of IPD in young children globally before the rollout of immunisation strategies. In Latin America, for instance, a study estimated that 18,000 annual pneumococcal deaths in young children occurred in 2005 before the introduction of PCVs (Valenzuela et al., 2009). In South Asian countries, *S. pneumoniae* was found to be associated with 3.0% (95% CI 4.0–21.7) to 28.4% (95% CI 22.7–79.5) of confirmed bacterial diseases in children in the community and hospital, respectively (Jaiswal et al., 2014b). Notably, these studies show the scarcity of data available from low- and middle-income countries. The estimates presented are based on four and eight studies, respectively, even though long periods were considered for publication years: from 1982 to 2010. In Africa, IPD case fatality ratios in the pre-PCV era ranged between 1.7 and 75% (Tam et al., 2017). In comparison, the case fatality ratio in Europe was 3.5% (Isaacman et al., 2010). Despite limitations, these estimates provided strong evidence of *S. pneumoniae* infections as a leading vaccine-preventable cause of morbidity and mortality worldwide.

Recent estimates of the burden of pneumococcal disease in children after introduction of PCVs in several countries underscore the need for scaling up immunisation with PCVs but also call for attention to careful monitoring of the vaccines' impact. Estimates by Wahl et al. (2018) indicate that in 2015, the burden of severe pneumococcal disease was lower than in 2008. However, it remains high with *S. pneumoniae* associated with 3.7 million (UR: 2.7–4.3 million) episodes of severe disease (including pneumonia, meningitis, and other invasive infections) and 317,300 deaths. This high global burden of *S. pneumoniae* in children disproportionately affects populations in resource-limited settings. For instance, most cases and a half (50%) of the estimated pneumococcal deaths in 2015 occurred in Africa and South-East Asia, where countries introduced PCVs later than in the rest of world and vaccine coverage is very low (Figure 1).

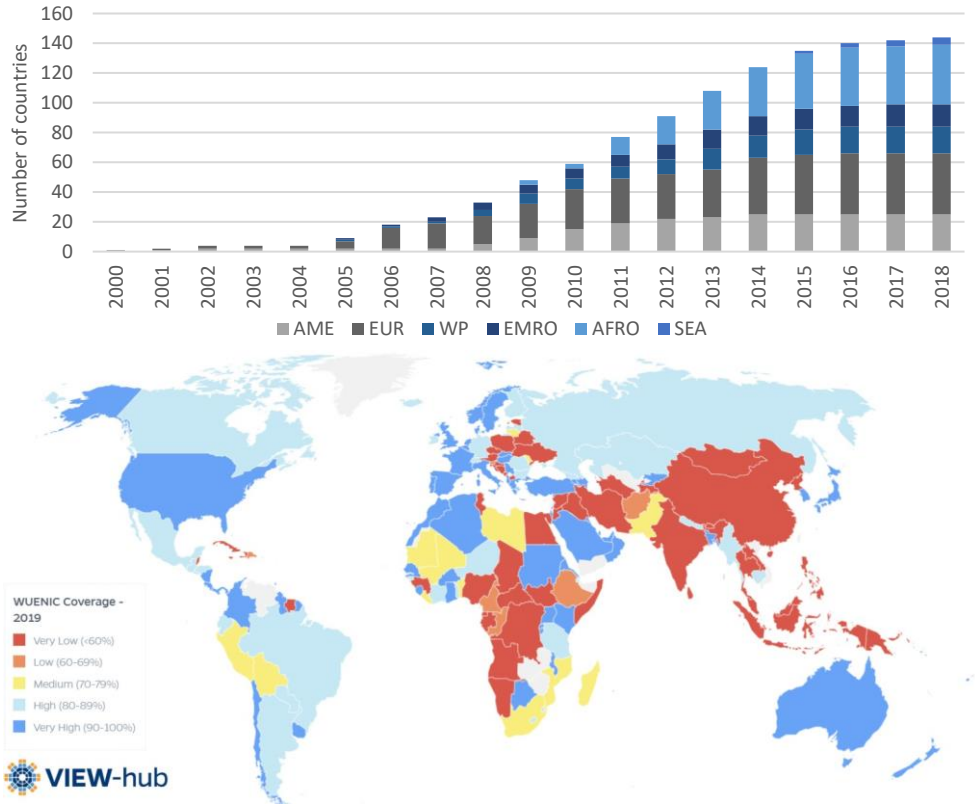


Figure 1 Use of PCVs globally since 2000 globally.
Top: progression of PCVs introduction by world region. Bottom: WHO and UNICEF Estimates of National Immunisation Coverage for PCV in 2019. *Source of data: (IVAC, 2018). AME: Americas, EUR: Europe, WP: Western Pacific, EMRO: Eastern Mediterranean Regional Office, AFRO: Africa, SEA: South East Asia. List of countries in Appendix 1*

The estimates by Wahl et al. (2018) also provide evidence that widespread immunisation with PCVs has dramatically changed the landscape of pneumococcal disease and draw attention to the challenges to improve the evidence base to address its burden. Some of these challenges are particularly linked to the large diversity of *S. pneumoniae* serotypes –the serologically and antigenically distinct varieties of the bacteria. Furthermore, the challenges are related to gaps in the evidence related to serotypes post-highly valent PCVs globally (e.g., serotype coverage and role of serotypes not included in conjugate vaccines). Characterising the role of serotypes across settings is a particularly important area where research is needed.

With over 80 serotypes not included in current formulations of vaccines available to prevent childhood IPD, it is important to monitor the impact on disease associated with both vaccine serotypes (i.e., included in the different formulations of PCVs) and non-vaccine types (i.e., serotypes not targeted by vaccines). This chapter focuses on the relevant microbiology and epidemiological aspects of *S. pneumoniae* to understand the changing epidemiology of global childhood IPD and the gaps regarding serotype epidemiology which this thesis aims to address.

1.1.2 Description of *S. pneumoniae*

S. pneumoniae is a gram-positive bacterium that is both a coloniser of the nasopharynx and a pathogen in humans. The bacterium was first identified in the 19th century as a cause of pneumonia. Because of its role in this disease, *S. pneumoniae* was referred to as "*Diplococcus pneumoniae*" and informally "*Pneumococcus"*. By the mid-70s, the name had been adapted to "*Streptococcus pneumoniae"* (Grabenstein and Klugman, 2012) and its role in causing a range of invasive and non-invasive diseases beyond pneumonia had been recognised (Geno et al., 2015). Humans are the sole reservoir of *S. pneumoniae.* As a normal inhabitant of the upper respiratory tract, the bacteria are well-positioned to cause a range of diseases, as explained in the following section (1.1.3).

1.1.3 Pathogenesis

There are two distinct stages to understand *S. pneumoniae* pathogenesis: carriage and infection, both described in this section.

Carriage

Carriage refers to the stage when *S. pneumoniae* is part of the commensal flora in the upper respiratory tract (e.g., nose, throat) along with many other microorganisms. In this mucosal environment, *S. pneumoniae* is commonly found as a harmless microorganism. It is also here where it can be transmitted to other hosts as small droplets (Bogaert et al., 2004). Carriage of *S. pneumoniae* varies across settings, particularly in terms of prevalence in different populations and serotype distribution. Nevertheless, a consistent finding is that prevalence of carriage declines with increasing age. Reviews of carriage studies indicate that populations with the highest prevalence of pneumococcal carriage are infants and children (with as many as 30% to 60% of children sampled in the nasopharynx testing positive for *S. pneumoniae*), while estimates in adults are lower (between one and ten per cent) (Bogaert et al., 2004, Song et al., 2013). As carriage of *S. pneumoniae* is more prevalent among the young, and carriage is a necessary precursor for infection, the risk of infection is also greatest in this population.

Infection

If immunological protection is evaded or when there is high-density colonisation of the upper respiratory tract, *S. pneumoniae* can spread from the nasopharynx. This spread can result in infection through three main ways: spread locally, causing non-invasive pneumococcal disease, or be aspirated or enter the blood systems causing IPD (Bogaert et al., 2004).

Non-invasive pneumococcal disease

When *S. pneumoniae* bacteria spread locally, they can cause non-invasive diseases, such as otitis media (infection of the middle ear), sinusitis or bronchitis. Non-invasive pneumococcal disease is outside the scope of this thesis. Still, it is worth mentioning that *S. pneumoniae* has been identified as the predominant bacterium in acute otitis media patients, especially children. Of 709 million cases of acute otitis media each year, over half of infections (51%) were in children under five years (Monasta et al., 2012). The frequency of *S. pneumoniae* detection in 38 studies was, on average, 27.8% (range: 9.9%–49.9%) (Ngo et al., 2016). Middle ear infections can lead to hearing

impairments or invasive disease, such as meningitis. When aspirated, *S. pneumoniae* can infect the respiratory system and cause pneumonia, which is considered non-invasive when the bacteria are not identified in the blood (non-bacteremic pneumonia).

Invasive pneumococcal disease

Invasive pneumococcal disease (IPD) occurs when *S. pneumoniae* is aspirated or enters the blood system, infecting normally sterile sites. For instance, in cases of pneumococcal pneumonia where *S. pneumoniae* reaches the blood (i.e., bacteremic pneumonia) or when it infects the pleura or pericardium, which can lead to empyema (accumulation of pus in an anatomical cavity). *S. pneumoniae* may also enter the bloodstream and cause septicaemia, which can result in the infection of different parts of the body. Other IPDs include osteomyelitis (infection of the bone) and septic arthritis (infection of a joint). The clinical features for common pneumococcal diseases vary by site of disease, as summarised in Table 1.

Table 1 Description of invasive pneumococcal disease

Disease	Description of infection	Clinical features
Meningitis	Inflammation of the meninges	Stiff neck, headache, confusion, sensitivity to light
Septicaemia/ Bacteraemia	Infection of the blood	Fever, chills, clammy skin, confusion, rapid heart rate, difficulty breading, severe pain
Pneumonia	Infection of the lungs	Chest pain, difficulty breathing/shortness of breath, cough, fever, chills

Risk factors

Although individuals of all ages can carry or be infected by *S. pneumoniae*, some population groups are at greater risk of disease. Here, I focus on risk factors for IPD since this is the main topic of the thesis.

Host-related: High-risk groups for IPD include young children (≤5 years), particularly infants and toddlers (≤2 years), and older adults (≥65 years) (Russell et al., 2011). Other people at high risk of IPD include:

1) people who are immunocompromised (e.g., due to chronic renal failure, congenital or acquired immunodeficiency, HIV infection, Hodgkin's disease, leukaemia, lymphoma, nephrotic syndrome),

2) those who are immunocompetent but with underlying medical conditions (e.g., chronic diseases of the heart, liver, or lung, diabetes, cochlear implants),

3) people with functional or anatomic asplenia (e.g. congenital or acquired asplenia, sickle cell disease) are also at high risk of IPD (ACIP, 1997).

Other risk factors: poverty, crowded housing conditions, and malnutrition are also associated with a greater risk of IPD, especially among children in LMIC (von Mollendorf et al., 2015).

Serotypes: Another important risk factor for pneumococcal infection is serotype as these differ in their ability to cause IPD. The next section describes the virulence factors of *S. pneumoniae* and explains the role of serotypes and invasiveness in more detail.

1.1.3.1 Virulence factors and immune response

S. pneumoniae has a thick cell wall that protects the cell membrane and intracellular space. The cell wall also contains surface proteins and capsular polysaccharides, which aid S*. pneumoniae* in its pathogenesis. These three features are shown in bold font in Figure 2 and explained in more detail in this section.

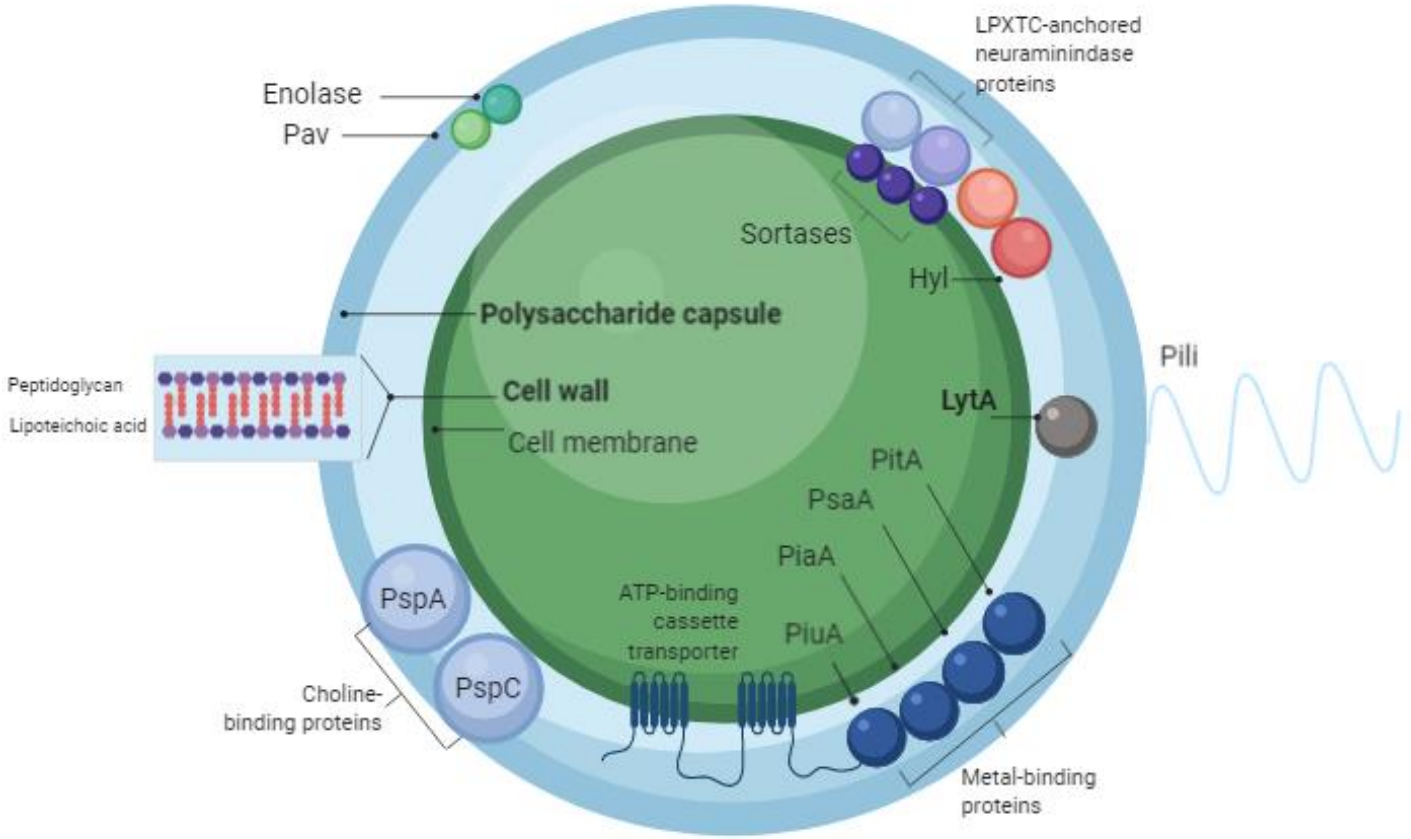
Capsule

The extracellular layer of capsular polysaccharides is particularly important because it enables *S. pneumoniae* to resist phagocytosis and, ultimately, to infect the host (Geno et al., 2015). Briefly, humans' innate immune response against *S. pneumoniae* involves white blood cells producing granules able to break down the cell wall of pathogens and the activation of the complement system. The complement system, which depends on opsonin (a molecule that enhances phagocytosis), requires activation of the classic complement pathway (Henriques-Normark and Tuomanen, 2013). In this pathway, type-specific antibodies (IgA, IgM, and IgG), complement factors, neutrophils, and phagocytosis cells interact to initiate phagocytosis and clear the bacterium (Geno et al., 2015, Brooks and Mias, 2018). This pathway is also essential to activate B cells that can differentiate into memory cells. Capsular polysaccharides can inhibit white blood cells entering the bacterium and the initiation of the complement system. Additionally, as capsular polysaccharides

are negatively charged, *S. pneumoniae* can avoid phagocytic cells by electrostatic repulsion (Brooks and Mias, 2018).

Figure 2 Structure of S. pneumoniae and virulence factors

Partial structure of *S. pneumoniae*, illustrating key virulence factors: **Cell wall** composed of peptidoglycan and lipoteichoic acids, **Polysaccharide capsule**, **Pneumococcal surface proteins** A and C (PspA and PspC), LytA. Pneumococcal iron uptake (PiuA), pneumococcal iron acquisition A (PiaA), pneumococcal surface antigen A (PsaA), pneumococcal iron transport (PitA). Hyaluronate lyase (Hyl): breaks down hyaluronan-containing extracellular matrix components proteins covalently linked to the bacterial cell wall by a carboxy (C)-terminal sortase (with LPXTG motif: Leu-Pro-any amino acid (X)-Thr-Gly). Pneumococcal adherence and virulence factor A (PavA) mediates pneumococcal binding to immobilised fibronectin and enolase (Eno) mediates binding to plasminogen. Adapted from (Kadioglu et al., 2008) using free software Biorender available online (biorender.com)



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Capsular polysaccharides are also important because they vary in their chemical composition, which provides diversity and adaptation properties to *S. pneumoniae.* Capsular polysaccharides determine the serologically and antigenically distinct varieties of the bacteria, known as serotype. As serotypes vary in terms of virulence, so does the ability of *S. pneumoniae* to cause infection or invasive disease, or "invasiveness" (Brueggemann et al., 2004, Geno et al., 2015). Invasiveness of a serotype can be understood as a serotype's ability to reach an otherwise sterile site upon colonisation of the nasopharynx (Barker et al., 1989, Smith et al., 1993). This feature was realised from the observation that although a wide range of serotypes are found in the nasopharynx, only a few were commonly detected in invasive disease. Measures of invasiveness include:

1) **Attack rate of a serotype** is the ratio of serotype specific IPD incidence to the rate of acquisition in carriage (Smith et al., 1993, Sleeman et al., 2006). It is estimated, as described in Equation 1.

Equation 1 Attack rate of serotypes

$$\boldsymbol{Attack\ rate\ of\ serotype}(\boldsymbol{x}) = \frac{\text{Incidence rate of IPD due to serotype (x)}}{\text{Incidence rate of acquisition of serotype (x)in carriage}} =$$

$$Attack\ rate\ of\ serotype\ (x) = \frac{\frac{New\ invasive\ diseases\ cases\ associated\ with\ serotype\ (x)}{Population\ at\ risk}}{\frac{New\ nasopharyngeal\ acquisition\ of\ serotype\ (x)}{Total\ population\ at\ risk}}$$

2) **The case: carrier ratio or "invasive capacity":** defined as the ratio of IPD incidence to carriage prevalence (Yildirim et al., 2010, Flasche et al., 2011) as described in Equation 2:

Equation 2 Case: carrier ratio

$$\boldsymbol{Case}\text{: }\boldsymbol{carrier\ ratio}\text{ for serotype (x)} = \frac{\text{Incidence rate of IPD due to serotype (x)}}{\text{Carriage prevalence serotype (x)}}$$

$$Case\text{: }carrier\ ratio\text{ for serotype (x)} = \frac{\frac{\text{New invasive diseases cases serotype (x)}}{\text{Population at risk}}}{\frac{\text{number of carriage isolates of serotype (x)}}{\text{Total population sampled for carriage}}}$$

3) **The invasive disease potential of serotypes in terms of an odds ratio (OR).** This OR can be estimated as described in Equation 3. It can be interpreted as the odds of a specific serotype (*x*) among people with invasive disease compared to the odds of serotype (x) without invasive disease (i.e., carriage of serotype (*x*)). It can be calculated by reference to a single serotype or to all other serotypes identified in a specific setting.

Equation 3 Invasive disease potential (odds ratio)

$$\mathbf{OR} = \left(\frac{\mathbf{a} \times \mathbf{d}}{\mathbf{b} \times \mathbf{c}}\right)$$

$$=$$

$$\frac{\text{number of invasive serotype X isolates} \times \text{number of non} - \text{x carriage isolates}}{\text{number of carriage serotype X isolates} \times \text{number of non} - \text{x invasive isolates}}$$

The invasive disease potential of serotypes is the most common indicator of invasiveness estimated in the literature. Table 2, adapted from the review by Song et al. (2013), summarises the key characteristics and findings of studies estimating the invasive disease potential of *S. pneumoniae* serogroups/types grouped. A serotype with an OR > 1 as more likely to invade and cause disease after colonisation than the comparator serotype with less invasive disease potential or with no association with IPD. There is evidence to suggest highly invasive serotypes are less likely to be found in the nasopharynx, which may be partially explained by differences in serotypes' carriage duration (Brueggemann et al., 2004). Nevertheless, a serotype that is commonly carried can also be associated with an important proportion of the overall disease, even if its relative invasive disease potential is low. Other serotypes, can be commonly carried but due to its low invasive disease potential, not be commonly associated with IPD.

Table 2 Characteristics and findings of studies estimating the invasive disease potential of S. pneumoniae serogroups/types

Study parameter	Smith et al. (1993)	Brueggemann et al. (2003)	Brueggemann et al. (2004)	Hanage et al. (2005)
Study years	1981-84	1994-01	1975-2002	1995-99
Location	P.N Guinea	UK	Seven settings*	Finland
Study population	"Children"	<59 months	Children	<24 months
Serotypes included in PCV13				
Highly invasive†	5, 14	1, 4, 18C	1, 5, 7	6B, 14, 18C, 19A
Highly invasive§	7	7F, 9V, 19A	4	4, 7F, 9V
Less invasive§	9, 19	3, 6B, 19F	18	3, 9, 19F, 23F
Less invasive†	6, 23	23F	6A, 3, 6B, 19, 9, 23	6A
Non-PCV13 serotypes				
Highly invasive†	2, 12, 45, 46			
Highly invasive§				38
Less invasive§	10, 33, 34	15BC		10, 15, 22
Less invasive†			8, 15, 33, 38	11A, 35F
Study parameter	**Sa-Leao et al. (2011)**	**Shouval et al. (2006)**	**Kronenberg et al. (2006)**	**Rivera-Olivero et al. (2011)**
Study years	2001-03	2000-04	2002-04	2006-08
Location	Portugal	Israel	Swiss	Venezuela
Study population	IPD: Children, adults. Carriage: <6 years	Children	All ages	
Serotypes included in PCV13				
Highly invasive†	1, 3, 4, 5, 7F, 14, 18C	1, 5	1, 4, 5, 7F, 9V, 14	7F, 18
Highly invasive§		9V, 18C, 19A, 19F	19A	3, 14, 19F
Less invasive§		3, 6A, 6B, 14, 23F	6B, 9, 23F	6A, 6B, 19A, 23F
Less invasive†	6A, 6B, 19F, 23F,		3, 19F, 23	
Non-PCV13 serotypes				
Highly invasive†	8, 9N, 9L, 12B, 20	12F	8	
Highly invasive§				
Less invasive§		11A, 15A, 15BC, 21, 35B	22	
Less invasive†	11A, 15BC, 16F, 34, 35F, 37		7, 10, 11, 15	

Notes: P.N Guinea: Papua New Guinea, *7 settings: Alabama, P. N. Guinea, Kenya, Toronto, Iceland, Oxford, Alaska. Serotypes are organised by availability in PCV13 – a pneumococcal conjugate vaccine with the broadest coverage (13 serotypes). IPD: Invasive pneumococcal disease. Highly invasive OR >1 and Less invasive: OR < 1. †Evidence in favour of an association (i.e., 95% CI around the OR does not cross the null value: 1) §No evidence in favour of an association (i.e., 95%CI include the null value: 1). Serotype 14 was used to estimate the invasive disease potential across sites because this was the most frequent disease-causing type at the time (Brueggemann et al., 2004).

Other characteristics

S. pneumoniae serotypes also differ in other properties that can enhance their virulence. For instance, the presence of pili has been shown to be associated with serotypes that express *rlr-A* islets (Barocchi et al., 2006) and are involved in adhesion to mucosal surfaces and the development of inflammatory responses by the host (Brooks and Mias, 2018). Capsular polysaccharides are also able to undergo phase variation, which leads to serotype switching (Brooks and Mias, 2018). The surface of *S. pneumoniae* colonies can vary through recombination events, which allow the bacteria to acquire new genetic material (Henriques-Normark and Tuomanen, 2013, Brooks and Mias, 2018).

Serotype switching is a concerning feature for the control of *S. pneumoniae* infections as this contributes to increasing the number of serotypes or leads to capsule-free non-typable strains, for which prevention, through immunisation for instance, is not available or with unknown properties (e.g. antibiotic resistance) (Mahmud et al., 2017, Gladstone et al., 2019, Lo et al., 2019).

Cell wall

The cell wall is composed of a thick layer of peptidoglycan and teichoic acids. The peptidoglycan in the cell wall provides structural strength and protection against the host's immune response. Glycan chains can undergo modifications to make the cell resistant to lysozyme, which is produced as part of the immune response by the host (Brooks and Mias, 2018). Teoichoic acids in the cell wall can cause an inflammatory response in hosts, and they also serve as anchors for surface proteins (Brooks and Mias, 2018).

Surface proteins

There are four types of pneumococcal surface proteins, as shown in Figure 1:

1) *Choline-binding proteins* (CBP), which include PspA (protective antigen), LytA, B, and C (autolysins), and CbpA (adhesin). CBPs protect and allow attachment of the bacteria to prevent the activation of the host's complement mechanism

2) *Metal-binding lipoproteins*: such as pneumococcal iron uptake (PiuA), pneumococcal iron acquisition A (PiaA), pneumococcal surface antigen A (PsaA), pneumococcal iron transport (PitA), which are involved in substrate transport

3) *Proteins covalently linked to the bacterial cell wall by a carboxy (C)-terminal sortase* (LPXTG, Leu-Pro-any amino acid (X)-Thr-Gly) are involved in the colonisation of the host aided by the enzyme sortases that modify surface proteins

4) *Non-classical surface proteins*, such as pneumococcal adherence and virulence factor A (PavA) and enolase (Eno), which mediate pneumococcal

binding to immobilised fibronectin and plasminogen, respectively (Brooks and Mias, 2018, Kadioglu et al., 2008).

Given the high pathogenic potential of surface proteins, the idea of vaccines using these as targets has also been proposed, but current formulations do not target these. Considering the key role in the pathogenesis of capsular polysaccharides, these serve as good vaccine antigens for pneumococcal vaccines.

This array of surface proteins, structural features, and capsular polysaccharides provide *S. pneumoniae with* the ability to evade humans' immune response and cause a range of diseases (described in 1.1.3). More importantly, these features give *S. pneumoniae* molecular, biochemical, and immunological diversity which underline the need to understand the role of serotypes in pneumococcal disease, specifically IPD, which vaccines are aiming to prevent.

Clinical specimen and laboratory diagnosis

The diseases and syndromes associated with *S. pneumoniae* infections have a similar clinical presentation to infections by other pathogens. Thus, identification of the causative bacterium through laboratory methods is necessary to confirm its association with an episode of disease. However, a definite aetiological diagnosis can be difficult to obtain in some cases of pneumococcal diseases, especially among cases of non-bacteraemic pneumococcal pneumonia (Werno and Murdoch, 2008). Presumed bacterial pneumonia or all-cause pneumonia can be tested for using nasopharyngeal specimens, but this has limited value as it could indicate carriage and not infection. Despite its challenges, evaluation of IPD with serotype-specific data has been the gold standard to guide public health policy (WHO, 2018). Specimens used to identify IPD are from sterile sites, such as blood, cerebrospinal fluid (CSF), sputum, pleural fluid or lung aspirate, joint fluid, bone, other abscesses, or tissue specimens.

1.1.3.2 Species identification

The current gold standard for the identification of *S. pneumoniae* is a bacterial culture followed by other laboratory methods: gram stain, catalase, and optochin tests (Werno and Murdoch, 2008). More recently developed assays include rapid antigen tests (e.g., latex agglutination, LAT) or enzyme immunoassay tests, both of which target capsular polysaccharides to identify the presence of the pathogen. Molecular methods, such as polymerase chain reaction (PCR) have also been developed. Recommendations and use of laboratory tests vary by the specimen, as summarised in Table 3, and explained in detail in this section. Recognising the application and differences in the laboratory methods is important to consider when examining the burden of disease and pooling data, as done in this thesis because it can influence the ability to compare data from different settings.

Table 3 Laboratory assays and specimen types for S. pneumoniae IPD by clinical syndrome

Test	Specimen type	Pros	Cons
Bacterial culture	Blood, CSF, specimens from other sterile sites	The gold standard, recommended by WHO (WHO, 2018). It provides a definite diagnosis Can be conducted in all specimen types	Expertise needed; time- and labour-intensive; mainly available in reference laboratories. High cost Difficult to obtain high-quality lower respiratory tract samples In suspected meningitis cases, bacteria may not grow in patients that have received antibiotics before sample collection
Antigen detection assays: Latex agglutination test (LAT) (detects capsular polysaccharide antigens)	CSF	Easy to use, especially in resource-limited settings as it results in visible agglutination when specimen with pathogen's antigens is mixed with reagents containing latex particles. Inexpensive	Low specificity, false positives common (urine samples), commercially available reagents do not differentiate all known pneumococcal serotypes
Antigen detection assay: rapid immunochromatographic test (detects the C polysaccharide cell wall antigen)	CSF, urine samples	May be useful to identify the presence of *S. pneumoniae* for clinical purposes and from non-invasive specimens, especially in settings with limited laboratory facilities	Not routinely used due to low sensitivity and specificity These tests need to be used in combination with others test to obtain a definite diagnosis
Polymerase chain reaction (PCR)	CSF	Recommended by WHO for a definite diagnosis in CSF samples as it is more sensitive than other specimens, the result can be obtained fast	High financial cost Depending on the target gene, it could lead to misidentification with other bacteria with similar genes
Notes: CSF: cerebrospinal fluid, WHO: World Health Organization.			

In individual settings, different factors will determine the choice of methods for laboratory testing. These may include on-site microbiological laboratory capacities, clinical presentation, and specimen type, among others. Prior

antibiotic treatment, improper handling or transport of specimens, or use of inappropriate culture media, may fail to isolate *S pneumoniae*. A summary of the tests involved in diagnosis by bacterial culture is provided below, as these remain the most used tests in clinical settings as well as in epidemiological studies.

Bacterial culture: Three tests, performed in parallel, are used to confirm the presence of *S. pneumoniae* in isolates from patients with suspected infection (WHO and CDC, 2011):

1. Gram stain test: The gram stain technique is used to differentiate gram-positive bacteria from gram-negative. If *S. pneumoniae*, or other gram-positive bacteria, are present in an isolate, the tests reagents will react with the peptidoglycans in the thick cell wall (Figure 2), turning purple. The presence of diplococci or gram-positive cocci in short chains is indicative of *S. pneumoniae* (WHO and CDC, 2011).
2. The catalase test: this test is useful to distinguish *Streptococci*, which are catalase-negative from other gram-positive cocci, such as *Staphylococci,* which are catalase-positive. The enzyme catalase is produced by bacteria that respire oxygen resulting in bubbles when exposed to hydrogen peroxide. *S. pneumoniae* is a facultative anaerobic organism, and thus, does not produce any bubbling (WHO and CDC, 2011).
3. The optochin test, followed by a bile solubility test, confirms *S. pneumoniae* in a specimen. *S. pneumoniae* is an alpha-hemolytic bile soluble species, which means the bacteria are sensitive to optochin (a chemical). Thus, when cultures of *S. pneumoniae* are exposed to optochin disks, a zone of inhibition becomes visible. For most other streptococci species, no zone of inhibition is seen, as they are optochin resistant. An additional bile solubility test, in which all cells in a sample of the specimen are lysed when exposed to bile salts (sodium deoxycholate) is necessary to confirm the presence of *S. pneumoniae*.

1.1.3.3 Serotyping

The gold standard method to determine the capsular serotype is the Quellung (or Neufeld) reaction (WHO and CDC, 2011). Alternative methods include latex

agglutination tests and PCR, which are less labour-intensive and less time-consuming than the Quellung reaction. A brief description of each of these procedures is provided below.

Quellung reaction: this method entails exposing the clinical specimen to pneumococcal typing sera (for serogroups or serotypes in specific) until a positive reaction or "swelling" of the capsule is observed. This process requires a high-quality microscope to visualise the swelling of the capsule that results from the antigen-antibody reaction and the use of counterstain (such as methylene blue). Based on this method, over 97 serotypes, which are grouped by immunological relatedness into over 45 serogroups, have been described to-date (Geno et al., 2015) and shown in Table 4.

Table 4 Pneumococcal serogroups and serotypes (based on Danish types)

Group	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Type						6A	7A		9A	10F	11F	12F			15F
						6B	7B		9L	10A	11A	12A			15A
						6C	7C		9N	10B	11B	12B			15B
						6D	7F		9V	10C	11C				15C
						6E					11D				
						6F					11E				
						6G									
						6H									
Group	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**27**	**28**	**29**	**31**	**32**
Type	16F	17F	18F	19F	20A		22F	23F	24F	25F		28F			32F
	16A	17A	18A	19A	20B		22A	23A	24A	25A		28A			32A
			18B	19B				23B	24B						
			18C	19C											
Group	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**41**	**42**	**43**	**44**	**45**	**46**	**47**
Type	33F		35F						41F						47F
	33A		35A						41A						47A
	33B		35B												
	33C		35C												
	33D														
	33E														

Source: (Geno et al., 2015)

Latex agglutination tests: These tests come in the form of kits and use anti-rabbit IgG-coated latex particles to pool serotype-specific antisera for categories of interest for rapid identification (e.g., serotypes included in different formulations of pneumococcal vaccines). This process leads to partial serotyping as it narrows down the type to a group of serotypes included in a pool, but it may result in non-typeable results.

Molecular-based methods: There are conventional multiplex and real-time PCR assays for detecting commonly identified types (~40 serotypes). Multiplex

PCR assays use capsular polysaccharide synthesis genes (CpsA) as targets, while real-time PCR serotyping assays use different target genes: autolysin (lytA), pneumolysin (Ply) and pneumococcal surface adhesion genes (PsaA) (WHO and CDC, 2011). Besides reducing the labour, time, and expertise required to conduct the Quellung reaction, PCR-based methods are useful for serotyping culture-negative samples.

Multiple serotype identification

The presence of multiple serotypes can occur in carriage and, more rarely, in IPD. A wide range of prevalence of multiple-serotype carriage has been reported. In the Gambia, 19% prevalence of co-colonisation or multiple carriage was identified among children in the period before PCVs were introduced. In Nepal, a similar proportion (20%) of children six to 24 months were identified as carrying more than one serotype (Kandasamy et al., 2015). An assessment of IPD isolates from surveillance during 2000–14 in South Africa identified 0.1% were co-infected with more than one serotype (whereas in the same specimen or different serotypes in different specimens from the same episode). In this setting, dual serotype IPD was associated with children under five years (adjusted odds ratio (aOR) 4.7 95% CI 1.8–11.7%, comorbidity other than HIV (aOR 2.8 95% 1.1–6.6) and death (aOR 3.5 95% CI 1.98 to 6.09%). In Sweden, five patients out of 16,992 IPD cases (0.03%) during 2006–15 were suspected of double infections (Naucler et al., 2017). As mentioned in the previous section, gene exchange between serotypes can occur, and interactions of multiple serotypes could facilitate or inhibit infections.

The diversity in serotypes and other multiple pneumococcal carriage underscores the complexity of pneumococcal biology and dynamics. These are particularly important features of *S. pneumoniae* to consider in the post-PCV era as vaccines target and decrease the role of dominant serotypes.

1.1.4 Treatment

Severe or invasive *S. pneumoniae* infections are treated with antibiotics. Penicillin has been widely used to treat *S. pneumoniae* infections since its

discovery in 1928. This drug selectively prevents the synthesis of peptidoglycan in the bacterial cell wall (Figure 1) and does not cause harm to other cells in the human body. Presently, IPDs, including sepsis and meningitis, are treated with beta-lactam antibiotics, which includes penicillin derivatives, cephalosporin and monobactams (Cherazard et al., 2017). However, due to resistance to these antibiotics, others may also be used (more information about drug resistance in this section). Decisions on the choice of treatment, length, and dosage for *S. pneumoniae* infections require consideration of the type of disease, presence of comorbidities, and available information on antimicrobial resistance (especially in terms of the minimum inhibitory concentration, MIC, the lowest concentration which prevents visible growth in culture) in a particular setting. An example of the treatment *S. pneumoniae* pneumonia is provided in Table 5 (Bradley et al., 2011, Mandell et al., 2007).

Table 5 Recommended treatment for the management of community-acquired pneumonia associated with S. pneumoniae

Setting/Population characteristics		
Children	If MICs for penicillin ≤ 2.0 µg/mL:	If MICs ≥ 4.0 µg/mL:
Preferred	*Parenteral therapy:* ampicillin or penicillin *Oral therapy*: Amoxicillin	*Parenteral therapy*: Ceftriaxone *Oral therapy*: Levofloxacin, linezolid
Alternative	*Parenteral therapy*: Ceftriaxone, Cefotaxime, or Clindamycin or Vancomycin *Oral therapy*: Second or third-generation cephalosporin (cefpodoxime, cefuroxime, cefprozil), oral levofloxacin, linezolid.	*Parenteral therapy*: Ampicillin, levofloxacin, linezolid, clindamycin, vancomycin *Oral therapy*: Clindamycin
Adults	Previously healthy and low levels of drug resistance	Presence of co-morbidities or use of antibiotics in the past three months or regions with >25% of infections with high-resistance level (MIC, ≥ 16 µg/mL)
Preferred	*Outpatient:* Macrolide (azithromycin, clarithromycin, or erythromycin)	*Outpatient:* Respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin), beta-lactam plus a macrolide (e.g., high-dose amoxicillin, amoxicillin-clavulanate or ceftriaxone, cefpodoxime, cefuroxime, doxycycline)
Alternative	*Outpatient*: Doxycycline	Beta-lactam plus doxycycline (e.g., high-dose amoxicillin, amoxicillin-clavulanate or ceftriaxone, cefpodoxime, cefuroxime)
Notes: Sources: (Bradley et al., 2011, Mandell et al., 2007) Abbreviations - MIC: Minimum inhibitory concentrations		

1.1.4.1 Antibiotic resistance

To-date, *S. pneumoniae* has accumulated resistance to both common and less commonly used antimicrobials to treat infections. It is noteworthy that the rates of drug-resistant *S. pneumoniae* infections have decreased in some countries.

This decline has been associated with the use of PCVs, explained in more detail in the next section, PCVs target serotypes with high levels of resistance (Sader et al., 2019, CDC, 2019, Latasa Zamalloa et al., 2018). However, not all highly resistant serotypes are included in these vaccines (Sheppard et al., 2016).

There are different mechanisms through which *S. pneumoniae* develops resistance to antibiotics. Resistance to penicillin, first noted in the late 1960s (Cherazard et al., 2017) is associated with modified structures of key proteins in the bacterial cell wall (Kadioglu et al., 2008). These modified penicillin-binding proteins peptidoglycan allow protein synthesis even when the bacteria are exposed to penicillin. For other antimicrobials, resistance can result from genetic alterations, for instance through alterations of ribosomal targets leading to resistance to lincosamides (which includes lincomycin, clindamycin, pirlimycin). Resistance to other antibiotics, such as fluoroquinolones, is driven by the acquisition of plasmid-encoded genes (Klugman, 2002, Cherazard et al., 2017).

Antimicrobial surveillance has shown geographical variations of *S. pneumoniae* resistance, and this is crucial to understanding of the impact of pneumococcal vaccines globally. A clear example is Europe where on average, 9.3% of isolates from people of all ages in 27 countries were non-susceptible to penicillin in 2017 (oral breakpoints ≥ 0.12 µg/mL). However, in the four countries, the percentage was between 25–50% (ECDC, 2018). Furthermore, isolates non-susceptible to macrolide were more frequently identified than isolates non-susceptible to penicillin in Europe. Based on a global antimicrobial surveillance programme, penicillin non-susceptibility of *S. pneumoniae* infections was 34% (range: 29–45%) among isolates of all ages from the Americas, Europe and Asia Pacific (oral breakpoints ≥ 0.12 µg/mL) (Sader et al., 2019). Due to data quality limitations, available regional estimates do not include data from high-pneumococcal burden countries such as India, China, or countries in Africa (Sader et al., 2019). The lack of data in these regions is concerning, as the burden posed by drug-resistant *S. pneumoniae* remains largely unknown. In comparison, in the US, where

antimicrobial resistance surveillance is available, 900,000 of *S. pneumoniae* infections and 3,600 deaths were associated with drug-resistant *S. pneumoniae* in 2014 (CDC, 2019).

1.1.5 Prevention

Two different types of pneumococcal vaccines have been developed to prevent pneumococcal disease: polysaccharide and conjugate vaccines. Both vaccines use capsular serotypes as antigens to promote an immune response (Grabenstein and Klugman, 2012). Besides having different serotype formulations (Table 6), there are important differences between these vaccines and their potential impact on global childhood IPD.

Table 6 Summary of vaccines available to prevent pneumococcal disease

Vaccine	Commercial name	Year licensed	Serotypes included
PPSV23	Pneumovax 23	1983	1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F
PCV7	Prevenar®	2000	4, 6B, 9V, 14, 18C, 19F, 23F
PCV10	Synflorix	2008-09	PCV7, plus 1, 3, 7F
PCV13	Prevenar®	2009	PCV10, plus 19A, 6A, 3
Notes: PPSV: Pneumococcal polysaccharide vaccines and PCV: Pneumococcal conjugate vaccine			

1.1.5.1 Polysaccharide vaccines

Pneumococcal polysaccharide vaccines (PPSV) were first licensed in the USA in 1977 (ACIP, 1997). This first version of the vaccine initially covered 14 different serotypes. These serotypes were selected because combined; they targeted 70–80% of IPD in the USA (Grabenstein and Klugman, 2012). The coverage of PPSV was subsequently expanded to 23 capsular types (PPSV23) to offer better coverage against serotypes that commonly cause disease as it was recognised that serotype prevalence differs over time, by age group and by geographic area (Grabenstein and Klugman, 2012). Despite an expanded serotype coverage, PPSV23 is of limited use to prevent the burden of pneumococcal disease as it is poorly immunogenic in children under two years, the population with the highest burden of IPD (ACIP, 1997). Other limitations of PPSV23 in children are that it does not provide protection against other pneumococcal diseases, such as otitis media and it does not have an impact on S*. pneumoniae* carriage (ACIP, 1997). Currently, PPSV23 is recommended in some countries among people ≥65 years and children over

two years of age at high risk of IPD due to co-morbidities (comorbidities described in section 1.1.2).

1.1.5.2 Pneumococcal conjugate vaccines

Pneumococcal conjugate vaccines (PCVs) differ from polysaccharide vaccines in that the former have purified capsular polysaccharides for specific serotypes linked to a carrier (conjugate) protein. As discussed in section 1.1.3.1, capsular polysaccharides serve as good vaccine antigens for pneumococcal vaccines. The first formulation developed was the heptavalent conjugate vaccine Prevenar® (PCV7), which has now been replaced by second-generation PCVs. It offered protection against seven serotypes (Table 6), linked to a nontoxic variant of diphtheria toxin, cross-reactive material (CRM) 197 (ACIP, 2000). In the same way as PPSV23, the selection was based on serotypes predominant in IPD among children in the USA (Grabenstein and Klugman, 2012).

Highly valent PCVs including 10 (PCV10) and 13 (PCV13) serotypes (Table 6) were subsequently developed; offering better coverage for serotypes that commonly cause pneumococcal disease in low- and middle-income countries (LMIC). The two formulations currently available are Synflorix ® (PCV10) and Prevenar13® (PCV13) (WHO, 2019b). PCV13 is conjugated to the same protein as PCV7, while PCV10 is conjugated to NTHi-derived protein D as a carrier protein (WHO, 2019b). Other PCV formulations with, for instance, nine and 11 serotypes were trialled in the Gambia, South Africa, and in the Philippines, but these were not licensed (Saaka et al., 2008, WHO, 2019b).

PCV implementation

Since 2007, the WHO has recommended the inclusion of PCVs in childhood national immunisation programmes for the prevention of IPD associated with serotypes included in the vaccines (see Table 6) (WHO, 2012). The introduction of highly valent PCVs in LMIC, which mainly began in 2008 (Figure 1), was supported by the 2009 pneumococcal Market Commitment, established by GAVI, the Global Vaccine Alliance. Global PCV use has rapidly increased, but PCV coverage remains dissimilar, and some countries remain

without nationwide PCV. By 2017, PCVs had been introduced in 142 countries (IVAC, 2018). However, the implementation of programmes varies, particularly in terms of vaccine formulation, introduction and maintenance of PCV programmes, and coverage with a third dose was estimated at 47% globally for 2018 (WHO, 2019a).

PCV programmes

In terms of vaccination schedules, WHO recommendations include two potential schedules for vaccination of children (WHO, 2012). For this thesis, in which data from different countries are pooled, it is important to consider the differences in schedules. There is a schedule consisting of three primary doses (at intervals of at least four weeks, with the first dose as early as six weeks of age) (3p+0). Alternatively, two primary doses can be administered (two months apart, starting at two months or six weeks for PCV13 and PCV10, respectively) plus a booster (at least six months after the second dose) (2p+1b) for either of the PCV formulations. Most countries globally are implementing PCV13 (n=90) and at least five dosing schedules have been reported (3p+0b = 44 countries; 2p+1b = 34; 3p+1b = 11; 2p+1b and 3p+1b = 1) (IVAC, 2018). Besides programmatic considerations to align PCV schedules with other childhood vaccinations in each country, WHO recommended these two different schedules because conjugate vaccines using a booster dose may prevent disease due to serotypes that are common among older children (Whitney et al., 2014).

Uptake and maintenance of PCV programmes also vary greatly among countries. High-income countries that implemented PCV7 did so for a limited number of years, ranging from one to ten. Complete immunisation uptake of PCV (defined as three doses of PCV) and target populations have also varied across and within countries. In 2017, the uptake of highly valent PCVs in individual countries ranged between 13% and 99% (IVAC, 2018). Only three countries had achieved very high coverage (90–100%, the USA and Australia) or high (80–89%, Norway) (IVAC, 2018). In the US, PCV13 was approved and recommended to be used routinely in series with PPSV23 for individuals of 65 years of age or more in 2014. This recommendation was removed in 2019 after

an evaluation showed minimal impact on disease caused by serotypes included in PCV13 in the elderly population (ACIP, 2019).

In some countries PCVs have not been introduced to the national immunisation programme or the mode of implementation has been heterogenous sub nationally. In Spain, for instance, PCVs were only included in the childhood immunisation programme by one regional government, while in others the vaccines were available in the private sector (Hernandez-Bou et al., 2018). In Sweden, each of the 21 counties decided what PCV to use, which resulted in some utilising PCV10 and others PCV13 (Naucler et al., 2017). In low-income countries, despite support to achieve introduction and early high coverage, several states with a high burden of pneumococcal disease have not yet introduced PCVs or those that have introduced it experienced declines in coverage as early as year two post-introduction (Olayinka et al., 2017). It is important to take into account differences in PCV programmes across settings, as this heterogeneity could be a source of variations in global estimates and have an impact on the serotype distribution.

Serotype epidemiology

The research questions in this thesis pertain to serotype epidemiology. The epidemiological characterisation of serotypes has been crucial to address the burden of *S. pneumoniae*. To be able to prevent pneumococcal disease further, it is indispensable to consider the role of serotypes after PCVs introduction. Based on evidence from pre- and early years after PCVs were introduced, there are two expectations from PCVs on childhood IPD:

1) vaccine serotypes will eventually be eliminated, and

2) the pathogenicity of non-vaccine serotypes will remain unchanged after vaccination.

Nevertheless, concerns remain. A key consideration to achieve these expectations is that the overall benefit from vaccination relies on whether the invasive disease potential of serotypes not included in PCVs is sufficient to lead to serotype replacement in IPD. This section provides a summary of the

evidence available in issues associated with serotypes. It highlights the gaps in each of these areas.

The proportional contribution of serotypes to IPD

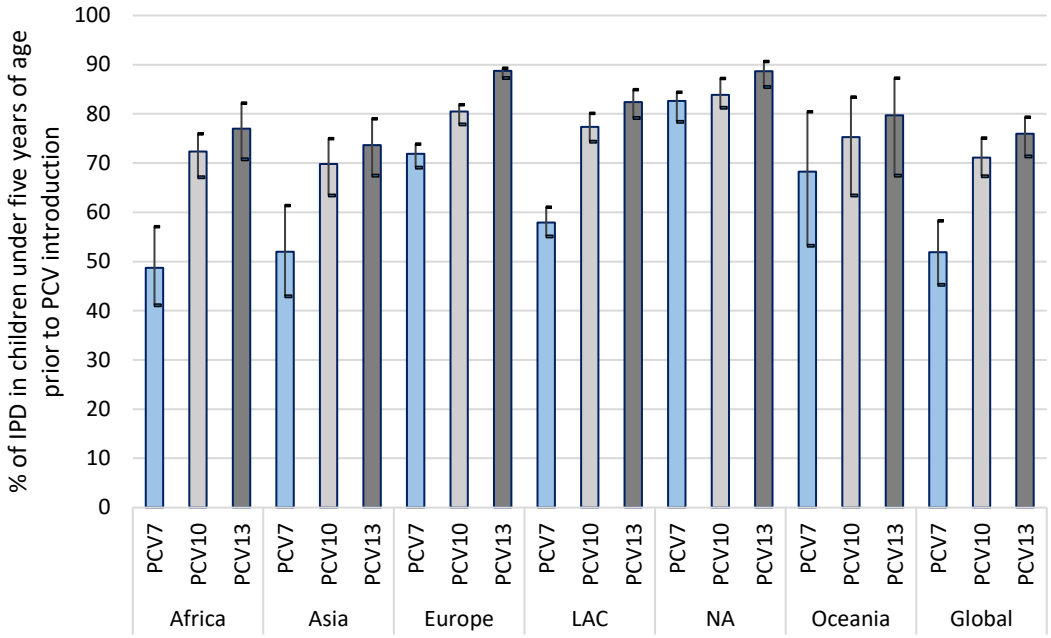
First, determining the serotype distribution in IPD is necessary to understand the potential coverage of available PCVs and the proportional contribution of non-vaccine types to severe pneumococcal disease. Two large meta-analyses have informed the contribution of individual serotypes to childhood IPD in specific settings and globally.

The study by Hausdorff et al. (2000) was the first meta-analysis to quantify the potential regional coverage by PCV7 using data from datasets representative of all world regions (n=70 studies). PCV7 contained the seven most common serogroups in North America and Oceania (accounting for 80–90% of IPD). However, its coverage was lower in other settings: six most common serotypes in Europe (coverage: 75% of IPD), five in Latin America (65%), and four in Asia (45%) and Africa (70%). These estimates were crucial to inform the development of highly valent PCVs (PCV10 and PCV13). However, these were highly susceptible to misclassification as data available at this time were based on serogroups (instead of sero*type* data). Furthermore, few studies from resource-limited settings were available.

Updated estimates of serotype distribution in childhood IPD were developed by Johnson et al. (2010) and published at the same time highly valent PCVs were licensed. These estimates of the proportional contribution of each serotype, including data from studies conducted up to 2007, allowed a more accurate calculation of potential coverage of vaccine formulations based on sero*types* and specifically in children under five years. This study confirmed the high potential for the public health impact of PCV7 as well as its limitations on a global scale. Figure 3 shows the proportion of IPD in children under five years of age due to serotypes in existing PCV formulations as estimated before the widespread use of the vaccines in different world regions (adapted from (Johnson et al., 2010)). Targeted serotypes in existing formulations were associated with 82−88% of IPD in North America, 72−88% in Europe, 68−79%

in Oceania, 58−82% in Latin America, 49−77% in Africa, and 52−74% in Asia. The study also confirmed that, from a public health perspective, between six and 11 types were required in vaccines to cover 70% of IPD in children in different world regions. The region where more diversity in serotypes was needed in Asia to reach this percentage. These regional differences are key to inform vaccine development and public health policy.

Figure 3 Proportion of IPD in children under five of age due to serotypes in existing formulations before the global introduction of PCVs



Adapted from (Johnson et al., 2010). LAC – Latin America and the Caribbean, NA: North America.

In this study, a key finding highlighted by the authors is that most common serotypes causing IPD vary greatly across world regions. Since these were the most prevalent at the time, there was little information about the proportional contribution of serotypes not included in PCVs. Among these, serotypes 2, 12F, 45, 15B were among the most common globally, but their proportional contribution was estimated to be less than 5%. As the role of vaccine-types in disease in a particular setting is expected to decrease after PCVs are introduced, it is important to estimate the proportional contribution of serotypes for which specific estimates of the associated burden of IPD in children are not

available. Such information is required to monitor the effects of current vaccines and to evaluate the need for novel immunisation options.

Serotype replacement

The second key issue related to serotype epidemiology that is pertinent to this thesis is the concept of serotype replacement. Serotype replacement occurs when there is an increase in the incidence of *S. pneumoniae* disease or carriage due to serotypes not targeted by vaccines (Weinberger et al., 2011). Complete serotype replacement in carriage has been consistently noted among vaccinated children and non-vaccinated populations (i.e., older children and adults). However, such consistency in replacement has not been seen for IPD.

PCVs offer both protection against colonisation in vaccinated individuals and of susceptible contacts (Davis et al., 2013, Weinberger et al., 2011). Among vaccinated children, replacement in carriage of vaccine serotypes with non-vaccine serotypes has resulted in a negligible or no change on overall carriage prevalence as serotypes targeted by the vaccine decrease, the offset in carriage has also been accompanied by changes in the serotype distribution among carriers. This replacement in carriage has been observed in both HIC: such as the UK (Southern et al., 2018), Greenland (Navne et al., 2017), Sweden (Galanis et al., 2016), Norway (Steens et al., 2013) and resource-limited settings such as Palestine (Seir et al., 2018)).

Conversely, serotype replacement in IPD was noted in high-income countries upon the introduction of PCV7, but it has not been consistently reported after PCV10 or PCV13. After widespread immunisation with PCV7, a meta-analysis demonstrated that there was an overall decrease in childhood IPD in industrialised settings from year one up to the seventh year (rate ratio (RR): 0.03, 95% confidence interval [CI] 0.01−0.10) (Feikin et al., 2013). Nevertheless, disease due to non-PCV7 serotypes increased over the same period (RR 2.81 95% CI 2.12−3.71). Serotype replacement was associated with an increased incidence of the six additional serotypes included in PCV13, specifically 19A. For instance, in the USA, the absolute rate increases of 19A-

IPD ranged from 0.4 to 8.5 cases per 100,000 population from pre-PCV implementation to the seventh year of use (Beall et al., 2011). This rise was associated with an increase of 19A with the rapidly emerging antimicrobial-resistant clonal complex (CC) 320 possibly due to capsular switching, clonal expansion, or antibiotic pressure (Moore and Whitney, 2008, Beall et al., 2011). Post-highly valent PCVs, the evidence of serotype replacement in IPD has been inconsistent. For instance, there have been reports of both no signs of serotype replacement after PCV13 implementation in the USA which contrast with reports of achieving the “maximum” protective effect after incidence rates of young children IPD started to increase after several years in decline (Pilishvili et al., 2017, Waight et al., 2015, Miller et al., 2011, Ladhani et al., 2018).

From a global health perspective, it is important to understand the impact of both highly valent PCVs (PCV10 and PCV13) in reducing the incidence of IPD in children under five years, with estimates for specific serotypes. Moreover, it is necessary to investigate to what extent reductions (or increases) have varied in different settings to assess the long-term effectiveness of available PCVs.

Invasive disease potential

The third key element to consider when describing the serotype epidemiology is the concept of invasive disease potential. Since nasopharyngeal colonisation is a key prerequisite for pneumococcal disease, the extent of serotype replacement in IPD is likely to be influenced by colonisation with non-vaccine types with low or high invasive disease potential (Weinberger et al., 2011). Regardless of the metric used, studies quantifying the invasive disease potential before PCV introduction (Brueggemann et al., 2003, Brueggemann et al., 2004), found three important features of *S. pneumoniae* serotypes:

1. Serotypes differ in their ability to cause IPD
2. Evidence indicates that the capsule type was more important than genotype in determining the ability to cause invasive disease
3. There was little evidence of any temporal change or major geographical differences in serotype-specific invasive disease potential.

The decreases in IPD and sustained prevalence of carriage after the introduction of PCVs in individual settings would suggest that non-vaccine types have a relatively low invasive disease potential. While individual studies have estimated the invasive disease potential of circulating serotypes, no comprehensive estimates have been developed. A pooled analysis could be helpful to understand better the role of individual non-vaccine serotypes globally, which may not be represented in a particular site.

1.2 Rationale for this research

Differences in PCV programmes coupled with differences in baseline pneumococcal disease burden, host population characteristics, and dominant serotypes in each country require an assessment of the serotypes causing IPD in young children after PCVs have been introduced to inform vaccine policies and development. Given the large diversity of pneumococcal serotypes and differences in their prevalence geographically, it is important to generate this information, in a comprehensive manner and from evidence from diverse settings to inform global health interventions.

1.3 Aim and objectives

This thesis aims to characterise the role of *S. pneumoniae* serotypes in childhood IPD in settings where PCVs have been implemented, with a focus on serotypes not included in current formulations, in order to inform research and future prevention strategies.

As such, the research in this thesis focuses primarily on children under five years of age, who are at high risk of IPD and its associated mortality or sequelae from pneumococcal infections. This study aims to fill important gaps in global childhood health to make progress in the control of severe diseases caused by *S. pneumoniae* and support efforts to address the burden of vaccine-preventable diseases.

1.3.1 Specific objectives

Epidemiology of serotypes causing IPD in young children after the introduction of PCVs (Chapter 3)

Objective: To assess and describe the shifting epidemiology and global distribution of serotypes causing IPD in young children after the introduction of PCVs to examine the contribution of individual serotypes.

Using data identified through a systematic review supplemented by data identified through a targeted internet-based search of grey literature and meta-analyses, I aim to provide estimates of vaccine impact as well as to provide an updated picture of the serotype distribution in childhood IPD cases globally.

Relative invasive disease potential of serotypes causing IPD in young children after the introduction of PCVs (Chapter 4)

Objective: To estimate the invasive disease potential of serotypes in children under five years of age by combining data from different settings with routine immunisation with pneumococcal conjugate vaccines.

Using similar methods to those that were used before the introduction of PCVs (Brueggemann et al., 2004), which include systematic review, collection of unpublished and re-analysed data and meta-analysis, in this chapter I seek to estimate the invasive disease potential of individual serotypes. I will develop these estimates in two different ways. Firstly, in relation to 19A (a hypervirulent serotype after PCV7 was implemented) to understand the spectrum of invasiveness of circulating serotypes. Secondly, I estimate the relative invasive disease potential of individual non-PCV13 serotypes compared to other non-PCV13 serotypes in each setting to gain insights into their replacement potential in the context of vaccine pressure and a decrease of serotypes included in the PCV formulations used in each setting.

Pneumococcal conjugate vaccination and paediatric IPD in Latin America: an overview of the evidence (Chapter 3)

Objective: to estimate what the effects of highly valent PCVs on the incidence of childhood IPD have been in Latin America with a focus on describing the role of non-PCV13 serotypes in this region.

The introduction of PCV programmes in Latin America and the Caribbean was strongly supported by regional studies that exposed weaknesses in the epidemiological evidence as well as the need to support regional initiatives. In this chapter, I examine and pool data from the regional surveillance system SIREVA-II, which was key to characterise the microbiology of vaccine-preventable diseases, including IPD.

1.4 Significance of this thesis' findings

Understanding the role of both serotypes included and not included in PCV formulations as disease-causing agents among the target population for vaccination is necessary to inform issues that could obstruct efforts for implementation and to minimise the burden of disease.

In this respect, up-to-date estimates of key features of circulating IPD-causing serotypes in children can help develop evidence to inform vaccine policies globally. For this reason, this thesis focuses on changes of incidence by serotype categories, the proportional contribution of individual serotypes to IPD and invasive disease potential, because learning more about these features can assist countries in improving surveillance and monitoring of vaccine impact. At the global level, answering questions on the serotype epidemiology of *S. pneumoniae* are crucial to informing the development of vaccines. It should be noted that the research conducted for this thesis was initially guided by a grant provided to the University of Edinburgh by Sanofi Pasteur to undertake literature reviews of the evidence on serotype epidemiology in the post-PCV era to inform the design of vaccine formulations.

Evidence of *S. pneumoniae* epidemiology can also be of use to donors and global health decision-makers to support the sustainability of PCV programmes and their expansion, including the required surveillance to monitor its impact, particularly in resource-limited settings.

2 Methodology overview

The previous chapter provided an overview of the global burden of childhood IPD and the gaps in the evidence regarding serotype epidemiology after PCV introduction to frame the aims and objectives of this thesis. This chapter provides a summary and rationale for the methods employed in this thesis.

2.1 Concepts and definitions

2.1.1 IPD

The main outcome of interest for the analyses in this thesis is childhood IPD, regardless of clinical presentation. I focused on IPD, though other pneumococcal diseases affect children because PCV immunisation programmes were initially intended to prevent this outcome given it is associated with a higher risk of mortality. In this thesis, IPD was defined as the identification of *S. pneumoniae* from a normally sterile site (e.g., blood, cerebrospinal, pleural effusions, or joint fluid) by any laboratory methods (e.g., PCR, culture).

For subgroup analyses by clinical syndrome, I focused on meningitis, pneumonia, and bacteraemia/septicaemia. I selected these categories because they cover the most frequent invasive pneumococcal infections in children. I did not establish specific criteria to define these syndromes before data collection to allow maximum consideration of data. During data collection, case definitions for each syndrome were assessed and compared. Only those data with comparable case definitions were combined for analyses for individual syndromes.

2.1.2 Carriage

Pneumococcal carriage was defined as the identification of *S. pneumoniae* from nasopharyngeal specimens from healthy children, either by culture or PCR.

2.1.3 Serotypes categories

Considering the global scope and focus on childhood IPD of this thesis, the term “non-vaccine serotypes” is not used to avoid ambiguity since non-vaccine

serotypes may differ by study period or setting, depending on the vaccine formulation used. Furthermore, the term “non-vaccine serotypes” could vary even within one location at different times, as described in section 1.1.5.2. Thus, serotypes were classified by the different conjugate vaccine formulations, as shown in Table 7.

Table 7 Categories of serotypes by vaccine formulation used in this thesis

Category	Serotypes
PCV7	4, 6B, 9V, 14, 18C, 19F, 23F
PCV10	PCV7 + 1, 5, 7F
PCV13	PCV10 + 3, 6A, 19A
PCV10non7	1, 5, 7F
PCV13non10	3, 6A, 19A
Non-PCV10	serotypes not included in PCV10 (even if included in PCV13 or PPSV23)
Non-PCV13	serotypes not included in PCV13 (even if included in PPSV23)
Notes: PCV: pneumococcal conjugate vaccine, Pneumococcal Polysaccharide Vaccine	

2.1.4 PCV implementation years

Study periods in each publication were classified according to the PCV administered during the study period. In each setting, the calendar year of the introduction of the first PCV used in that setting, regardless of month, was considered the year of introduction (year 0) and the following years were considered years to be “after PCV introduction”. This classification means that in countries that transitioned from PCV7 to PCV10 or PCV13, any year after PCV7 introduction was considered post PCV introduction. A post-PCV7 year was defined as a 12-month period in which PCV7 was implemented in the study setting before the introduction of a post-highly valent PCV (i.e., PCV10 or PCV13). A post-highly valent PCV year was defined as a 12-month period in which PCV10 and/or PCV13 was implemented.

“PCV eras” and categories for analysis were established for different Chapters to address issues of small sample sizes. Estimates of the impact of PCVs on the incidence and serotype distribution (Chapter 3) were analysed for post-PCV7 and post-highly valent PCVs separately. However, to estimate the invasive disease potential (Chapter 4), I included all available IPD data from eligible years after the initial eligible year. This was done for two main reasons: 1) it was expected that the annual number of IPD isolates available for eligible post-PCV years would be low in some settings and 2) that carriage data would

mostly be available for short periods and from cross-sectional studies and not for every year in the post-PCV period. Thus, the decision to consolidate data in this way was taken after considering data availability.

2.1.5 Invasive disease potential

Invasive disease potential was defined as the odds of invasive disease due to individual serogroup or serotype divided by the odds of carriage for the same serogroup or serotype (Brueggemann et al., 2004). Although other indicators of invasive disease capacity exist (as explained in Chapter 1.2), an OR-based approach was chosen as it does not require an estimate of the catchment population, which was expected to not be available across sites.

Invasive disease potential of individual serotypes was estimated using two different comparator groups: 1) by reference to all other circulating serotypes and 2) by reference to a single serotype. The former is particularly useful to assess the invasive disease potential in individual settings, while the latter was the methods used to pool data from different settings. For the main analysis in this thesis, the invasive disease potential of all serotypes was estimated using a common reference serotype as described in Equation 4:

Equation 4 Invasive disease potential (fixed reference serotype)

$$\mathbf{OR} = \left(\frac{\mathbf{a} \times \mathbf{d}}{\mathbf{b} \times \mathbf{c}}\right)$$

$$=$$

$$\frac{\text{number of invasive serotype X isolates} \times \text{number of carriage reference isolates}}{\text{number of carriage serotype X isolates} \times \text{number of invasive reference isolates}}$$

A modified version of this formula (Equation 5) was used to estimate the invasive disease potential of non-PCV13 serotypes compared to other non-PCV13 in each setting.

Equation 5 Invasive disease potential (other serotypes)

$$\boldsymbol{OR} = \left(\frac{\boldsymbol{a} \times \boldsymbol{d}}{\boldsymbol{b} \times \boldsymbol{c}}\right)$$

=

$$\frac{\text{number of invasive serotype X isolates} \times \text{number of other isolates in carriage}}{\text{number of carriage serotype X isolates} \times \text{number of other isolates in IPD}}$$

2.1.6 Vaccine impact

Vaccine effects can be measured using different study designs depending on the type of effect of interest. In this thesis, I focused on estimating what Hanquet et al., 2013 refer to as “impact of a vaccination programme” (Hanquet et al., 2013). This type of vaccine impact can be assessed by comparing individuals in a population exposed to a programme (vaccinated and unvaccinated persons) to a reference population (i.e., individuals without the said programme). Three main methods can be used to examine the impact of a vaccination programme: comparison of pre- and post-vaccination at the population level, cluster randomised vaccination trials, and modelling studies. In this thesis, considering that most data on IPD are from observational studies, I aimed to identify before-and-after studies to assess the overall impact of PCVs among young children.

2.1.7 Vaccine failure

Vaccine failure refers to IPD cases of serotypes included in the PCV used in each setting after the primary course of immunisation and/or after completing the full immunisation course, including the booster (Oligbu et al., 2016b).

2.2 Data acquisition and data sources

2.2.1 Systematic reviews

Systematic reviews were first developed to synthesise evidence that could establish the effectiveness of different treatments on a health outcome from randomised controlled trials. As a method, reviews have evolved and been widely applied to synthesise incidence and prevalence data from observational studies (Munn et al., 2015). Systematic reviews have been the methodology of choice to examine the global epidemiology of childhood IPD pre- and post-PCV introduction (Johnson et al., 2010, Wahl et al., 2018, O'Brien et al., 2009, Brueggemann et al., 2004). Data acquisition through a systematic review methodology supplemented by targeted searches of grey literature was selected as suitable method considering the global scope and the objectives of this thesis.

For the systematic reviews, I developed search strategies that included database-specific MeSH and free search terms. For Chapter 3, I sought to collect incidence and proportion-based data by serotype categories or individual serotypes, causing childhood IPD. Thus, the logic for the search focused on IPD. For Chapter 4, I sought to identify both carriage and IPD data from similar study periods and similar settings to allow the calculation of serotype-specific invasive disease potential. To be as comprehensive as possible in the search for published data, I developed the search strategies for seven electronic medical databases: Medline, Embase, and Global Health (via Ovid); EMRO, SEARO, and WPRO regional databases (Global Health Library), LILACS, and Web of Science. The search strategies were reviewed with the assistance of a medical librarian at the University of Edinburgh.

2.2.2 Grey literature

Data acquisition for the thesis through systematic reviews was supplemented by data from grey literature. Grey literature included: publicly available surveillance data from national laboratories or ministries of health and re-analysed/unpublished data obtained directly from authors or organisations upon request.

Regarding the use of surveillance data, previous reviews on the global burden of disease have pointed towards the need to consider these sources as abundant and useful IPD and serotype data have been found from countries where no or minimal published literature has been identified (Gorham et al., 2012, Agudelo et al., 2018).

As mentioned in Chapter 1.4, the research conducted for this thesis was initially guided by a research grant to undertake literature reviews of the evidence on serotype epidemiology after PCV introduction to inform the design of vaccine formulations. Based on an initial screening of the literature, I was aware that some of the data would not be available in sufficient detail or for the categories required to pool data from different settings. Thus, investigators identified as likely to have the necessary serotype data for IPD and carriage identified were contacted. I invited researchers to collaborate with this multi-

site analysis and in publications resulting from analyses in which their data were included. The results from analyses conducted in Chapter 4, with data from nine different settings, were published in the journal PLoS One. The reference to the paper is available in Appendix 2.

More information and details for each of the reviews (e.g., dates when the searches were conducted, grey literature search approaches, eligibility criteria) are provided in each of the relevant chapters.

2.2.3 SIREVA-II

The analysis in Chapter 5 of this thesis relies primarily on the analysis of data from SIREVA-II annual reports. SIREVA (an acronym for its name in Spanish: *Sistema de Redes de Vigilancia de los Agentes Responsables de Neumonias y Meningitis Bacterianas*) is a regional laboratory surveillance network for bacterial pathogens. It was established in 1993 by the Pan-American Health Organization (PAHO). The main purpose of this regional initiative was to create a multicentre surveillance network that could inform countries about *S. pneumoniae* serotypes causing disease, to strengthen epidemiological and laboratory capacity, and to create a repository of strains to monitor important microbiological and clinical features of IPD (di Fabio et al., 1997). The second phase of this project, SIREVA-II, increased the number of countries in the network and has, since 2000, provided information about *S. pneumoniae* serotypes and antimicrobial resistance in 22 countries (PAHO) (Di Fabio et al., 2001). Data available from this network have previously been used to assess the impact of PCVs on morbidity and mortality associated with pneumococcal diseases in the region. For specific serotypes, the focus has been on 19A (de Oliveira et al., 2016, Bardach et al., 2017, Agudelo et al., 2018), but no study has pooled data for different serotypes.

2.3 Quality assessment

Appraisal of quality of reporting and the risk of bias is an important element of systematic reviews and meta-analyses. The appraisal criteria depend on the type of studies to be included in a review. The epidemiological data sought for this thesis on serotypes in pneumococcal carriage and IPD were most likely to

be reported in observational studies. With this in mind, the Johanna Briggs Institute (JBI) Critical Appraisal Checklist for Studies Reporting Prevalence Data was considered to be an appropriate tool for the critical appraisal and synthesis of reporting characteristics for the systematic reviews conducted for this thesis (Munn et al., 2015).

The JBI checklist contains nine general questions as detailed in Table 8, for which there are four possible answers: Yes, No, Unclear, or Not applicable. The overall appraisal score can be used to inform eligibility of a study in the review or a particular analysis. However, in this thesis, quality appraisal is used to document and summarise the risk of biases across studies. The quality of studies was ranked as high (0–3 no/unclear), medium (4–6 no/unclear), or low (7–9 no/unclear).

Table 8 List of questions in the JBI Critical Appraisal Checklist for studies reporting prevalence data

Question (Q)	Interpretation
Q1. Was the sample frame appropriate to address the target population?	Target populations in this thesis include children under five years of age with IPD, otherwise healthy or colonised with *S. pneumoniae*. A sample frame was considered to be appropriate if all members of the target population were included (i.e., complete national surveillance data was used) or if the study population was representative of the target population for the particular study setting.
Q2. Were study participants sampled appropriately?	Sampling was considered to be appropriate if when conducted (e.g., in carriage studies) the methods sections reported how it was performed. When all cases were included/analysed (e.g., complete surveillance/registry data), sampling was deemed to be appropriate if efforts were made to avoid duplications (e.g., specimens from the same patient within 3-4 weeks).
Q3. Was the sample size adequate?	The sample size was considered adequate when sampling was conducted (e.g., in carriage studies), and the methods sections reported a sample size calculation. If the case studies were based on a review of national/large databases, a sample size calculation was not deemed necessary.
Q4. Were the study subjects and the setting described in detail?	A study sample or population was deemed to be described in detail when information on the sociodemographic and comorbidity characteristics of cases was provided. The setting was considered to be described when details on PCV uptake were provided with enough details to determine comparability across populations
Q5. Was the data analysis conducted with sufficient coverage?	This question aims to assess coverage bias, sufficient coverage was judged based on information provided in each study about the coverage of the sources in the surveillance network or the sampling frame.
Q6. Were valid methods used for the identification of the condition?	The main conditions of interest in this thesis are serotype-specific IPD or carriage data. As this question aims to assess measurement or classification bias, the validity of methods was assessed based on the description of a case definition (for IPD or carriage) and laboratory methods
Q7. Was the condition measured in a standard, reliable way for all participants?	For the conditions (serotype specific IPD or carriage data) to be considered to have been measured in a standard, reliable way, I sought information on whether any (or no) changes may have occurred in the methods for identification of cases, collection of isolates, or serotyping cases during the study period.
Q8. Was there an appropriate statistical analysis?	For statistical analyses to be considered appropriate, studies needed to report numerator and denominator (incidence or proportion) data, and describe how specific variables were measured.
Q9. Was the response rate adequate, and if not, was the low response rate managed appropriately?	Considering the two main outcomes are serotype-specific IPD and serotype-specific carriage, the large number of not found data could come from IPD isolates not serotyped. For the management of data to be considered appropriate, a clear explanation of how missing serotype data were managed was needed

2.4 Data extraction

Incidence and proportion-based data in Chapter 3 were extracted and standardised as follows: Incidence rates were standardised per 100,000 population per year and for three categories of serotypes: any serotype-IPD, PCV10 or PCV13 serotypes, non-PCV10 or non-PCV13 serotypes. These categories were selected for three main reasons. Firstly, these are the categories most likely to be reported in studies. Secondly, these are the minimum necessary categories to assess serotype replacement. Thirdly, to ensure incidence rates were based on sufficiently large numbers, as categories with the fewer number of cases or independent serotypes would be affected by a low frequency of this event at the population level.

For Chapter 4, incidence, carriage, and IPD serotype data were extracted (or requested from collaborators) for three age groups (0–<12, 12–23, and 24–59 months). I analysed the very young infants (0–<12 months) and toddlers, who are known to be at higher risk of IPD and are the target population for PCVs. After an assessment of data availability, analyses were conducted for two age groups: 0–<24 months or 0–59 months.

For Chapter 5, the number of cases by serotype and the total number of isolates serotyped were extracted from SIREVA-II annual reports. To minimise errors in the extraction of data, I converted PDF files into Word and then managed and combined annual data using Excel and R.

Serogroups or serotypes data were extracted as reported from any of the sources. This extraction means that no corrections were made for isolates with missing serotype information (e.g., attributing a serotype to cases with no serotype available by assuming the serotype distribution was the same as among cases with the serotype available for the same year and age group). The tables that summarise the characteristics of studies include documentation as to whether study authors conducted these adjustments or not. Serotypes with documented cross-reactivity were analysed as follows: 6C was not included in summary estimates of PCV13 to be able to assess its role independently. The results for serotype 6C are presented together with

PCV13-specific types acknowledging its cross-reactivity with 6A, which is included in PCV13. For 15BC data for 15B and 15C were analysed as a single serotype because of the reported reversible switching between these two serotypes (van Selm et al., 2003, van Tonder et al., 2016) and because it was not possible to disaggregate the data when reported as a single serotype.

Studies reporting eligible data for a single IPD clinical presentation (e.g., meningitis, bacteraemia/septicaemia) were included in the review. However, if there were multiple studies from the same setting with overlapping study periods, the most representative of childhood IPD in that setting (i.e., larger sample size, or reporting data for any IPD rather than a single syndrome) was included in a meta-analysis.

2.5 Countries classification

For geographical analyses, countries were classified according to WHO regional groupings (Appendix 1). A modification was made for the Americas, considering the differences in the implementation of PCV programmes in this region. Thus, the region was subdivided as North America (the USA and Canada) and Latin America (including the Caribbean).

To determine resource-limited settings based on income levels, I used the World Bank classifications (The World Bank, 2020). Non-high-income countries (HIC) were considered resource-limited settings regardless of their classification as upper-middle-income countries (UMIC), lower-middle-income countries (LMIC), or low-income countries (LIC). Additionally, settings such as Navajo and White Mountain Apache and Alaska Native people in the United States were considered LMIC as these are resource-limited settings.

2.6 Data analysis and reporting

Incidence rate data and trends: For Chapter 3, it was expected that a large proportion of IPD annual incidence rate data would be available from figures, without clear numerator and denominator. Thus, the main analysis planned for annual incidence rate data by serotype categories was a narrative synthesis. Where sufficient data were available, a pooled analysis of annual incidence

rates per serotype categories was conducted. In Chapter 5, a meta-analysis of incidence rates data using surveillance (SIREVA-II) and population size data (UNICEF) was planned.

The proportional contribution of serotypes to childhood IPD: For individual studies, these data are presented for three categories: 1) PCV10 or PCV13 types, according to the main vaccine currently used in the study setting, 2) non-PCV10 or non-PCV13 types and 3) not typed. As proportion-based data were extracted for the overall post-PCV study period reported, a meta-analysis was deemed suitable to develop estimates of the relative contribution of serotypes by geographic area (regions).

2.6.1.1 Meta-analysis

Meta-analysis is a useful method to combine epidemiological data from observational studies from different settings and to develop indicators such as proportions, incidence rates, and odds ratios. In this thesis, three summary measures are estimated using meta-analysis: incidence, proportions (Chapter 3) and odds ratios (Chapter 4).

Meta-analyses were conducted in R (Chapter 3 and 5) and STATA, version 14 (Chapter 4). The relative contribution of individual serotypes to childhood IPD was estimated using the "*metaprop*" (Chapter 3), and "*metainc*" (Chapter 3 and 5) commands. In previous studies, the overall proportion of IPD has been estimated using the "*metan*" command in the software R (Johnson et al., 2010, Balsells et al., 2017). However, there are limitations to "*metan"* when dealing with proportion-based data which "*metaprop*" is designed to avoid (Nyaga et al., 2014). "*Metan*" uses the normal distribution based on the asymptotic variance to estimate confidence intervals for proportions, and it cannot estimate a standard error when the proportion is zero or one. The use of the asymptotic variance can lead to confidence intervals with impossible values (<0 or >1) and the inability to estimate a standard error for values at the limits (0, 1) leads to the exclusion of values that should be included in the overall estimate or the use of continuity correction. Exclusion of these values at the limits can introduce bias to the estimates through an over- or underestimate.

"*Metaprop*" uses the score statistic, the exact binomial method, and incorporates the Freeman-Tukey double arcsine transformation of proportions to perform a meta-analysis and avoid issues that occur with "*metan*" (Nyaga et al., 2014).

Odds ratios as a measure of invasive disease potential were conducted using the command "*metan*" in STATA. I report 95% CIs estimates for meta-analyses (proportions or ORs) and the heterogeneity for each estimate using the I^2. I describe the heterogeneity level as low to moderate and considerable (Higgins et al., 2003); where a value below 50% denotes low to moderate heterogeneity, 50%-75% as moderate to considerable, and above 75% considerable heterogeneity. I use the Bonferroni correction to address issues of multiple comparisons in Chapter 4.

2.6.1.2 Subgroup and sensitivity analyses

Subgroup or sensitivity analyses were conducted to assess the role of different data characteristics that could have an impact on the meta-estimates. Categories considered for subgroup and sensitivity analyses included: country's income level, HIV prevalence, PCV formulation and PCV uptake.

2.7 Ethical approvals

The research conducted in this thesis was performed using secondary data, published in the public domain and, when requested, these would not contain any personally identifiable information. Following the University of Edinburgh ethical approval processes, I completed a Level 1 ethical review in the form of a self-audit checklist. A copy of the Level 1 forms is available in Appendix 3.

2.8 Summary

This chapter summarised the main methods utilised in this thesis and the rationale for their selection. The next chapter presents the first systematic review and meta-analysis. The results provide an overall picture of the shifting epidemiology of IPD in children under five as well as the distribution of serotypes, causing childhood IPD in countries where PCV programmes have been implemented.

3 The epidemiology of *S. pneumoniae* serotypes causing invasive disease in children after the introduction of PCV

3.1 Background

As described in Chapter 1.1.5.2, characterising and estimating the role of serotypes causing IPD was essential for the design and development of pneumococcal vaccines effective in children, PCVs. The importance of monitoring the epidemiology of serotypes was further highlighted after individual countries implementing PCV7 noticed an increase in the incidence of non-PCV7 IPD among infants and toddlers, the target population. While the increase in these industrialised settings was not sufficient to offset the declines in overall IPD across settings (Feikin et al., 2013), the confirmation of and extent of serotype replacement observed was crucial to support the introduction of second-generation PCVs globally. As PCV programmes continue to be introduced and to mature in individual countries, including resource-limited settings, the extent to which morbidity due to IPD associated with serotypes included in current formulations or not has changed remains to be systematically quantified.

3.2 Objective

This chapter reports the results of a systematic review and meta-analysis to examine and quantify the changes in the incidence of IPD in young children and the proportional contribution of serotypes after the introduction of PCVs.

3.3 Research questions

More specifically, the chapter addresses the following research questions:

- What has been the impact of vaccination with highly valent PCVs on the incidence of IPD in young children globally?
- What is the distribution of serotypes causing IPD in young children globally after the introduction of PCVs? An earlier iteration of the research conducted for the second research question was published in

the journal PLoS One, reference available in Appendix 2 (Balsells et al., 2017).

3.4 Methods

3.4.1 Search methods

To identify relevant data, I searched two main sources of publications: six electronic medical databases and websites for national ministries or departments of health. The databases searched were Medline, Embase, and Global Health (Ovid), Global Health Library (WPRO, EMRO, and SEA), Web of Science, and LILACs. These sources were selected to ensure the search was comprehensive and drew from regionally focused publications. Annual national surveillance reports from countries were reviewed if the electronic medical databases retrieved surveillance publications (subnational or quarterly reports). Two searches were conducted: one in January 2016 and an update on 1 April 2019. The search strategy was designed to capture publications using the following logic: *S. pneumoniae* AND (IPD or clinical syndromes) AND pneumococcal conjugate vaccines AND serotypes. Searches were limited to children and with a publication date between January 2000 and 2019. The terms used in the search strategies included MESH terms and free text specific to each database to increase the sensitivity of the search. The terms used in each database are available in Appendix 4.

3.4.2 Eligibility criteria

The eligibility criteria for this review were adapted from previous reviews assessing serotype replacement and serotype distribution in childhood IPD (Feikin et al., 2013, Johnson et al., 2010), and are described in Box 1. Briefly, publications were eligible for inclusion if they were peer-reviewed studies or surveillance reports. To be included in this review, publications should report IPD incidence rates for at least two categories (PCV serotypes, non-PCV serotypes) and/or case counts by serotype in children under five years from a setting where the introduction of a PCV in the study area was well described and above 25%. Any description of a PCV programme was deemed acceptable to allow for the inclusion of studies with a range of PCV

implementation experiences. For the study periods of highly valent PCVs use, uptake data from WHO/UNICEF was available. These estimates were used to enable comparison as these are based on the definition. No language restrictions or publication type were imposed at this stage. Abstracts and titles in languages other than English, Spanish and French were screened with the help of Google Translate. The bibliographies of eligible studies were examined to identify potential studies for inclusion.

Box 1 Eligibility criteria for inclusion of studies

Inclusion
• Observational studies or annual national surveillance reports from selected departments/ministries of health from settings with PCV uptake of at least 25% during the study period described • Study reports data for invasive disease (defined as isolates from normally sterile sites) in children younger than five years of age • The study population was representative of the general population, not a selected group with specific co-morbidities • Surveillance conducted for at least 12 continuous months • For publications reporting incidence rate data: - Incidence rate data before and after PCV introduction in the study/surveillance setting *and* - Data provided for at least the following categories: vaccine types and non-PCV types (according to each site's PCV use) during the study period • For publications reporting proportion-based data on serotype distribution: - Studies reporting at least 20 serotyped isolates overall *and* with at least 50% of reported IPD cases were serotyped
Exclusion
• Case reports, narrative reviews, quarterly or province-level surveillance reports, if annual and/or national were available • Serotype data from studies with a high risk of bias focusing on specific cases: e.g., a selected severe presentation, vaccine failure or cases showing antimicrobial resistance • Data for years after PCV introduction are not extractable independently, or the study does not describe PCV use in the area • Data only reported for selected serotypes or those included in PCVs (PCV7, PCV10, PCV13) • Serotype data included isolates obtained from non-sterile sites (e.g., nasopharynx) or not extractable specifically for otherwise healthy children (i.e., study population includes all immunocompromised population or adults) • Data overlapped with other studies included in the analysis and the study period/sample size was smaller (studies with the longest study period or larger sample size were preferred)

3.4.3 Data collection

I independently reviewed identified publications and extracted relevant data into a template (Microsoft Excel). I extracted the following information from each study: author, publication year, country/setting, study period years, vaccine programme characteristics (i.e., vaccine formulation, schedule, and

uptake), case ascertainment methods (case definition, *S. pneumoniae* detection method, serotyping method, corrections made for missing serotype information) and outcome data. The main data extracted for this review were:

1. annual incidence rates of IPD in young children by serotypes categories, based on the current PCV in each setting, and
2. the number of IPD cases associated with individual serotypes, the total number of IPD isolates serotyped, and the total number of IPD cases in young children

3.4.3.1 Incidence rate data

Annual incidence rates were extracted for the serotype and age categories reported in each study. To extract incidence data reported in figures, I used the data extraction tool WebPlotDigitizer (freely available https://automeris.io/WebPlotDigitizer/). Denominator data were calculated for studies that did not provide these data but reported using census-based population estimates for incidence rate calculation. For this, the number of cases of all-type IPD (numerator) was divided by the incidence rate and multiplied by the factor reported (e.g., 100,000 children under five). Incidence rates were calculated by the same categories and standardised to 100,000 children in two selected age groups: children under two and under five years of age. This standardisation was done to ensure data from different studies were comparable and suitable for meta-analysis Information on the current formulation, and vaccine uptake in each setting was obtained from the global monitoring of PCV introduction hub International Vaccine Access Center (IVAC).

When reported, indicators of change in incidence (e.g., incidence rate ratios (IRR) and 95% CI) were extracted from studies comparing study periods before and after the introduction of highly valent PCVs.

3.4.3.2 Proportion-based data

From each study, I extracted the total number of IPD cases, the total number of cases serotyped, and the number of cases for each serotype. To extract

proportion-based data, I used the tool Datathief III (http://datathief.org/), which is also available for free online.

For studies identified in the initial search (with publication years 2000-15, inclusive), a second reviewer (Laurie Guillot, University of Edinburgh) independently extracted data from eligible studies reporting proportion-based data for manuscript publication. Any discrepancies on the eligibility of studies or inconsistencies in the data were resolved by discussion between reviewers. For studies with publication date 2016 onwards, I independently extracted data to include the most up-to-date data for this thesis.

3.4.4 Data analysis

3.4.4.1 Incidence rate data

For incidence data provided in figures, without sufficient further information necessary to conduct detailed analyses (e.g., clearly reported several cases or population denominator data), trends and magnitude of the changes reported after implementation of highly valent PCVs are summarised in a narrative synthesis.

When sufficient comparable data were available (more than three studies), IRR by age group and the following categories were calculated and pooled to develop overall estimates:

1. *All-type IPD*: cases associated with any serogroup or serotype
2. *PCV10 or PCV13 serotypes:* according to the PCV used in each setting
3. *Non-PCV10 or non-PCV13 serotypes:* according to the PCV used in each setting

The command "*metainc*" in R (version 3.6.0) using a random-effects model (DerSimonian-Laird estimator) was used as heterogeneity and small samples sizes across studies were expected. The random-effects model was selected to minimise the discounting effects of studies with smaller sample sizes that can occur when pooling data from different studies. A random-effects model gives more weight to smaller sample sizes as compared to the alternative, fixed-effects, which assumes the effect size of all studies regardless of sample size is similar. A random-effects model also allows the estimation of the mean

of a distribution of effects. As a result, confidence intervals resulting from the random-effects model are larger than when using a fixed-effect model because the former considers between-studies variance. In contrast, the latter only considers uncertainty from within-study error (thus resulting in narrower confidence intervals) (Borenstein et al., 2009).

I conducted a sensitivity analysis to explore the influence of two characteristics of the studies that could influence the magnitude of changes in disease incidence (Weinberger et al., 2011). First, summary IRR estimates were developed for HIC and resource-limited settings, separately. Second, summary IRR were estimated separately for studies with a similar setting and similar before and after PCV periods in terms of length, previous PCV use, and socio-economic status.

3.4.4.2 Proportion-based data

Proportion-based data were used to estimate the serotype-specific contributions to IPD. This proportion was estimated as a percentage of the total number of cases for each study (Equation 6) and the categories below:

Equation 6 Serotype-specific contribution to IPD

$$\%\ \text{serotype x} = \frac{total\ number\ of\ cases\ serotype\ x}{\text{total IPD isolates serotyped}} \times 100$$

1. *All-type IPD*: cases associated with any serogroup or serotype
2. *PCV7*: 4, 6B, 9V, 14, 18C, 19F, 23F
3. *PCV10non7*: 1, 5, 7F
4. *PCV13non10*: 3, 6A, 19A
5. PCV13: 4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, 7F, 3, 6A, 19A
6. *non-PCV13 serotypes*: Serotypes not included in PCV13

Most studies reported data for serotypes, rather than serogroups. The data reported as serogroups were not redistributed into serotypes since most of these data were for the years after PCV7 implementation and before highly valent PCVs introduction. Instead, data belonging to serogroups related to vaccine serotypes (6, 7, 9, 18, 19, or 23) were included in the number of cases for the category “PCV13” and the others were considered as non-PCV13.

Using "*metaprop*" in R (version 3.6.0), I calculated pooled estimates and 95% confidence intervals (95% CI) to estimate serotype-specific contributions to IPD. I selected the Freeman-Tukey double arcsine transformation to pool data and report Clopper-Pearson confidence intervals, which are based directly on the binomial distribution (Nyaga et al., 2014). All reported serotyped isolates were included in the calculation of the denominator, while samples not serotyped were excluded. All data points were included in serotype-specific meta-analyses, including those without a case count for the specific serotype. In cases where no data were reported, zero cases were assumed, as it was possible to be reasonably certain that case counts of isolates serotyped had been reported because the sum of all reported isolates was the same as the total reported.

To normalise the sum of pooled estimates for individual serotypes, so they summed to 100%, these were divided by the sum of the proportions (Johnson et al., 2010). The uncertainty range (95% CI) for each serotype proportion was then adjusted by increasing or decreasing the boundaries from the point estimate by the same proportion as in the one obtained from the meta-analysis. I report overall and regional pooled estimates with 95% CI.

3.4.5 Quality assessment

I used the Joanna Briggs Institute (JBI) Critical Checklist for Studies Reporting Prevalence Data to assess the quality of peer-reviewed publications included in this review. The main purpose for using the tool was to document the risk of biases and not to exclude studies from meta-analyses. This quality assessment tool was selected as it is designed to evaluate reports of observational studies, which were the type of studies to be included in this review. I established specific criteria for each of the nine questions in this tool to systematically assess issues relevant to IPD (described in Chapter 2, section 2.3). For each question, there were four possible answers: Yes, No, Unclear, Not applicable. The quality of studies was then ranked as *high*: if 0 to 3 answers were no/unclear, *medium*: if 4 to 6 were no/unclear, or *low*: if 7 to 9 were no/unclear. The quality of surveillance reports was not assessed because

these did not provide sufficient information. The limitations of the data from these sources are considered in the discussion.

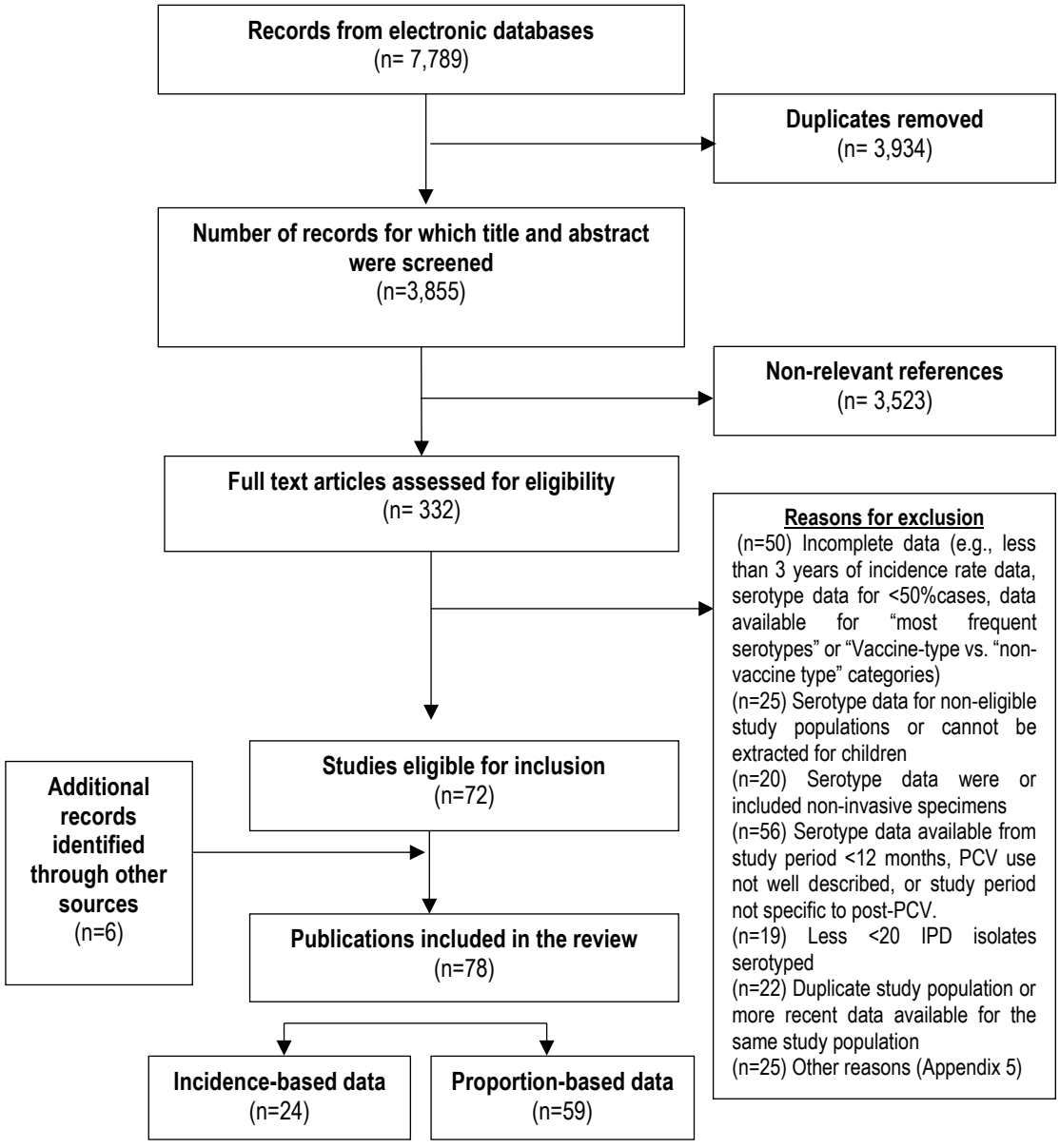
3.5 Results

3.5.1 Literature review

A total of 7,789 records were identified through databases search. After de-duplication, I identified 306 potentially relevant articles for full-text examination (Figure 4). Of these, 73 articles met the pre-defined eligibility criteria.

Additionally, six surveillance publications were retrieved through electronic medical databases. Annual data were identified from five individual countries, and one source included Latin American and Caribbean countries reporting to the regional surveillance system (SIREVA-II). The annual reports from the latter were considered as one publication.

Figure 4 PRISMA flowchart depicting the literature review process to assess the serotype distribution of S. pneumoniae in settings where PCV has been implemented

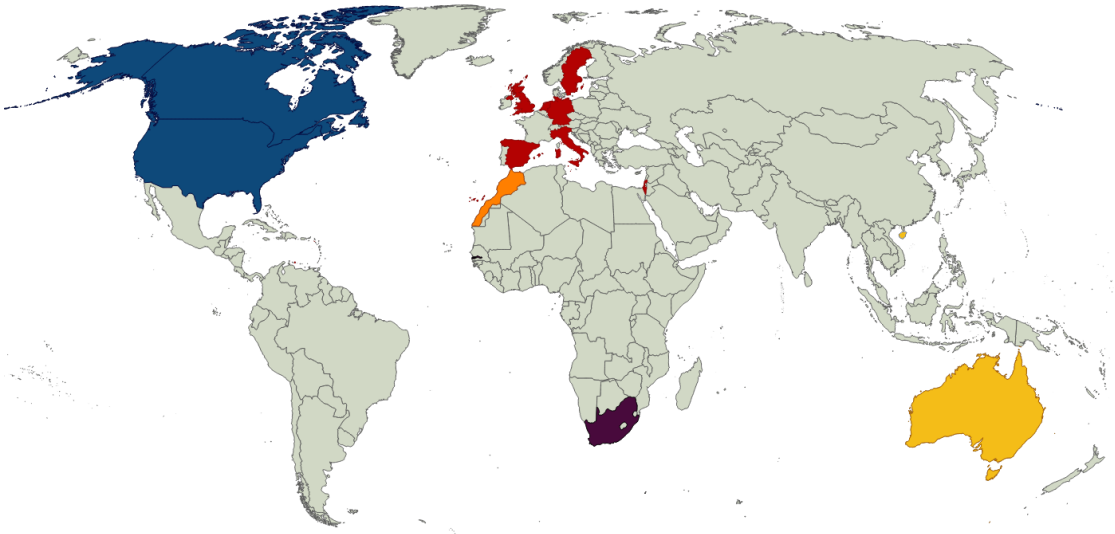


3.5.2 Incidence of childhood IPD by serotype categories

3.5.2.1 Characteristics of included studies

In total, 24 eligible publications reporting the effect of childhood high valency PCVs on IPD using incidence rate data were identified. Most publications provided data from high-income settings (20/24, 83.3%), predominantly in Europe (Figure 5). Data from five resource-limited settings were identified in North America (Alaska native and Nunavik populations), in Africa (South Africa and The Gambia), and the Eastern Mediterranean region (Morocco).

Figure 5 Map depicting the countries from which studies reporting incidence rate data were included



Notes: WHO regions by colour: blue: North America, orange: Eastern Mediterranean, purple: Africa, red: Europe, yellow: Western Pacific.

Most studies reported data from population-based surveillance systems, whereas regional/province-wide (n=14) or nationwide (n=5) (Table 9). Additionally, three studies included data from sentinel surveillance sites; one was a single hospital-based and one study reported data from a defined catchment area. The case definition for IPD and serotyping method were similar in all studies. Most studies reported using culture to identify IPD cases, but ten reported applying molecular methods, such as PCR, for either *S. pneumoniae* or *serotype* detection. Regarding case detection, eight studies (33%) reported excluding duplicate samples from the same patient within 21–30 days and eight studies (33%) reported making corrections to address missing serotype data.

Table 9 Characteristics of included studies reporting incidence rate data with study periods before and after highly valent PCV use

	(Baldovin et al., 2016)	(Ben-Shimol et al., 2018)	(Bruce et al., 2015)	(Camilli et al., 2017)	(CDC, 2017)	(Ciruela et al., 2018)	(Diawara et al., 2015)
Country	Italy	Israel	USA	Italy	USA	Spain	Morocco
Surveillance characteristics (setting)	Population-based: regional surveillance (Veneto)	Population-based: Nationwide, <1% of blood cultures obtained outside surveillance centres	Population-based: State-wide (Alaska)	Population-based: Regional surveillance (5 Italian regions) >30% of Italian population	Population-based: Sentinel Active Bacterial Core (ABC) (10 regions)	Population-based: Provincial Microbiological Reporting System (Catalonia)	Hospital-based: 52% of capacity management of patients in Grand Casablanca; all serious cases referrals
Study period years	2007–14	2000–16	2005–13	2008–14	1997–2017	2006–14	2011–14
Age groups considered	<5, 5-14, 15-29, 30-49, 50-64, >65 years	<5 years: <12, 12-23, 24-59 months	<2, 2-4, <5, 5-17, 18-44, ≥45, 18+ years	0-4 years	<5 years	<2, 2–4, 5–64, ≥65 years	≤2, >2-5 years
PCV during study period	PCV7, PCV13	PCV7, PCV13	PCV7, PCV13	PCV7, PCV13	PCV7, PCV13	PCV7, PCV13	PCV13, PCV10
Schedule	2+1	2+1	3+1	2+1	3+1	2+1	2+1
PCV uptake	80%	93%	93%	80%	93%	80.2% PCV7, 92.5% PCV10 or PCV13	…
Source population denominator	Veneto Regional Authority	Israeli Central Bureau of Statistics	Alaska census data	National Institute for Statistics	Surveillance sites population estimates	Census-based	Census data, with adjustments for population growth
Case definition	A clinically suspected bacterial disease, mainly meningitis, sepsis, and pneumonia, established from the isolation of *S. pneumoniae* from blood or another normally sterile site	Illness episode during which *S. pneumoniae* was isolated from blood, CSF or both	Isolation of *S. pneumoniae* from a normally sterile site in an Alaska resident	IPD cases reported to the laboratory database	Isolation of *S. pneumoniae* from a normally sterile site (e.g., blood, cerebrospinal fluid, or, less commonly, joint, pleural or pericardial fluid)	Isolation of *S. pneumoniae* by culture from a normally sterile site such as blood, cerebrospinal fluid, or pleural fluid, with compatible clinical manifestations	Isolates from normally sterile sites
Exclusion criteria	…	Non-culture diagnoses PCR, antigen testing, gram stain results or clinical diagnosis (approximately <5%). Positive cultures from	None reported	Duplicates from the same patient. Only CFS isolate was included for characterisation in	…	Duplicates from the same episode (separated by <30 days) or with the same serotype	When an isolate was recovered from CSF, the case was categorised as meningitis

	(Baldovin et al., 2016)	(Ben-Shimol et al., 2018)	(Bruce et al., 2015)	(Camilli et al., 2017)	(CDC, 2017)	(Ciruela et al., 2018)	(Diawara et al., 2015)
Country	Italy	Israel	USA	Italy	USA	Spain	Morocco
		other sterile sites than blood or CSF		meningitis cases if there was also blood			
Detection method	Standard laboratory procedures	Culture	Colony morphology, susceptibility to ethylhydrocuprein e hydrochloride and bile solubility	Culture	Culture, PCR	Culture	Standard procedures of bacteriology, i.e., alpha-haemolysis, optochin, susceptibility and bile solubility
Serotyping method	Pneumotest kit for Neufeld testing with type-specific antisera (SSI)	No details provided	Slide agglutination, Quellung reaction (SSI)	Latex agglutination, Quellung reaction	Culture, PCR	Quellung reaction or dot-blot assay. When not possible to identify serotype: PCR	Checkboard method with Pneumotest-latex (serogroup), Quellung capsule swelling (serotyping)
Remarks about serotyping procedures	Not reported	Redistribution for missing serotypes (<5% of all isolated pneumococci)	None reported	Statistical analysis was corrected for missing serotypes by assuming that reports with no serotyping had the same serotype distribution of reports with a known serotype	…	Retrospective differentiation between serotype 6A and 6C by PCR (63.3% of 6A cases reported before 2009 retyped). The proportion of cases with missing serotypes decreased from 34.6% in 2006 to 11.7% in 2014 ($p < 0.001$). For cases with missing serotypes, assumed the serotype distribution was the same as among cases with the serotype available for the same year and age group	None reported

Notes: PCV: Pneumococcal conjugate vaccine, PCR: polymerase chain reaction, CSF: cerebrospinal fluid, NIP: National Immunisation Programme, IPD: invasive pneumococcal disease, SSI: Statens Serum Institute, Copenhagen, Denmark

	(Farnham et al., 2015)	(Ho et al., 2019)	(Guevara et al., 2014)	(Jayasinghe et al., 2017)	(Ladhani et al., 2018)	(Latasa Zamalloa et al., 2018)	(LeMeur et al., 2019)
Country	USA	Hong Kong	Spain	Australia	England and Wales	Spain	Canada
Surveillance characteristics (setting)	State-wide, New York City Department of Health and Mental Hygiene	Territory-wide surveillance	Population-based, passive laboratory-based (Navarre)	National, passive surveillance	Population-based: national surveillance	Population-based: regional surveillance (Madrid)	Population-based: (Nunavik)
Study period years	2007-12	1995-2017	2001-13	2002-04	2000-16	2008-15	1997-16
Age groups considered	<5, >65 years	<5 years	<5, 5-64, ≥65 years	<2, 2-4, 5-14, 15-49, 50-64, >65 years	<2, 2-4, 5-14, 15-44, 45-64, >65 years	0-4, 5-14, 15-39, 40-59, >59 years	<5, ≥5 years
PCV use during the study period	PCV7, PCV13	PCV7, PCV10, PCV13 After 2009: NIP, before the private market	PCV7, PCV10, PCV13	PCV7, PCV13	PCV7, PCV13	PCV7, PCV13	PPV23 (mass vaccination), PCV7, PCV13
Schedule	3+1	3+1	3+1	3+0	2+1	3+1	3+1
PCV uptake	93%	<2009: low, PCV in private market only ≥2009: >97%	Low, PCV in the private market only	>92% receiving each PCV7/PCV13 dose by 12-month	>90% targeted age groups, 94% primary by 12 months of age, 92% 12-month booster by 24 months of age	>90% in children <5 years	92%: 4 doses PCV7
Source population denominator	Intercensal population denominator	US Census Bureau Population Estimate Program	National Statistics Institute	Australian Bureau of Statistics mid-year resident population estimates	Census-based	Register of the Institute of Statistics of Madrid	Quebec Statistics Institute
Case definition	Isolation of *S. pneumoniae* from normally sterile body site in New York City residents	Isolation (from January 2015 onward, culture and/or PCR detection) of *S. pneumoniae* in blood and/or other normally sterile sites	All cases of *S. pneumoniae* detected in invasive samples	Isolation of *S. pneumoniae* by culture or detection of nucleic acid from a normally sterile body site	*S. pneumoniae* isolated from a normally sterile site	Disease caused by *S. pneumoniae*, with isolation, DNA or antigen detection in samples from normally sterile sites	Clinical infection associated with the identification of *S. pneumoniae* by culture or nucleic acid amplification test in a normally sterile body fluid or site
Inclusion/ Exclusion criteria		Only one isolate from each patient was included.	Culture-negative cases were not included in this analysis. Only one IPD episode per patient was included unless clinical sample dates were >30 days apart or	Individuals not identified as Indigenous from all jurisdictions except the Northern Territory were included in the study. These exclusions were due to earlier	Repeat samples within 30 days from the same individual were regarded as part of the same episode and also adjusted for improvement of	Residents only	(Not specific for children): Majority of specimens were blood specimens during the 20 years, only 2 CFS and two aspirates. Antibiotics are

	(Farnham et al., 2015)	(Ho et al., 2019)	(Guevara et al., 2014)	(Jayasinghe et al., 2017)	(Ladhani et al., 2018)	(Latasa Zamalloa et al., 2018)	(LeMeur et al., 2019)
Country	USA	Hong Kong	Spain	Australia	England and Wales	Spain	Canada
			the serotypes of isolates were different	commencement of PCV7 funding for all Indigenous children nationally and programmatic use of PCV10 for two years between discontinuation of PCV7 and commencement of PCV13 in the Northern Territory.	notification, from voluntary to mandatory. Non-culture pneumococcal PCR testing is rarely done by local hospital laboratories, is usually restricted to CSF and pleural fluid samples, and does not provide serotype information		prescribed to all patients with clinics signs of acute infections before any airlift. Blood cultures are not systematically prescribed
Detection method	Culture	Culture (prior to 2015) and/or PCR (2015 onwards)	Culture	Culture, PCR	Culture	Culture, PCR, antigen detection	Culture, PCR
Serotyping method	Quellung test method with capsular typing antiserum	Multiplex PCR (covering 35 serotypes and including all PCV13 serotypes), the Quellung reaction	Quellung reaction or by dot-blot assay	…	Slide agglutination test	Latex agglutination test (Pneumotest-Latex), the Quellung reaction	..
Corrections made for missing serotype information	Redistribution of unknown serotypes. The proportion of IPD cases with serotyping performed increased from 48.7% in 2007 to 96.3% in 2012. One case in 2007 with both a PCV13-type disease and a non– PCV13-type disease isolates simultaneously was counted as one 0.5 cases of PCV13-type disease and one 0.5 cases of non–PCV13 type disease.	None reported	Serotypes 6A and 6C were prospectively distinguished from each other from 2010 onwards by PCR and retrospectively retested for previous years	Redistribution of unknown serotypes.	The proportion of total isolates serotyped improved over time, from 48% in 2000/01, to 79% in 2005/06, to 90% in 2009/10, and remained between 91% and 97% in subsequent years. Corrected missing age (<1% of cases) and serotype information, by assuming that the reports had the same age and serotype distribution as those	86.6% serotyped for all ages	Not reported

	(Farnham et al., 2015)	(Ho et al., 2019)	(Guevara et al., 2014)	(Jayasinghe et al., 2017)	(Ladhani et al., 2018)	(Latasa Zamalloa et al., 2018)	(LeMeur et al., 2019)
Country	USA	Hong Kong	Spain	Australia	England and Wales	Spain	Canada
					with complete data in that year		
Notes: PCV: Pneumococcal conjugate vaccine, PCR: polymerase chain reaction, CSF: cerebrospinal fluid, NIP: National Immunisation Programme, IPD: invasive pneumococcal disease							

	(Mackenzie et al., 2016)	(Mahmud et al., 2017)	(Naucler et al., 2017)	(Richter et al., 2019)	(Rinta-Kokko et al., 2018)	(Vissers et al., 2018)	(von Gottberg et al., 2014)
Country	The Gambia	Canada	Sweden	Austria	Finland	Netherlands	South Africa
Surveillance characteristics (setting)	Population-based catchment population, active (Upper River Region)	Population-based: routine regional surveillance (Manitoba)	Population-based: routine national surveillance	Population-based: active surveillance all paediatric wards	Population-based: mandatory notification, (>97% of case isolates sent to the national reference laboratory)	Population-based: sentinel surveillance (25% national coverage)	Population-based: sentinel surveillance (all provinces in the country)
Study period years	2008-14	2001-14	2007-16	2009-17	2002-16	2004-16	2005-12
Age groups considered	0–<2, 2–4, 5–14, 15+ years	0-4, 5-17, 18-64, >65 years	<5, 5-64, ≥65 years	<5, 5-49, ≥50, <2, 2-4, 50-59, ≥60 years	3-78 months	<5, >65 years	<2, <15, >15 years
PCV during study period	PCV7, PCV13	PCV7, PCV13	PCV7, PCV10 or PCV13	PCV10	PCV10	PCV7, PCV10	PCV7, PCV13
Schedule	3+0	Not reported	3+0	2+1	2+1	2+1	2+1
PCV uptake	96%	79%	97%	≥2 doses PCV10 among <2 years: 9% (2009) to 72% (2011–15). Cumulative vaccination coverage was 5.8% (2009) to 62.6% 2013–2016 among <5 years	85%	95%	60%
Source population denominator	Enumerated population every four months	Manitoba's Population Registry, 2006 Canada census population	Statistics Sweden	Mid-term population. No source reported	Finnish Population information system	Sentinel sites population estimates	Mid-year population estimate
Case definition	Suspected pneumonia, sepsis, or meningitis with isolation	Clinical evidence of invasive disease with the isolation of S. pneumoniae or demonstration of S. pneumoniae nucleic	Isolation of pneumococci from sterile locations (blood, cerebrospinal fluid.)	Patient with a specimen obtained from a normally sterile site (e.g., blood, cerebrospinal fluid), which tested culture or	IPD case was defined as isolation of *S. pneumoniae* from blood or cerebrospinal fluid	Isolates from blood or cerebrospinal fluid	Hospitalised persons from whom Streptococcus pneumoniae was cultured from specimens that are

	(Mackenzie et al., 2016)	(Mahmud et al., 2017)	(Naucler et al., 2017)	(Richter et al., 2019)	(Rinta-Kokko et al., 2018)	(Vissers et al., 2018)	(von Gottberg et al., 2014)
Country	The Gambia	Canada	Sweden	Austria	Finland	Netherlands	South Africa
		acid by NAAT from a normally sterile site		PCR positive for *S. pneumoniae*			normally sterile (e.g., cerebrospinal fluid, blood, or joint fluid)
Inclusion/ Exclusion criteria	Malaria coinfection systematically tested for during the rainy season	Residents only (based on postcode)	Cases with >30 days apart. For two patients, different serotypes were isolated 19 and 30 days apart, respectively. These were classified as different episodes. Five cases were excluded due to suspected double infections (isolation of 2 serotypes on the same day)	…	No adjustments made for comorbidities or influenza vaccination because of the small number of cases, evenly distributed comorbidities and the low coverage of influenza vaccinations between periods compared	If the same serotype was isolated from one patient multiple times within 30 days, this was considered as a single episode, and therefore only one IPD case was counted.	Duplicate isolates cultured within 21 days after the initial positive culture were excluded
Detection method	Culture, identification techniques (morphology and optochin sensitivity)	Culture, NAAT	Culture	Culture, PCR	Culture	Culture	Culture
Serotyping method	Latex agglutination assay, PCR. Serotyping repeated in reference laboratory for quality assessment	Not reported (sent to reference laboratory)	Gel diffusion and/or Quellung reactions	Quellung reaction	Quellung and PCR	Co-agglutination, Quellung reaction	Quellung reaction
Corrections made for missing serotype information	Corrected for unobserved cases during flooding in 2010 and before surveillance in 2008	Not reported	None reported. 95% isolates serotyped	73% cases <5 years serotyped (172/237). Proportion serotyped before and after PCV10 did not differ	None reported	None reported	Among cases of the disease with missing pneumococcal isolates: assumed the distribution was the same as the proportion among cases with available data each year.

	(Mackenzie et al., 2016)	(Mahmud et al., 2017)	(Naucler et al., 2017)	(Richter et al., 2019)	(Rinta-Kokko et al., 2018)	(Vissers et al., 2018)	(von Gottberg et al., 2014)
Country	The Gambia	Canada	Sweden	Austria	Finland	Netherlands	South Africa
							Serotype 6C was distinguished from 6A throughout
Notes: PCV: Pneumococcal conjugate vaccine, PCR: polymerase chain reaction, NIP: National Immunisation Programme, IPD: invasive pneumococcal disease, NAAT: nucleic acid amplification tests							

	(Wei et al., 2015)Wei	(Weinberger et al., 2018)	(Wijayasri et al., 2019)
Country	Taiwan	Germany	Canada, Ontario
Surveillance characteristics (setting)	Population-based: enhanced surveillance	National, active. 2 data sources: paediatric surveillance unit (ESPED), response rate >95% and PneumoWeb laboratory sentinel surveillance (Robert Kock Institute)	Population-based: passive and enhanced surveillance, Ontario's Integrated Public Health Information System (iPHIS)
Study period years	2008-13	1997-2015/16	2007-17
Age groups considered	<2, 2-5 years	<2, 2-4, 5-15 years	<1, 1-4, 5-49, 50-64, 65+ years
PCV during the study period	PCV7, PCV13	PCV7, PCV13	PCV7 (2005-09), PCV10 (2009-10), PCV13 (2010)
Schedule	3+1	2+1	3+1 PCV7/10, 2+1 PCV13
PCV uptake	Estimate based on doses imported: complete PCV7 immunisation (private market) 33.2%, PCV10: 10.5%, PCV13: 85.9%	83%	75.50%
Population denominator	Department of Household, Ministry of the Interior	German Federal Statistical Office	Population estimates (2007–2016) and projections (2017) obtained from Statistics Canada
Case definition	Isolation of *S. pneumoniae* from a normally sterile site	Children treated in a paediatric hospital because of an acute infection with cultural identification of pneumococci in a physiologically sterile site in both data sources	Clinical evidence of invasive disease and the isolation of S. pneumoniae or detection of *S. pneumoniae* DNA from a normally sterile site (e.g., blood, cerebrospinal fluid, excluding the middle ear)
Considerations numerators	…	Corrected cases by capture-recapture between two different systems (to minimise reporting bias as a source of annual changes)	Improvements in the completeness of serotype data made over time during the study period
S. pneumoniae detection method	Culture	Culture	Culture, NAAT (2009 onwards)
Serotyping method	No details	Neufeld Quellung reaction using type and factor sera	Yes
Corrections made to serotype information	None reported	Extrapolation of serotype distribution for about 30% of the cases	Serotype information available for 78.6% (all ages). No corrections reported
Notes: PCV: Pneumococcal conjugate vaccine, PCR: polymerase chain reaction, NIP: National Immunisation Programme, IPD: invasive pneumococcal disease, NAAT: nucleic acid amplification tests, DNA: Deoxyribonucleic acid			

PCV implementation and post-vaccine follow-up periods

The vaccine strategy and lengths of the periods of observation before and after the introduction of high-valency PCVs varied across studies (Table 10). Twenty studies (83.3%) examined the impact of PCV13, one study compared before any PCV (South Africa) and 19 studies in comparison with PCV7. In two of these studies, PCV10 was also briefly implemented in the study setting, but PCV13 was the main vaccine during the study period evaluated. Four studies examined changes after PCV10, three of which were in comparison with no PCV and one in comparison with incidence during years in which PCV7 was implemented.

Table 10 Pre and post PCV13 vaccination years in studies reporting incidence rate data

Reference	Country-Setting (if not nationwide)	PCV use in the reference period *(PCV7 Intro year)*	Reference period years	Higher valent PCV (introduction year Month)	Post-vaccination years								
					0	1	2	3	4	5	6	7	
(Bruce et al., 2015)	USA-Alaska	PCV7 (2000)	2005–08	PCV13 (2010 Apr)	Apr/2010–13								
(CDC, 2017)	USA-ABCs	PCV7 (2000)	2001–09	PCV13 (2010)	2010	2011	2012	2013	2014	2015	2016		
(Farnham et al., 2015)	USA-NY	PCV7 (2000)	2007-09	PCV13 (2010)		2011-12							
(Mahmud et al., 2017)	Canada-Manitoba	PCV7 (2004)	2006–09	PCV13 (2010)	2010	2011	2012	2013	2014				
(Wijayasri et al., 2019)	Canada-Ontario	PCV7/10 (2005, 2009)	2007–09	PCV13 (2010)	2010	2011	2012	2013	2014	2015	2016	2017	
(Weinberger et al., 2018)	Germany	PCV7 (2006)	2007/08-09/10	PCV13 (2010)	2010/11	2011/12	2012/13	2013/14	2014/15	2015/16			
(Baldovin et al., 2016)	Italy-Veneto	PCV7 (~2003)	2007–10	PCV13 (2010 Jul)		2011–14							
(Camilli et al., 2017)	Italy-5 regions	PCV7 (~2001)	2008-09	PCV13 (2010)		2011	2012	2013	2014				
(Ben-Shimol et al., 2018)	Israel	PCV7 (2009)	Jul09-Jun10	PCV13 (2010)		11-12	12-13	13-14	14-15	15-16			
(Ciruela et al., 2018)	Spain-Catalonia	PCV7 (~2001)	2006–09	PCV13 (2010 Priv, 2016-NIP)	2010-14								
(Guevara et al., 2014)	Spain-Navarre	PCV7 (~2001)	2004–09	PCV13 (2010 Jun)	2010–13								
(Latasa Zamalloa et al., 2018)	Spain-Madrid	PCV7 (2006 Nov)	2008-10	PCV13 (2010 Jun)		2011-12		2013-15					
(Naucler et al., 2017)	Sweden	PCV7 (2009 NIP, 2007-08)	2007-09	PCV10/13 (2009)					2013-16				
(Ladhani et al., 2018)	UK- England & Wales	PCV7 (2006 Nov)	2008–10	PCV13 (2010 Apr)	2010/11	2011/12	2012/13	2013/14	2014/15	2015/16	2016/17		
(Jayasinghe et al., 2017)	Australia	PCV7 (2004)	2008/09-2010/11	PCV13 (2011)	2011	2012	2013	2014					
(Wei et al., 2015)	Taiwan	PCV7 (2005)	2008-10	PCV13 (2010)		2011-12	2013						
(Mackenzie et al., 2016)	The Gambia	PCV7 (2009)	2008/10	PCV13 (2011)				2013/14					

Reference	Country-Setting (if not nationwide)	PCV use in the reference period *(PCV7 Intro year)*	Reference period years	Higher valent PCV (introduction year Month)	Post-vaccination years								
					0	1	2	3	4	5	6	7	
(von Gottberg et al., 2014)	South Africa	PCV7 (2009)	2005-08	PCV13 (2011)	2011	2012							
(LeMeur et al., 2019)	Canada-Nunavik	PCV7 (2002)	2004-09	PCV10 (2009), PCV13 (2010)	2010-16								
(Ho et al., 2019)	Hong Kong	PCV7 (Priv 2006; NIP: Sep 09-Sep10)	2006-09	PCV10 (2010-11), PCV13 (2011 Dec)	2010-14					2015-17			
Notes: studies in bold indicates those included in the meta-analysis. Merged cells indicate data were provided as a single data point for the years noted. *Abbreviations*: USA: United States of America, UK: United Kingdom, PCV: pneumococcal conjugate vaccine, NIP: national immunisation programme, Priv: Private setting. ABCs: Active Bacterial Core surveillance													

Table 11 Pre and post PCV10 vaccination years in studies reporting incidence rate data

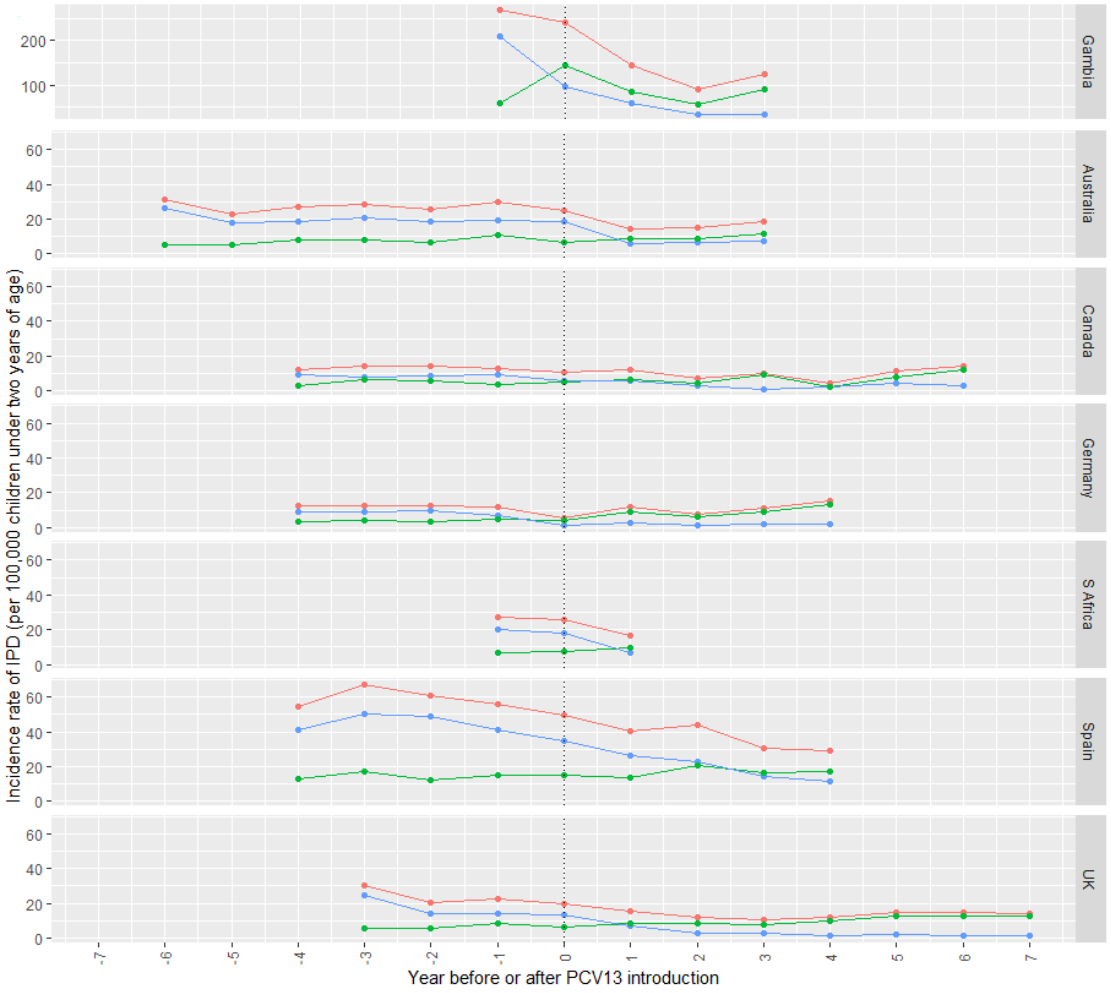
Reference	Country-Setting (if not nationwide)	PCV use in the reference period *(PCV7 Intro year)*	Reference period years	High valency PCV evaluated (intro year)	Post-vaccination years							
					0	1	2	3	4	5	6	7
(Richter et al., 2019)	Austria	No PCV	2009-11	PCV10 (2012 Jan)		2013-16						
(Vissers et al., 2018)	The Netherlands	PCV7 (2006)	2004-08	PCV10 (2010)	2008-10	2010-12		2012-14		2014-16		
(Rinta-Kokko et al., 2018)	Finland	No PCV	2002-08	PCV10 (2010 Sep)	2010-16							
(Diawara et al., 2015)	Morocco- Grand Casablanca	No PCV	2007-10	PCV13 (2010), PCV10 (2012)	2011	2012	2013	2014				
Notes: Merged cells indicate that data were provided as a single data point for the years noted. *Abbreviations*: PCV: pneumococcal conjugate vaccine, NIP: national immunisation programme, Priv: Private setting.												

3.5.2.2 Incidence rates and change in IPD incidence after PCV13 introduction

Children under two years

Nine studies reported incidence rates for post-PCV13 years in children less than two years of age. The length of the reference period (i.e., pre-highly valent PCV) ranged from one to six years. These study periods accounted for either the entire period of PCV7 use or for the years immediately before switching to PCV13. The length of PCV13 periods ranged from one year (in South Africa) to seven years (in the UK). Incidence rates extracted from studies by serotype categories in these studies are shown in Table 12 and depicted in Figure 6.

Figure 6 Incidence rate of IPD per 100,000 children under two years post-PC7 and post-PCV13



Notes: Dotted vertical line indicates the introduction of PCV13. All data pre-PCV13 shown were for years when PCV7 was implemented in each setting. Red: shows all-type IPD, blue: PCV13-IPD and green: non-PCV13 serotypes. *The scale of the y-axis for The Gambia differs for other countries to allow visualisation of data considering the large difference in rates.*

Table 12 Annual incidence rates per 100,000 children under two years pre- and post-PCV13 introduction

Reference	Country/setting	Year pre-PCV13 (*PCV7 intro year)							PCV13 Intro	Year post-PCV13							Average incidence rate		
		-7	-6	-5	-4	-3	-2	-1		1	2	3	4	5	6	7	Pre	Post	Change
All type-IPD																			
(Mackenzie et al., 2016)	The Gambia*						225.3†	269.7	240.6	144	89.3	125.2					269.7	119.5	-56.0%
(von Gottberg et al., 2014)	South Africa						42.6†	26.9	25.8	16.5							26.9	16.5	-39.0%
(Weinberger et al., 2018)	Germany			†	12.3	12.7	12.8	11.9	5.8	12.1	7.4	10.9	15.5				12.4	11.5	-8.0%
(Ciruela et al., 2018)	Spain-Navarre*				54.4	67.5	60.7	56.2	49.7	40.2	43.8	30.5	29				59.7	35.9	-40.0%
(Ladhani et al., 2018)	UK*				48.4†	30.7	20.4	22.9	20.1	15.7	11.8	10.7	12.1	14.5	14.6	14	24.6	13.3	-46.0%
(Wijayasri et al., 2019)	Canada			†	11.8	14.3	14	12.8	10.7	12	7.1	9.7	4.2	11.6	14.5		13.4	6.6	-26.0%
(Bruce et al., 2015)	Alaska Native*			270.8						103.4							270.8	103.4	-62.0%
(Bruce et al., 2015)	Non-Alaska Native*			39.7						15.5							39.7	15.5	-61.0%
(Jayasinghe et al., 2017)	Australia*	98.8†	31.3	22.8	26.9	28.7	25.4	30.0	25.2	14.6	15.0	18.6					27.5	16.1	-42.0%
(Wei et al., 2015)	Taiwan*		*			12.9			10.3	10.2							12.9	10.2	-21.0%
PCV13-IPD																			
(Mackenzie et al., 2016)	The Gambia						166.7†	211.1	97.4	58.1	34.2	34.2					211.1	42.2	-80.0%
(von Gottberg et al., 2014)	South Africa						34†	20	18.3	6.9							20	6.9	-66.0%
(Weinberger et al., 2018)	Germany			†	8.9	8.9	9.4	6.9	1.6	2.8	1.0	2.2	1.9				8.5	1.9	-77.0%
(Ciruela et al., 2018)	Spain				41.2	50.2	48.8	41.2	35	26.3	23.1	14.1	11.6				45.3	18.8	-59.0%
(Ladhani et al., 2018)	UK				43.3†	25	14.3	14	13.4	7.2	3.1	3	1.6	2.1	1.6	1.4	17.8	2.9	-84.0%
(Wijayasri et al., 2019)	Canada			†	8.9	7.8	8.2	9.3	5.7	5.7	2.9	0.6	2.2	4	2.7		8.3	3.4	-65.0%
(Bruce et al., 2015)	Alaska Native			174.7						30.2							174.7	30.2	-83.0
(Bruce et al., 2015)	Non-Alaska Native			29.7						5.2							12.2	5.2	-82.0
(Jayasinghe et al., 2017)	Australia	93.1†	26.3	17.8	18.9	21.0	18.9	19.5	18.6	5.6	6.3	7.2					20.4	6.4	-69.0%
(Wei et al., 2015)	Taiwan		†			10.8			8.5	8.3							10.8	8.3	-23.0

Notes: Merged cells indicate that data were available as a single data point for those years. *Abbreviations*: UK: United Kingdom, USA: United States of America, IPD: invasive pneumococcal vaccine, PCV: pneumococcal conjugate vaccine, *Included in meta-analysis. Shaded cells indicate the year of †PCV7 introduction

Reference	Country/setting	Year pre-PCV13 (*PCV7 intro year)							PCV13 Intro	Year post-PCV13							Average incidence rate		
		-7	-6	-5	-4	-3	-2	-1		1	2	3	4	5	6	7	Pre	Post	Change
Non-PCV13 IPD																			
(Mackenzie et al., 2016)	The Gambia						58.6†	58.6	143.2	85.9	55.1	91					58.6	77.3	32.0%
(von Gottberg et al., 2014)	South Africa						8.6†	6.9	7.5	9.6							6.9	9.6	39.0%
(Weinberger et al., 2018)	Germany			†	3.4	3.8	3.4	5.0	4.2	9.3	6.4	8.7	13.6				3.9	9.5	144.0%
(Ciruela et al., 2018)	Spain				13.2	17.3	11.9	15	14.7	13.9	20.7	16.3	17.4				14.4	17.1	19.0%
(Ladhani et al., 2018)	UK				4.8†	5.8	5.8	8.5	6.5	8.2	8.5	7.6	10.1	12.8	12.8	12.5	6.7	10.4	55.0%
(Wijayasri et al., 2019)	Canada			†	2.9	6.5	5.8	3.5	5	6.3	4.2	9.1	2	7.6	11.8		5.1	6.8	46.0%
(Bruce et al., 2015)	Alaska Native			78.6						73.3							78.6	73.3	-7.0%
(Bruce et al., 2015)	Non-Alaska Native			9.9						10.4							9.9	10.4	5.0%
(Jayasinghe et al., 2017)	Australia	5.7†	5.0	5.0	7.9	7.7	6.5	10.5	6.6	9.0	8.6	11.4					7.1	9.7	36.0%
(Wei et al., 2015)	Taiwan		†			2			1.9	1.9							2	1.9	-5.0%

Notes: Merged cells indicate that data were available as a single data point for those years. *Abbreviations*: UK: United Kingdom, USA: United States of America, IPD: invasive pneumococcal vaccine, PCV: pneumococcal conjugate vaccine, *Included in meta-analysis Shaded cells indicate the year of †PCV7 introduction

Changes in the incidence of IPD by serotype categories

Considering all studies, average annual incidence rates of all-type IPD during PCV7 periods ranged from 12.4 cases per 100,000 children under two in Germany to 270 cases per 100,000 children under two in low-income settings (The Gambia and among Alaska native children). The minimum average annual incidence rate during the years after PCV13 was introduced was 6.0 cases per 100,000 children under two in Canada (considering six years of PCV13) and the highest was in The Gambia with 119.5 cases per 100,000 children under two (considering three years of PCV13 use).

Figure 6 shows there was a decrease in all-type IPD in the immediate years after PCV13 introduction in most settings, except Germany and Canada. Based on average annual rates, (Table 12), IPD due to PCV13 serotypes decreased in all settings, with a reduction ranging from -84% to -23%. These reductions resulted in a decrease of all-type IPD (range: -62.0% to -8.0%). The incidence of non-PCV13 types increased in eight settings and decreased in two (range: 144.0% to -7.0%). The largest increases in non-PCV13 IPD were reported in countries with PCV13 programmes in place for over five years (Germany 144.0% increase, UK 55.0%, and Canada 46.0%).

Meta-analysis

IRR in children aged under two years (seven data points) was extracted from six studies. Results from the meta-analysis are shown as a “forest plot” in Figure 7. The pooled IRR estimate indicated an overall reduction of any type-IPD. The high heterogeneity across studies [I^2= 94%] reduces the reliability of this summary estimate (44% 95% CI: 13–64%). In sensitivity analyses, the estimate for an overall change in all-type IPD was similar in both HIC and in resource-limited settings (Figure 8). The heterogeneity decreased when data from HIC were considered, but it remained high [I^2 = 72%] though estimates from all, except one, individual settings indicated a decline (IRR below one) and thus should be interpreted with caution. The meta-estimate from resource-limited settings should also be interpreted with caution, as there were only two

studies from these settings. In both settings, the magnitude of the decline was similar (IRR: 0.45 95%CI 29-69 and 0.38 95%CI 24-61).

The subgroup analysis revealed a reduction of PCV13 type-IPD and an overall increase of non-PCV type-IPD. High heterogeneity was present in the meta-analysis of PCV13-type IPD incidence data (IRR: 0.27, 95% CI: 0.16–0.44 [I^2 = 88%]) but it was negligible in the meta-estimate of non-PCV13-type IPD (32% IRR: 1.32, 95% CI: 1.14–1.53 [I^2= 0%]). When studies were separated by income status of the location, the point estimate suggested a slightly higher reduction of PCV13-IPD, but the high heterogeneity persisted [I^2= 90%] and thus the limited reliability of this summary result. The meta-estimate increased for non-PCV13 IPD in HIC more than in resource-limited settings, but the effect is similar when the confidence intervals are considered (Figure 9). Heterogeneity remained negligible in the estimates for non-PCV13 IPD.

Restricting analyses to studies from similar settings with similar follow-up periods was possible for HIC assessing the first three/four years of highly valent PCVs. The pooled estimate from these studies suggested an overall decrease of all-type IPD as shown in Figure 10. However, there was no sufficient evidence to exclude the possibility of no overall effect during the early PCV13 programme years as the 95% CI included the null value (IRR 0.67 95% CI: 0.44–1.01) and heterogeneity was high [I^2=87%]. While there was evidence of a decline in incidence rates of PCV13-IPD (IRR: 0.44; 95% CI: 0.33–0.58), the direction of change of non-PCV13 IPD was unclear, with a point estimate suggesting an increase; still, there was variability in the data reflected in confidence intervals (IRR 1.18; 95% CI: 0.95–1.45). The heterogeneity after pooling the data for non-PCV13 IPD was negligible [I^2=0%].

Figure 7 Meta-analysis of incidence rate ratios post-PCV13 among children under two years of age

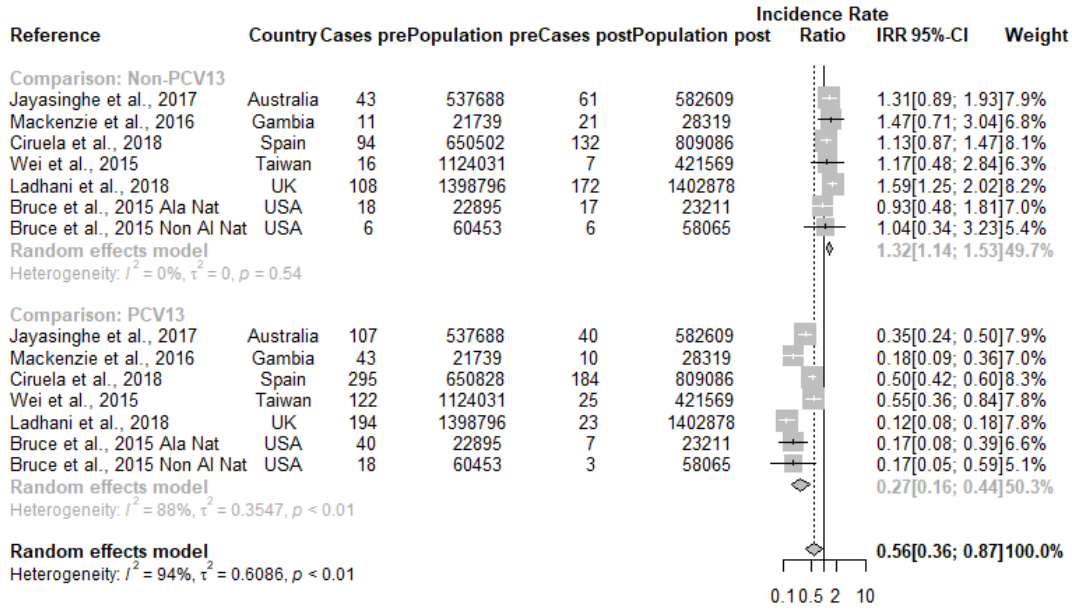


Figure 8 Meta-analysis of all-type IPD incidence rate ratios post-PCV13 among children under two years by settings' economic status

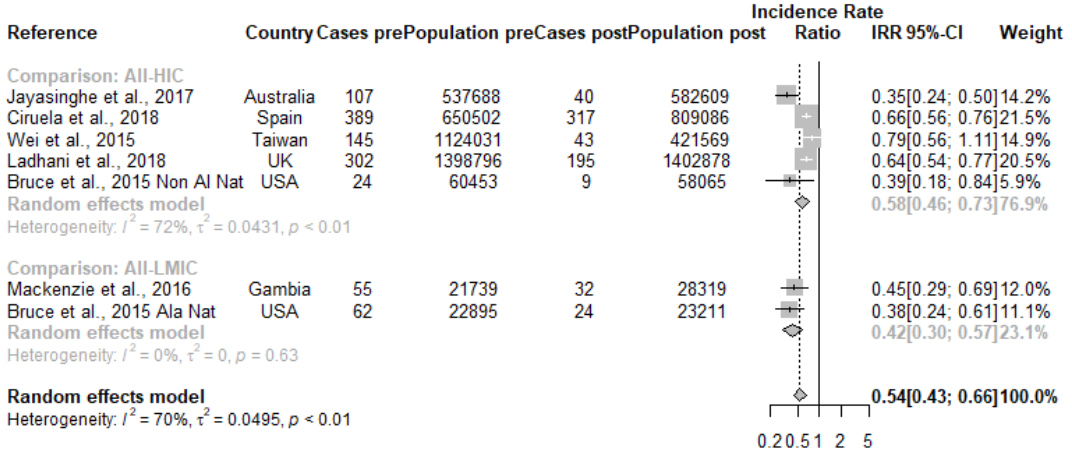


Figure 9 Meta-analysis of all-type IPD incidence rate ratios post-PCV13 among children under two years by serotype categories and settings' economic status

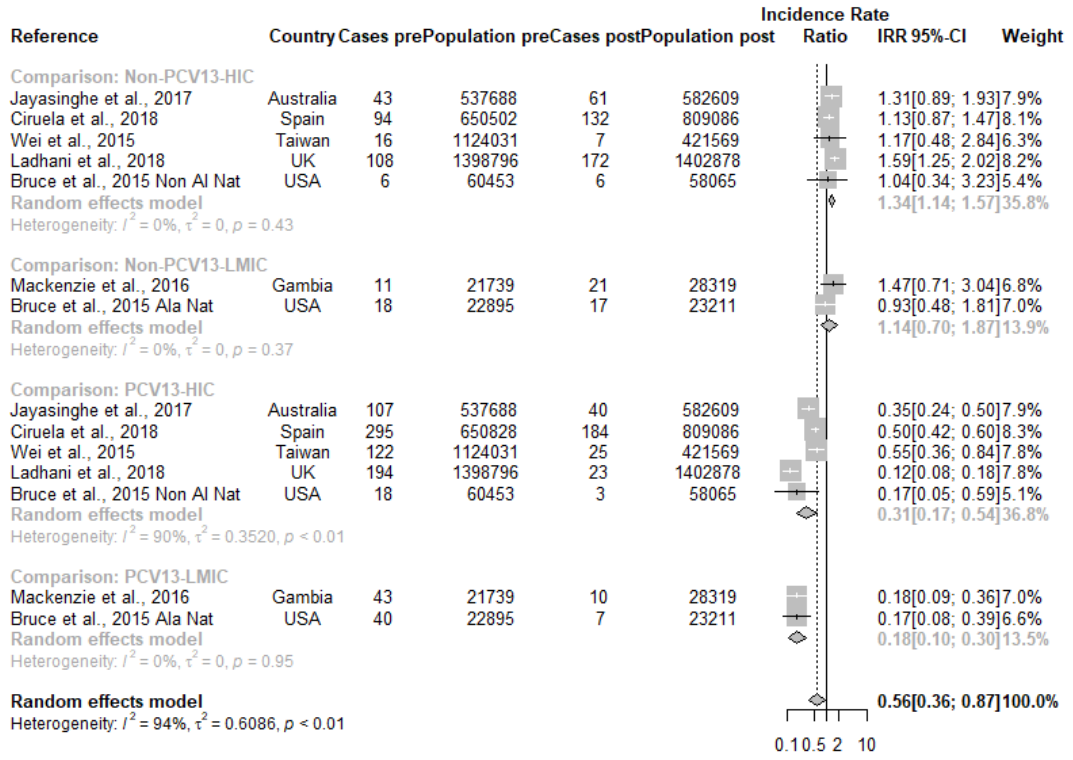
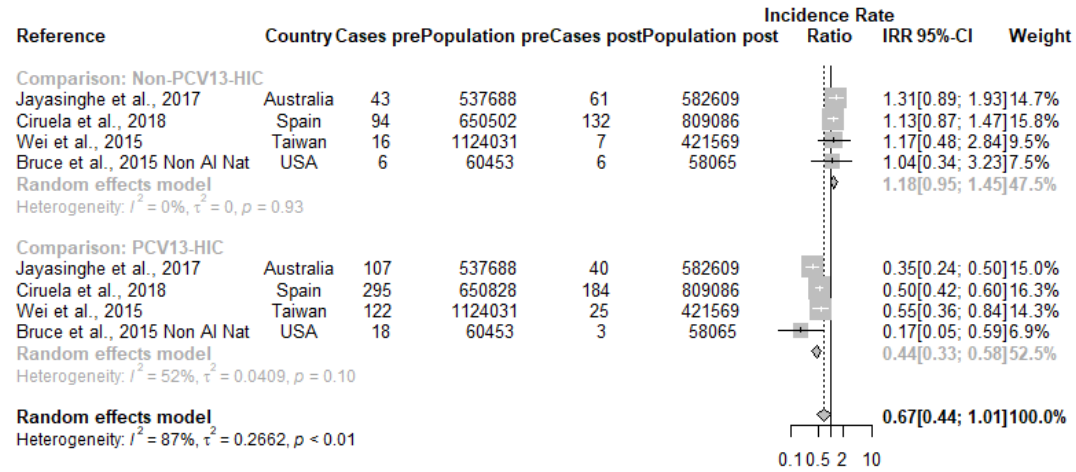


Figure 10 Meta-analysis of incidence rate ratios post-PCV13 among children under two years by serotype categories – studies in HIC with a similar follow-up period

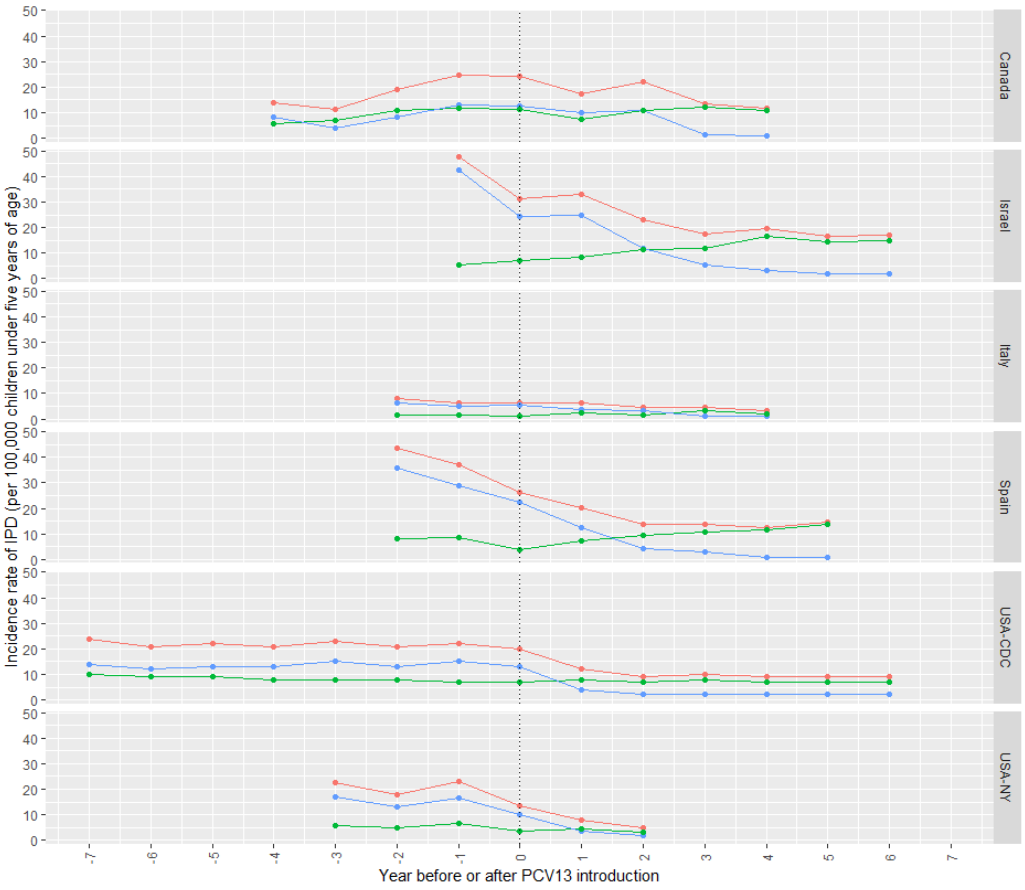


Children under five years

Twelve studies reported incidence rates for pre- and post-PCV13 years in children under five years. Incidence rate data were mainly available as single data points from before and after studies (Table 13). Based on all data available, pre-PCV13 average annual incidence rates of all type-IPD ranged from 6.2 cases in Germany to ≥150 per 100,000 children under five among native communities in Alaska and Canada. After the introduction of PCV13, incidence rates ranged from 2.9 cases to 212 per 100,000 children under five in these settings.

For studies that reported annual incidence rates, a decline of PCV13-IPD compared to the period prior to PCV13 implementation can be observed (Figure 11). Incidence rates of non-PCV13-IPD fluctuated with some increases in Canada, Israel, Italy, and Spain by the fourth year after PCV13 introduction. Conversely, the rate of non-PCV13-IPD remained stable in the USA.

Figure 11 Annual incidence rates of IPD per 100,000 children under five years post-PC7 and post-PCV13



Notes: Dotted line indicates the introduction of PCV13. All data pre-PCV13 shown were for years when PCV7 was implemented in each setting. CDC: Centers for Disease Control

Table 13 IPD incidence rates per 100,000 children under five years, pre- and post-PCV13 introduction

Reference	Country, setting	Years pre-PCV13 introduction (†PCV7 #PCV10 Introduction)										Intro Year	Years post-PCV13 introduction							Average incidence rate		
		10	-9	-8	-7	-6	-5	-4	-3	-2	-1		1	2	3	4	5	6	7	Pre	Post	Change
All type-IPD																						
(Baldovin et al., 2016)	Italy Veneto*				†				6.2				2.9							6.2	2.9	-53.2%
(Ben-Shimol et al., 2018)	Israel*										47.9*	31.4	33.1	23.1	17.3	19.6	16.5	16.8		47.9	21.1	-55.9%
(Camilli et al., 2017)*	Italy		†							7.9	6.5	6.5	6.2	4.7	4.5	3.2				7.2	4.7	-34.7%
(Ciruela et al., 2018) *	Spain Catalonia		†					46.6					27.9							46.6	27.9	-40.1%
(Latasa Zamalloa et al., 2018) *	Spain Madrid		†			60.7					#		18.7							60.7	18.7	-69.2%
(Guevara et al., 2014) *	Spain Navarre									43.7†	37.3	26.3	20.1	13.7	13.9	12.4	14.5			37.3	14.9	-60.1%
(Naucler et al., 2017)	Sweden								13.0†						5.1					13.0	5.1	-60.8%
(Ladhani et al., 2018)	UK							†	13.5				8.1							13.5	8.1	
(Bruce et al., 2015) *	USA Alaska Native		†				149.2						60.8							149.2	60.8	-59.2%
(Bruce et al., 2015) *	USA Non-Alaska Native		†				27.9						11.6							27.9	11.6	-58.4%
(CDC, 2017)	USA Nationwide	†	41	24	24	21	22	21	23	21	22	20	12	9	10	9	9	9		16.2	9.7	-40.1%
(Farnham et al., 2015) *	USA NY	†							22.7	18	22.9	13.4	7.9	5						21.2	6.4	-69.8%
(LeMeur et al., 2019)	Canada Nunavik			†		154					#		212							154	212	37.7%
(Mahmud et al., 2017)	Canada Manitoba					†		13.9	11.1	18.9	24.9	24.3	17.3	22	13.3	11.9				17.2	16.1	-6.4%
(Jayasinghe et al., 2017)	Australia				†	18.1							12.5							18.1	12.5	
(Ho et al., 2019)	Hong Kong								10.5				7					8.5		10.5	7.8	-25.7%
(Wei et al., 2015)	Taiwan					†			15.6				11.3							15.6	11.3	
(Mackenzie et al., 2016)	The Gambia									†	169.8		75.2							169.8	75.2	

Reference	Country, setting	Years pre-PCV13 introduction (†PCV7 #PCV10 Introduction)										Intro Year	Years post-PCV13 introduction							Average incidence rate		
		10	-9	-8	-7	-6	-5	-4	-3	-2	-1		1	2	3	4	5	6	7	Pre	Post	Change
Notes: Merged cells indicate that data were provided as a single data point for the years noted. †denotes PCV7 and # PCV10 introduction. *Abbreviations*: USA: United States of America, NY: New York, IPD: invasive pneumococcal vaccine, PCV: Pneumococcal conjugate vaccine.																						
PCV13-IPD																						
(Baldovin et al., 2016)	Italy Veneto				†				4.3				1.1							4.3	1.1	-74.4%
(Ben-Shimol et al., 2018)	Israel										42.4	24.5	24.9	11.8	5.4	3.2	2	2		42.4	8.2	-80.7%
(Camilli et al., 2017)	Italy 5 regions		†							6.2	5	5.4	3.9	3.1	1.3	1.1				5.6	2.4	-57.1%
(Ciruela et al., 2018)	Spain Catalonia		†					37.7					18.3							37.7	18.3	-51.5%
(Latasa Zamalloa et al., 2018)	Spain Madrid		†			47.8					#		9.3							47.8	9.3	-80.5%
(Guevara et al., 2014)	Spain Navarre									35.6	28.9	22.3	12.6	4.3	3	0.9	0.8			28.9	4.3	-85.1%
(Naucler et al., 2017)	Sweden								11.6†						1.9					11.6	1.9	-83.6%
(Ladhani et al., 2018)	UK							†	9.1				1.1							9.1	1.1	
(Bruce et al., 2015)	USA Alaska Native		†				87						17.4							87	17.4	-80.0%
(Bruce et al., 2015)	USA Non-Alaska Native		†				19.2						2							19.2	2	-89.6%
(CDC, 2017)	USA Nationwide	†	34	16	14	12	13	13	15	13	15	13	4	2	2	2	2	2		88	16.1	-81.7%
(Farnham et al., 2015)	USA NY	†							17	13.2	16.4	9.9	3.5	2						15.3	2.7	-82.4%
(LeMeur et al., 2019)	Canada Nunavik			†		59					#		18							59	18	-69.5%
(Mahmud et al., 2017)	Canada Manitoba					†		8.3	4.1	8.1	13.1	12.8	9.9	11	1.2	1.1				8.4	5.8	-31.0%
(Jayasinghe et al., 2017)	Australia				†	12.7							5.4							12.7	5.4	
(Ho et al., 2019)	Hong Kong								9.4				5.7					6.5		9.4	6.1	-35.1%
(Wei et al., 2015)	Taiwan					†			14.1				5.6							14.1	5.6	

Reference	Country, setting	Years pre-PCV13 introduction (†PCV7 #PCV10 Introduction)										Intro Year	Years post-PCV13 introduction							Average incidence rate		
		10	-9	-8	-7	-6	-5	-4	-3	-2	-1		1	2	3	4	5	6	7	Pre	Post	Change
(Mackenzie et al., 2016)	The Gambia									†	13 9.9		33.3							139. 9	33.3	
Notes: Merged cells indicate that data were provided as a single data point for the years noted. †denotes PCV7 and # PCV10 introduction. *Abbreviations*: USA: United States of America, NY: New York, IPD: invasive pneumococcal vaccine, PCV: Pneumococcal conjugate vaccine. Shaded cells indicate a change in vaccine use																						
Non-PCV13-IPD																						
(Baldovin et al., 2016)	Italy Veneto				†				1				1.1							1	1.1	10.0%
(Ben-Shimol et al., 2018)	Israel										5.5	6.9	8.2	11. 3	11. 9	16. 4	14. 5	14. 8		5.5	12.9	134.5%
(Camilli et al., 2017)	Italy 5 regions		†							1.7	1.5	1.1	2.3	1.6	3.2	2.1				1.6	2.3	43.8%
(Ciruela et al., 2018)	Spain Catalonia		†					9.3					9.7							9.3	9.7	4.3%
(Latasa Zamalloa et al., 2018)	Spain Madrid		†			13.4					#		8.6							13.4	8.6	-35.8%
(Guevara et al., 2014)	Spain Madrid									8.1	8.4	4	7.5	9.4	10. 9	11. 5	13. 7			8.4	10.6	26.2%
(Naucler et al., 2017)	Sweden								1.4†						3.2					1.4	3.2	128.6%
(Ladhani et al., 2018)	UK							†	4.4				7							4.4	7	
(Bruce et al., 2015)	USA Alaska Native		†				51.5						39.9							51.5	39.9	-22.5%
(Bruce et al., 2015)	USA Non-Alaska Native		†				8.6						9.5							8.6	9.5	10.5%
(CDC, 2017)	USA Nationwide	†	7	8	1 0	9	9	8	8	8	7	7	8	7	8	7	7	7		6.5	8.2	26.2%
(Farnham et al., 2015)	USA NY	†							5.7	4.8	6.5	3.5	4.4	3						5.7	3.7	-35.1%
(LeMeur et al., 2019)	Canada Nunavik			†		95					#		166							95	166	74.7%
(Mahmud et al., 2017)	Canada Manitoba					†		5.6	7	10.8	11.8	11.5	7.4	11	12. 1	10. 8				8.8	10.3	17.0%
(Jayasinghe et al., 2017)	Australia				†	5.4							7							5.4	7	
(Ho et al., 2019)	Hong Kong								1.1				1.3					2		1.1	1.7	54.5%
(Wei et al., 2015)	Taiwan					†			1.1				1.4							1.1	1.4	

Reference	Country, setting	Years pre-PCV13 introduction (†PCV7 #PCV10 Introduction)										Intro Year	Years post-PCV13 introduction							Average incidence rate		
		10	-9	-8	-7	-6	-5	-4	-3	-2	-1		1	2	3	4	5	6	7	Pre	Post	Change
(Mackenzie et al., 2016)	The Gambia									†	29.9		40.5							29.9	40.5	

Notes: Merged cells indicate that data were provided as a single data point for the years noted. * denotes PCV7 and # PCV10 introduction. *Abbreviations*: USA: United States of America, NY: New York, IPD: invasive pneumococcal vaccine, PCV: Pneumococcal conjugate vaccine.

Changes in the incidence of IPD by serotype categories

Considering data from all studies, the incidence of type-IPD decreased between the PCV7 and PCV13 period in all settings (range change: -6.4 to -69.8%), except in Canada among Nunavik population (Table 13).

Meta-analysis

The overall IRR pooled estimated (n=12 studies, 13 data points) corresponded to a reduction (Figure 14) in all-type IPD in children under five driven by decreases in PCV13 IPD. There is high heterogeneity in the estimate and thus should be interpreted with caution [I^2= 95%], despite large agreements in the direction of change of IPD due to vaccine types in most settings. The incidence of PCV13-targeted serotypes decreased in almost all settings (12 out of 13), with declines in individual settings ranging from 48% to 89% compared to the pre-PCV period.

The direction of change for non-PCV13 targeted serotypes was more variable, with estimates of IRR from individual settings ranging from reductions (IRR: 0.64 95% CI 0.37–1.14) to increases (IRR: 5.45 95% CI 0.67–44.27). Considering the confidence intervals of estimates from individual sites or when pooled IRR: 1.14 95% CI 0.95–1.37 [I^2=56] (Figure 13) the possibility of no change could not be excluded. Heterogeneity in the pooled estimate was moderate.

In the analysis stratified by income status of the settings, there was evidence of an overall decline of all-type IPD in HIC; but the reliability of this estimate is reduced as there was high heterogeneity (IRR: 0.54; 95%CI 0.46–0.63 [I^2=79%]) (Figure 12). The magnitude of the decline of all-type IPD was similar when the analyses was restricted to studies in HIC with a post-vaccine follow-up period of the first three to four years of PCV1. The high heterogeneity remained [I^2= 91%] (Figure 15). The pooled estimate of the impact of PCV13 on all-type IPD in children under five in resource-limited settings included the possibility of no overall decline but the reliability of this meta-estimate is reduced as there was high heterogeneity (IRR: 0.58; 95% CI: 0.33–1.04 [I^2= 80%] in the three studies included. In two of the studies, in Gambia and among

Alaska Natives, the reduction was similar, but an increase was reported among First Nations in Canada (Figure 12).

The subgroup analysis by serotype categories indicated a reduction of PCV13-type IPD and pointed towards an increase of non-PCV13-type IPD (Figure 14). While the was high heterogeneity in the meta-analyses for an overall reduction of PCV13-IPD [I^2= 92%] it was moderate in the pooled estimate of non-PCV13 IPD which included the possibility of no overall change [IRR 1.14 95% CI 0.95–1.37 I^2= 56%]. The results for the increases (in non-PCV13 IPD) and declines (in PCV13-IPD) were similar between HIC and resource-limited settings when data by serotype categories were stratified by income level (Figure 15). High heterogeneity (I^2=>80%) was found in both pooled estimates from HIC and resource limited settings meta-analyses regarding PCV13-IPD, even though there was consistency in the direction of change in individual settings, especially in HIC. Heterogeneity was moderate in the pooled estimates of non-PCV13 IPD in both HIC and resource settings [I^2= 53–60%] in the analysis of settings stratified by income level of individual sites (Figure 15)

Figure 12 Meta-analysis of all-type IPD incidence rate ratios post-PCV13 among children under five years by settings' economic status

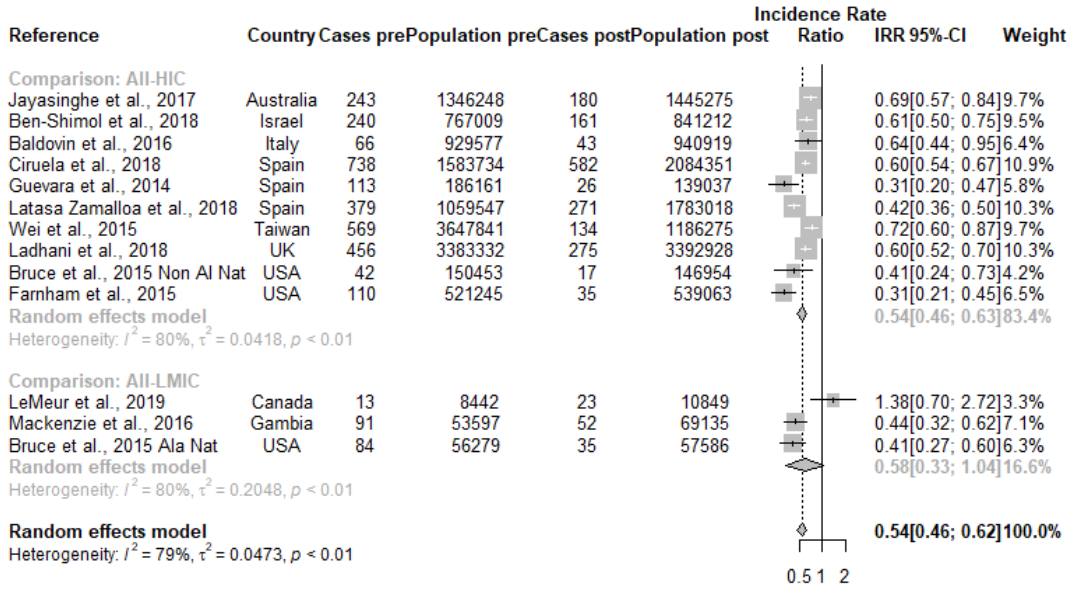
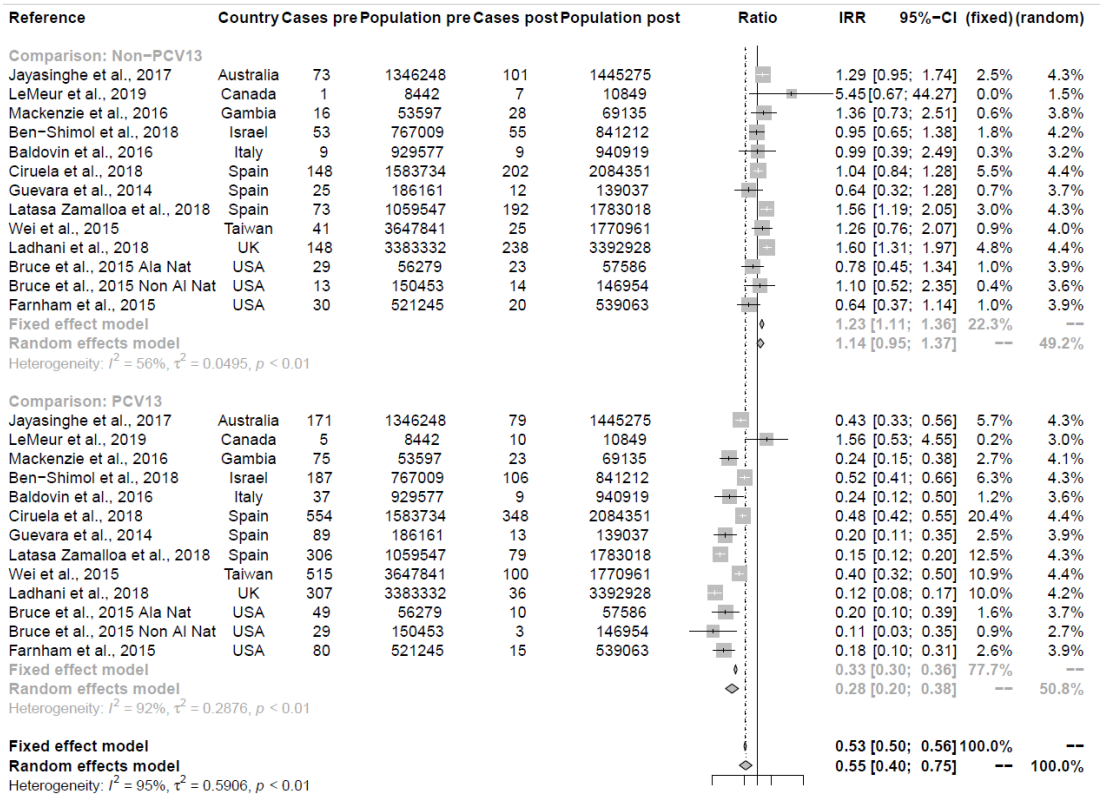


Figure 14 Meta-analysis of incidence rate ratios post-PCV13 among children under five years



Notes: All refers to all-type IPD, HIC: high-income country, LMIC: low and middle-income countries (or resource-limited settings)

Figure 13 Meta-analysis of incidence rate ratios post-PCV13 among children under five years by serotype categories – studies in HIC with similar follow-up period

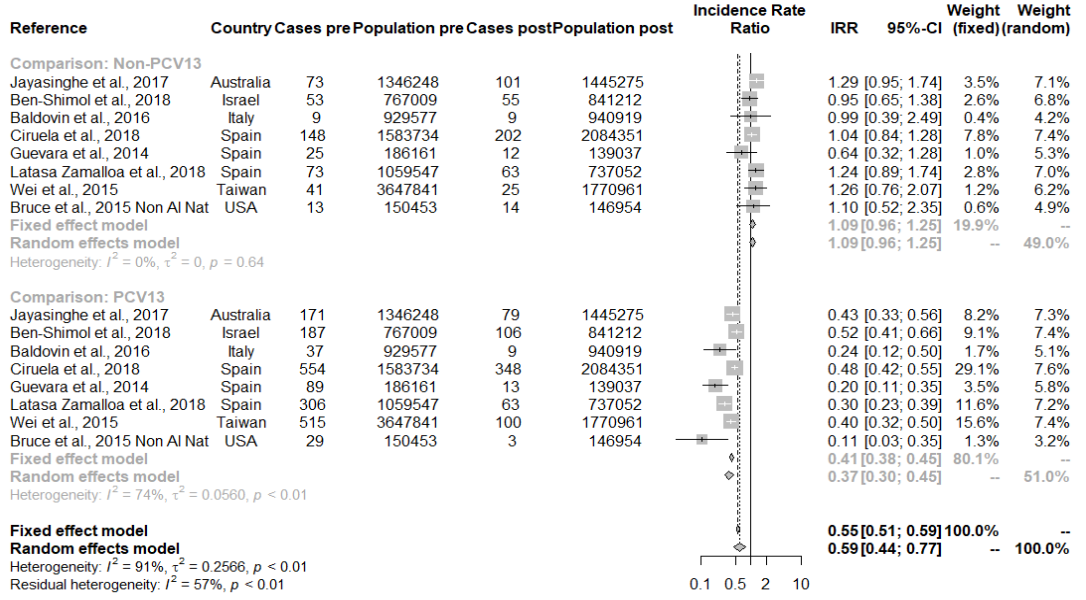
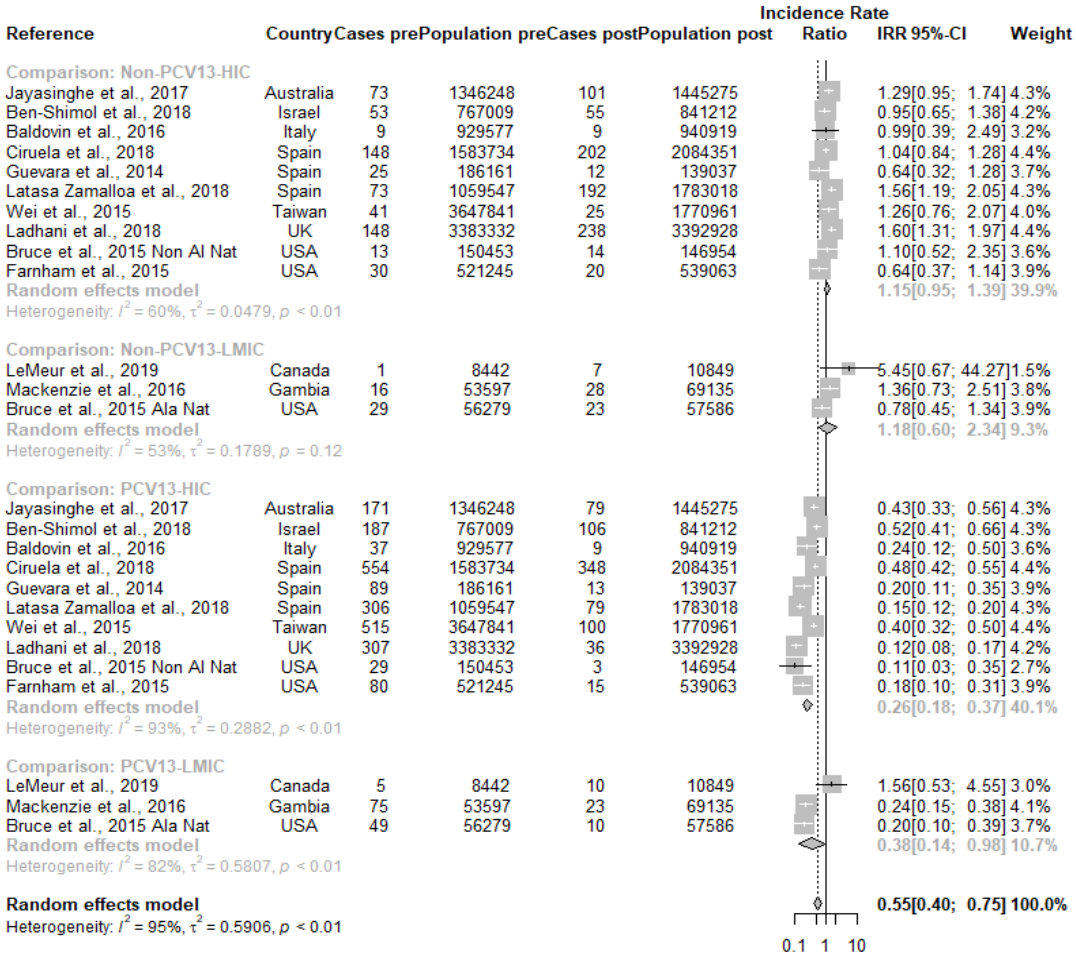


Figure 15 Meta-analysis of incidence rate ratios post-PCV13 among children under five years by serotype categories and settings' economic status



Notes: All refers to all-type IPD, HIC: high-income country, LMIC: low and middle-income countries (or resource-limited settings)

3.5.2.3 Incidence rates and change in IPD incidence after PCV10 introduction

Four studies provided data for change in IPD incidence rates, by serotype categories, in settings where PCV10 had been implemented (Diawara et al., 2015, Vissers et al., 2018, Rinta-Kokko et al., 2018, Richter et al., 2019). Table 14 provides the data for studies reporting annual incidence rates pre- and post-PCV10 introduction in each setting for children under five years. The study from Austria is not included in this table as it reported monthly average incidence rates in the pre- and post-PCV10 period. Except for the Netherlands, where PCV7 was used prior to PCV10, data for the impact of PCV10 identified in this review are from PCV naïve settings. Due to the limited comparability of the data, no meta-analysis was conducted. Results from these studies are synthesised in a narrative format.

The three studies from Europe reported an overall reduction of all-type IPD in children under five years after PCV10 introduction. The data from these settings span five to seven years of post-vaccination follow-up periods, reflecting the impact of mature PCV10 programmes. Compared to pre-PCV10 rates, a decrease of 70–80% in the incidence rate of all-type IPD occurred in Finland and Austria. In the Netherlands, a small increase was noted (IRR: 1.38; 95% CI: 0.78–2.47), though the estimate was non-significant (i.e., 95% CI of IRR including the null value). The overall non-increasing changes in childhood IPD post-PCV10 in these countries are a combination of declines in the incidence of PCV10-IPD and not significant changes in non-PCV10 types.

The changes in the incidence of IPD due to targeted serotypes post-PCV10 ranged from 58% decline in monthly incidence rates after five years of PCV10 introduction in Austria (IRR: 0.42; 95% CI: 0.26–0.70) to 94.3% (95% CI: 91.5–96.3) after seven years of PCV10 use in Finland. In the Netherlands, rates of PCV10 types reached nearly negligible values as it decreased from 2.6 at the time of PCV10 introduction to 0.2 per 100,000 five years after its use (IRR 0.09; 95% CI: 0.01–0.73).

Regarding the incidence of non-PCV10 IPD, non-significant changes were reported in all three settings. In Austria, the increase of non-PCV10 serotypes

excluding those in PCV13 (3, 6A, 19A) was of 15% (95% CI: -42–49). For the individual PCV13 unique types, the estimates also included the null value in the 95% CI. In Finland, the estimate available included PCV13 unique types, and the estimated change suggested an increase of 51.3%, yet the effect included the null value (95% CI: -4.1–148.6). In the Netherlands, the estimate available compared post-PCV10 rates to those from pre-PCV7 indicating a 102% increase of non-PCV10 IPD in young children (95% CI: -11 to 357) (IRR: 2.02 95% CI: 0.89–4.57).

Morocco was the only study reporting incidence rates after PCV10 introduction in a resource-limited setting. The post-PCV10 follow-up period was short (two years) while the pre-PCV10 period was the year in which PCV13 was introduced (and replaced by PCV10).

Table 14 IPD annual incidence rates per 100,000 children under five pre- and post-PCV10 introduction

Country (reference)	**Years pre-PCV10** (†PCV7, #PCV13 introduced)				**Intro year**	**Years post-PCV10**						**Average incidence rate**	
	-4	**-3**	**-2**	**-1**		**1**	**2**	**3**	**4**	**5**	**6**	**Pre**	**Post**
All-type IPD													
Morocco				15.4#	13.6	15.1	10					15.4	12.55
Netherlands	19.9†		13.8		7.8	7.8		4.5		6.1		6.7	6.13
Finland	42.9					9.2						42.9	9.2
PCV10-IPD													
Morocco				10.3#	3.4	6.7	8.3					10.3	7.5
Netherlands	4.0†		3.5		5.1	5		3.1		5.2		4.6	4.4
Finland	10.7					7.3						10.7	7.3
Non-PCV10													
Morocco				5.1#	10.2	8.4	3.3					5.1	5.85
Netherlands	15.9†		10.3		2.7	2.8		1.4		0.9		13.1	1.4
Finland	32.3					1.9						32.3	1.9

Notes: References by countries: *Morocco*: (Diawara et al., 2015), *Netherlands*: (Vissers et al., 2018) and *Finland*: (Rinta-Kokko et al., 2018) Merged cells indicate data were provided as a single data point for the years noted. In bold: data were available for meta-analysis, but due to the limited data, no meta-analysis was conducted. † denotes PCV7 and # PCV13 introduction. *Abbreviations*: IPD: invasive pneumococcal vaccine, PCV: Pneumococcal conjugate vaccine

3.5.2.4 Quality assessment

The publications reporting changes in IPD incidence by serotype categories were of high (13/24) and moderate quality (11/24) (Table 15). Notably, most studies lacked a description of study subjects (e.g., comorbidity status, ethnic characteristics).

Table 15 Quality assessment of studies reporting incidence rate of IPD pre- and post- highly valent PCV

Reference	1. Was the sample frame appropriate to address the target population?	2. Were study participants sampled appropriately ?	3. Was the sample size adequate?	4. Were the study subjects and the setting described in detail?	5. Was the data analysis conducted with sufficient coverage of the identified sample?	6. Were valid methods used for the identification of the condition?	7. Was the condition measured in a standard, reliable way?	8. Was there appropriate statistical analysis?	9. Was the response rate adequate ?	Overall appraisal of quality
(Baldovin et al., 2016)	Yes	Unclear	Not required	No	Unclear	Yes	Yes	Yes	Unclear	Medium
(Ben-Shimol et al., 2018)	Yes	Yes	Not required	No (subjects)	Yes	Unclear	Yes	Yes	Yes	High
(Bruce et al., 2015)	Yes	Yes	Not required	Yes	Yes	Yes	Yes	Yes	Unclear	High
(Camilli et al., 2017)	Yes	Yes	Not required	No (subjects)	Yes	Yes	Yes	Yes	Yes	High
(CDC, 2017)	Yes	Unclear	Not required	No	Unclear	Yes	Yes	Yes	Unclear	Medium
(Ciruela et al., 2018)	Yes	Yes	Not required	No (subjects)	Yes	Yes	Yes	Yes	Yes	High
(Diawara et al., 2015)	Yes	Yes	Yes	No (subjects)	No	Yes	Yes	Yes	No	Medium
(Farnham et al., 2015)	Yes	Yes	Not required	No (subjects)	Yes	Yes	Yes	Yes	Yes	High
(Ho et al., 2019)	Yes	Yes	Not required	No	Unclear	Yes	Unclear	Yes	Unclear	Medium
(Guevara et al., 2014)	Yes	Yes	Not required	No	Unclear	Yes	Yes	Yes	Unclear	High
(Jayasinghe et al., 2017)	No	No	Not required	No	No	Yes	Yes	Yes	Yes	Medium
(Ladhani et al., 2018)	Yes	Yes	Not required	No (subjects)	Yes	Yes	Yes	Yes	Yes	High
(Latasa Zamalloa et al., 2018)	Yes	Yes	Not required	No (subjects)	Yes	Yes	Yes	Yes	Unclear	Medium

Reference	1. Was the sample frame appropriate to address the target population?	2. Were study participants sampled appropriately ?	3. Was the sample size adequate?	4. Were the study subjects and the setting described in detail?	5. Was the data analysis conducted with sufficient coverage of the identified sample?	6. Were valid methods used for the identification of the condition?	7. Was the condition measured in a standard, reliable way?	8. Was there appropriate statistical analysis?	9. Was the response rate adequate ?	Overall appraisal of quality
LeMeur et al. (2019)	Yes	Unclear	Not required	No (subjects)	Unclear	No	Yes	Yes	Yes	Medium
(Mackenzie et al., 2016)	Yes	Yes	Yes	No (subjects)	Unclear	Yes	Yes	Yes	Yes	High
(Mahmud et al., 2017)	Yes	Yes	Not required	Unclear	Yes	Unclear	Yes	Yes	Unclear	Medium
(Naucler et al., 2017)	Yes	Yes	Not required	Unclear	Yes	Yes	Yes	Yes	Yes	High
(Richter et al., 2019)	Yes	Unclear	Not required	No	Yes	Yes	Yes	No	No	Medium
(Rinta-Kokko et al., 2018)	Yes	Unclear	Not required	Unclear	Yes	Yes	Yes	Yes	No	High
(Vissers et al., 2018)	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Unknown	High
(von Gottberg et al., 2014)	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	High
(Wei et al., 2015)	Yes	Unclear	Not required	Yes	Unclear	Yes	Unclear	Unclear	Yes	Medium
(Weinberger et al., 2018)	Yes	Yes	Not required	Yes	Yes	Yes	Yes	Yes	Unclear	High
(Wijayasri et al., 2019)	Yes	Yes	Not required	No	Yes	Yes	No	No	Unclear	Medium

3.5.3 The proportional contribution of serotypes to IPD

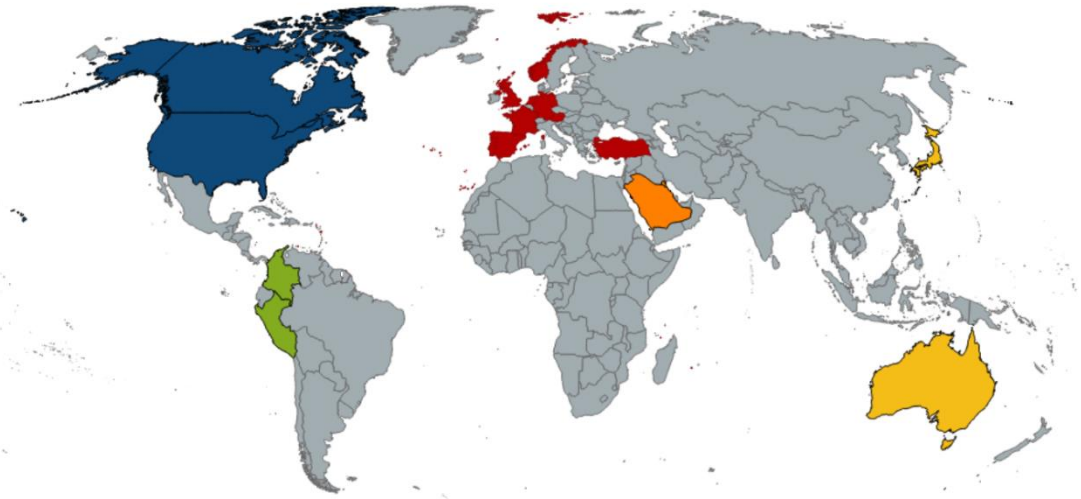
Data from 36 countries and 73 data points were extracted from publications after implementation of the PCVs considered. The results from the analysis of the proportional contribution of serotypes to IPD in young children are presented by PCV implemented (post-PCV7/pre-highly valent and post-highly valent PCVs)

3.5.3.1 Characteristics of included studies

After PCV7 implementation

In total, 32 data points from 17 countries were extracted from publications reporting periods of PCV7 administration (Table 16, Figure 16). Most data were available from the European region (n=17/32 data points, nine countries) followed by North America (n=8, two countries). Data from countries in the Western Pacific (n=3, three countries), Latin America and Eastern Mediterranean regions (n=2 each) were also identified and included in the review. All countries were upper middle income (n=2) or high-income countries (n=30).

Figure 16 Countries reporting post-PCV7 serotype distribution data by WHO regions



Notes: Countries for which data were identified are shown in colour by WHO region: Americas is divided into North America (blue), Latin America (green), Europe (red), Eastern Mediterranean (orange), and Western Pacific (yellow). Grey: no data.

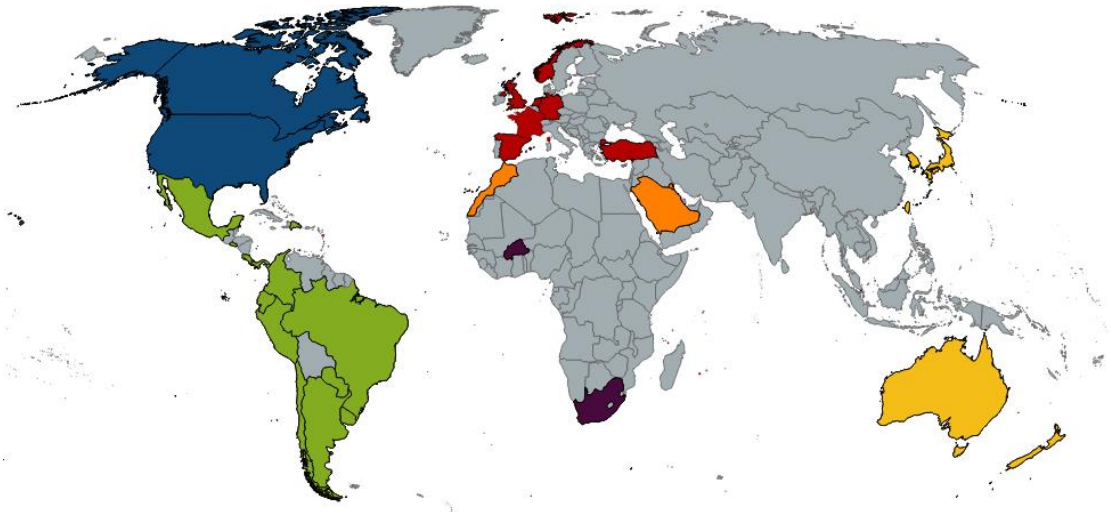
The total number of IPD isolates considered in the meta-analysis was 6,673 (Table 16). In individual studies, the number of isolates ranged from 36 (Rendi-Wagner et al., 2009) to 609 (Kaplan et al., 2013). Most data were reported for

the age interval of 0–<5 or 0–4 years (n=22/32, 68.7%). The Quellung reaction was the most common serotyping method (n=24/32; 78%). The length of study periods ranged from one to six years. The earliest study period began in 2001 in the USA, and the latest year was 2013 in Japan. Studies described different modalities of PCV7 use, and a variety of descriptions were provided regarding vaccine uptake levels. In terms of modalities, PCV7 use was described as "recently licensed, introduced into national immunisation programmes", in settings where PCV7 was "available through the private system" (e.g., in Spain, Portugal, and Austria), uptake was high, or it was routinely administered (e.g., US, Canada). Regarding estimates of PCV7 uptake, for over half of data points (n=20/32, 62.5%) no estimate or details for the estimate reported were available in the publication. In contrast, in others, the uptake was reported as a specific number of doses with (8/32) or without (3/32) an age parameter. As estimates of immunisation coverage by WHO/UNICEF are available from 2008 onwards, these could not be used to assess uptake during post-PCV7 data.

After the introduction of highly valent PCVs

A total of 41 data points were extracted from publications where PCV10 and/or PCV13 have been implemented (Table 17). These data were representative of 33 countries in five WHO world regions (Figure 17). The Americas region (considering both North and Latin America) was the most represented (n=17 data points from 15 countries), followed by Europe (n=11, seven countries), Western Pacific (n=5, five countries), Eastern Mediterranean region (n=4, three countries) and Africa (n=4, two countries). Out of all data points, 29 were from HIC, 11 from MIC and one from a LIC.

Figure 17 Countries reporting post-highly valent PCV serotype distribution data by WHO regions



Notes: Countries for which data were identified are shown in colour by WHO region: Americas, North America (blue), Latin America (green), Africa (purple), Europe (red), Eastern Mediterranean (orange), and Western Pacific (yellow). Grey: no data.

A total of 10,280 isolates with serotype data were reported post-highly valent PCVs (Table 17). Except for one study from Burkina Faso on meningitis patients, all studies reported on IPD cases. The majority of data were from settings implementing PCV13 (n=33/41, 80.5%) and from settings that had transitioned from PCV7 to a higher valency PCV (n=32/41, 78.0%). Data from PCV10 settings were available from six countries, five in Latin America and one study from the Netherlands. Data from three countries were for study periods in which a combination of PCV10/13 was used.

The number of isolates in individual studies ranged from 24 (Taiwan) to 1,021 (Australia). Five publications reported fewer than 50 isolates and an additional ten reported 50 or more but less than 100. Data were mostly representative of the age group 0–<5 years (n=29/41 data points, 70.7%), but data for younger children (e.g., <0–2 years) or older (e.g., 0–14 years) were also included (n=8 and 4, respectively). Information on serotyping method was available from peer-reviewed studies (n=21 studies, 24 data points). The Quellung reaction was reported as the method in the majority of studies (17/21, 81.0%). Study periods post-highly valent PCV ranged from one to 6.5 years, with 2009 as the earliest year reported and 2018 as the latest year included. Uptake of three doses of PCV, based on immunisation coverage by WHO/UNICEF available for 80.5% (33/41) of data points, ranged from 45.5% to 96.5%.

Table 16 Characteristics of studies reporting the proportional contribution of serotypes to childhood IPD post-PCV7

Reference	Country	Income level	Outcome	Serotyping method	Introduction	Study year	Uptake§	Age (y)	N
(Mokaddas et al., 2018)	Kuwait	HIC	IPD	Quellung reaction	2006	2006-10	…	≤5	40
(Mokaddas et al., 2018)	Saudi Arabia	HIC	IPD	Quellung reaction, checkerboard titration	2009	2009-10	…	≤5	237
(Rendi-Wagner et al., 2009)	Austria	HIC	IPD	Quellung reaction	2003	2005-06	…	<5	36
(Lepoutre et al., 2015)	France	HIC	IPD	Latex agglutination	2006	2008-09	89.0%	<2	483
(Varon et al., 2015)	France	HIC	IPD	Latex agglutination	2006	2008-09	89.0%	<2	388
(van der Linden et al., 2015)	Germany	HIC	IPD	Quellung reaction	2006	2007-10	79.3%	<5	542
(Knol et al., 2015)	Netherlands	HIC	IPD	Reference provided	2006	2008-11	96.0%	<3	128
(Steens et al., 2013)	Norway	HIC	IPD	Quellung reaction	2006	2006-10	89.0%	<5	165
(Aguiar et al., 2008)	Portugal	HIC	IPD	Quellung reaction	2001	2003-05	…	≤5	90
(Aristegui et al., 2007)	Spain	HIC	IPD	Quellung reaction	2001	2002-03	…	<5	77
(Barricarte et al., 2007)	Spain	HIC	IPD	Quellung reaction, dot blot	2001	2001-05	…	2m-<5	85
(Calbo et al., 2006)	Spain	HIC	IPD	…	2001	2002-04	…	≤5	64
(Guevara et al., 2014)	Spain	HIC	IPD	Quellung reaction, dot-blot	2001	2004-09	…	<5	106
(Munoz-Almagro et al., 2011)	Spain	HIC	IPD	Quellung reaction, multiplex-PCR assay	2001	2009	…	<5	130
(Perez-Trallero et al., 2009)	Spain	HIC	IPD	Quellung reaction, multiplex-PCR assay	2001	2002-07	…	<5	45
(Rodriguez et al., 2011)	Spain	HIC	IPD	Quellung reaction, latex agglutination assay	2006	2007-09	…	<5	366
(Salleras et al., 2009)	Spain	HIC	IPD	Quellung reaction	2001	2005-07	…	<2	240
(Ceyhan et al., 2016)	Turkey	HIC	IPD	Quellung reaction	2009	2008-10	95.0%	≤5	146
(Miller et al., 2011)	UK	HIC	IPD	Culture, PCR, polysaccharide antigen assay	2006	2008-10	89.0%	<5	528
(Parra et al., 2013)	Colombia	UMIC	IPD	…	2009	2010-11	34.0%	≤2	84
(Luna-Muschi et al., 2019a)	Peru	UMIC	IPD	Quellung reaction	2009	2009-11	82.5%	<18	57
(Bettinger et al., 2010)	Canada	HIC	IPD	Quellung reaction	2005	2006-07	…	≤4	212
(De Wals et al., 2012)	Canada	HIC	IPD	Quellung reaction, PCR (if culture-negative)	2004	2007-10	…	<5	113
(Black et al., 2007)	USA	HIC	IPD	Quellung reaction	2000	2001-05	93%	<5	84
(Bruce et al., 2015)	USA	HIC	IPD	Quellung reaction, slide agglutination	2001	2005-08	93%	<5	126
(Kaplan et al., 2013)	USA	HIC	IPD	Quellung reaction	2000	2007-09	93%	Children	609
(Pilishvili et al., 2010)	USA	HIC	IPD	Quellung reaction, latex agglutination	2000	2006-07	93%	<5	519
(Sharma et al., 2013)	USA	HIC	IPD	Quellung reaction	2000	2008-09	93%	6m-5	47
(Weatherholtz et al., 2010)	USA	HIC	IPD	Quellung reaction	2000	2001-06	93%	<5	115
(Williams et al., 2011)	Australia	HIC	IPD	…	2005	2006-07	…	<2	201
(Chiba et al., 2014)	Japan	HIC	IPD	Quellung reaction	2010/11	2011-12	…	<18	302
(Suga et al., 2015)	Japan	HIC	IPD	Quellung reaction, latex agglutination	2010/11	2011-13	…	<5	308
(Lepoutre et al., 2008)†	France	HIC	IPD	Latex particles	2006	2006	…	<2	158
(Levy et al., 2011)‡	France	HIC	MENG	Quellung reaction	2006	2007-08	89.0%	<5	182
(Hernandez-Bou et al., 2018)‡	Spain	HIC	BACT	…	2001	2011-14	…	3m-3	42

Notes: §Average WHO and UNICEF PCV3 estimates, y: year, m: month, PCV: Pneumococcal conjugate vaccine HIC: high-income country, UMIC: upper-middle-income country, IPD: invasive pneumococcal disease, MENG: meningitis, BACT: bacteraemia, PCR: polymerase chain reaction "…": No data/Not reported, ‡: not included in the meta-analysis

Table 17 Characteristics of studies reporting the proportional contribution of serotypes to childhood IPD post-highly valent PCVs

Reference	Country	Income level	Serotyping method	Introduction year of PCVs			Study period	PCV uptake§	Age (y)	Isolates
				PCV7	PCV10	PCV13				
PCV10/PCV13										
(Diawara et al., 2015)	Morocco	HIC	Quellung reaction, latex agglutination		2012	2010	2011-14	88.0%*	<5	45
(del Amo et al., 2014)	Spain	HIC	Quellung reaction, fluorescent PCR, fragment analysis capillary electrophoresis	2007	2009	2010	2007-11	<50%*	<6y	159
PCV10										
(Knol et al., 2015)	Netherlands	HIC	Reference provided	2006	2011		2011-14	96.0%	<3	57
(PAHO, 2008-15)	Brazil	HIC	…		2010		2011-15	91.4%	<5	841
(PAHO)	Chile	HIC	…		2011		2012-15	85.8%	<5	633
(PAHO)	Colombia	UMIC	…		2010		2011-15	79.4%	<5	473
(PAHO)	Ecuador	UMIC	…		2010		2011-15	84.3%	<5	113
(PAHO)	Peru	UMIC	…	2009	2011		2010-15	85.0%	<5	86
PCV13										
(Kambire et al., 2018)	Burkina Faso	LIC	PCR			2013	2014-15	91.0%	<5	173
(von Gottberg et al., 2014)	South Africa	UMIC	Quellung reaction	2009		2011	2011-12	76.5%	<2	843
(Cohen et al., 2017a) [HIV positive]	South Africa	UMIC	Quellung reaction, real-time lytA PCR (culture-negative CSF)	2009		2011	2011-14	76.5%	2m-<5	240
(Cohen et al., 2017a) [HIV negative]	South Africa	UMIC	Quellung reaction, real-time lytA PCR (culture negative CSF)	2009		2010	2011-14	76.5%	<5	75
(Mokaddas et al., 2018)	Kuwait	HIC	Quellung reaction	2006		2010	2010-16	99%*	≤5	27
(Al-Sheikh et al., 2014)	Saudi Arabia	HIC	Latex agglutination test, PCR	2009		2010	2009-12	*	<15, 40% <5y	78
(Shibl et al., 2012)	Saudi Arabia	HIC	Quellung reaction, checkerboard titration	2009		2010	2010	*	≤5	108
(Varon et al., 2015)	France	HIC	Latex agglutination	2006		2009	2012-13	89.0%	<2	181
(van der Linden et al., 2015)	Germany	HIC	Quellung reaction	2011	2009	2009	2010-14	85.0%	<5	567
(Steens et al., 2013)	Norway	HIC	Quellung reaction	2006		2011	2011-12	92.0%	<5	47
(Guevara et al., 2014)	Spain	HIC	Quellung reaction, dot-blot assay	2001	2009	2010	2010-13	78.0%*	<5	25
(Fenoll et al., 2015)	Spain	HIC	Quellung reaction, dot blot assay, and/or real-time PCR	2001	2009	2010	2010-13	<50*	<2	584
(Ceyhan et al., 2016)	Turkey	HIC	Quellung reaction	2008		2011	2011-14	96.5%	≤5	69

Reference	Country	Income level	Serotyping method	Introduction year of PCVs			Study period	PCV uptake§	Age (y)	Isolates
				PCV7	PCV10	PCV13				
(Waight et al., 2015)	UK	HIC	No details	2006		2010	2013-14	93.0%	<5	247
(Ladhani et al., 2018)	UK	HIC	Slide agglutination	2006		2010	2016-17	92.0%	<5	237
(Health Protection Scotland, 2015)	UK	HIC	…	2006		2010	2010-15	91.6%	<5	206
(Demczuk et al., 2013)	Canada	HIC	Quellung reaction using a pool, PCR multiplex	2001		2010	2010-12	73.6%	0-4	886
(Bruce et al., 2015)	USA	HIC	Quellung reaction, slide agglutination	2000		2010	2010-13	93.0%	<5y	52
(Kaplan et al., 2013)	USA	HIC	Quellung reaction	2000		2010	2010-11	93.0%	Children	283
(Moore et al., 2015)	USA	HIC	Quellung reaction	2000		2010	2012-13	93.0%	<5	177
(PAHO)	Argentina	HIC	…			2012	2013-15	85.6%	<5	519
(PAHO)	Costa Rica	UMIC	…	2008		2011	2011-15	85.6%	<5	57
(PAHO)	El Salvador	LMIC	…			2010	2011-15	93.6%	<5	50
(PAHO)	Mexico	UMIC	…	2008		2011	2012-15	92.8%	<5	266
(PAHO)	Panama	HIC	…	2010		2011	2011-15	68.4%	<5	113
(PAHO)	Paraguay	UMIC	…			2012	2013-15	90.0%	<5	94
(PAHO)	Dominican Rep	UMIC	…			2010	2014-15	45.5%	<5	58
(PAHO)	Uruguay	HIC	…	2008		2010	2010-15	93.0%	<5	138
(Australian DoH, 2012-17)	Australia	HIC	…	2005		2011	2012-17	92.3%	≤4	1021
(Nakano et al., 2016)	Japan	HIC	Quellung reaction	2010/11		2013	2014	96.0%	2m-<16 (93% <5y)	126
(New Zealand Ministry of Health, 2015)	New Zealand	HIC	…	2008	2011	2014	2014-18	93.5%	≤4	193
(Ministry of Health Singapore, 2012-14)	Singapore	HIC	…	2009		2011	2012-17	72.8%	<14	109
(Su et al., 2015)	Taiwan	HIC	Quellung reaction, PCR	2005		2011	2012-14	80.0%*	<5	24

Notes: §Average WHO and UNICEF PCV3 estimates, *As reported in the study, WHO and UNICEF coverage data not available for study years. y: year, m: month, PCV: Pneumococcal conjugate vaccine HIC: high-income country, UMIC: upper-middle-income country, LMIC: low, middle-income country, LIC: low-income country, IPD: invasive pneumococcal disease, PCR: polymerase chain reaction, "…": No data/Not reported.

3.5.3.2 Serotype distribution

In this section, I present results for the distribution of serotypes by categories in individual studies and meta-analyses by PCV era: post-PCV7 (pre-highly valent PCVs) and post-highly valent PCVs.

After PCV7 introduction

On average, PCV13-specific serotypes (3, 6A, 19A) combined were the most prevalent serotype category in post-PCV7 study periods (range: 11.1–59.7%), followed by non-PCV13 serotypes (range: 2.8–65.5%). The proportional contribution of PCV10-specific types to IPD combined was only more extensive than PCV13-specific types in seven studies, from five different countries (Saudi Arabia, Germany, Norway, Spain, and the UK) (Table 18).

Table 18 Distribution of serotypes (%) by categories among IPD in children in during PCV7 implementation

Reference	Country	Isolates (n)	PCV7	PCV10non7	PCV13non10	Non-PCV13
Mokaddas et al. (2018)	Kuwait	40	35.0	5.0	17.5	42.5
Mokaddas et al. (2018)	Saudi Arabia	237	70.5	13.9*	11.8	3.8
Rendi-Wagner et al. (2009)	Austria	36	75.0	11.1	11.1	2.8
Lepoutre et al. (2015)	France	483	11.2	27.3	32.9	28.6
Varon et al. (2015)	France	388	6.7	22.4	38.4	32.5
van der Linden et al. (2015)	Germany	542	23.2	25.3*	19.6	31.9
Knol et al. (2015)	Netherlands	128	3.9	21.1	27.3	47.7
Steens et al. (2013)	Norway	165	23.0	23.6*	22.4	30.9
Aguiar et al. (2008)	Portugal	90	30.0	25.6	30.0	14.4
Aristegui et al. (2007)	Spain	77	18.2	10.4	59.7	11.7
Barricarte et al. (2007)	Spain	85	41.2	7.1	38.8	12.9
Calbo et al. (2006)	Spain	64	28.1	20.3	29.7	21.9
Guevara et al. (2014)	Spain	106	9.4	30.2	38.7	21.7
Munoz-Almagro et al. (2011)	Spain	130	6.9	47.7*	25.4	20.0
Perez-Trallero et al. (2009)	Spain	45	33.3	35.6*	17.8	13.3
Rodriguez et al. (2011)	Spain	366	4.9	42.1*	27.9	25.1
Salleras et al. (2009)	Spain	240	31.7	15.0	31.3	22.1
Ceyhan et al. (2016)	Turkey	146	57.5	7.5	12.3	22.6
Miller et al. (2011)	UK	528	8.0	33.5*	28.2	30.3
Parra et al. (2013)	Colombia	84	38.1	10.7	21.4	29.8
Luna-Muschi et al. (2019)	Peru	57	59.6	7.0	12.3	21.1
Bettinger et al. (2010)	Canada	212	18.4	18.9	32.5	30.2
De Wals et al. (2012)	Canada	113	4.4	8.8	50.4	36.3
Black et al. (2007)	USA	84	11.9	4.8	17.9	65.5
Bruce et al. (2015)	USA	126	2.4	19.8	39.7	38.1
Kaplan et al. (2013)	USA	609	3.9	15.6	48.1	32.3
Pilishvili et al. (2010)	USA	519	2.1	9.8	55.9	32.0
Sharma et al. (2013)	USA	47	0.0	8.5	51.1	40.4
Weatherholtz et al. (2010)	USA	115	15.7	28.7	32.2	23.5
Williams et al. (2011)	Australia	201	18.9	2.5	45.8	32.8

Reference	Country	Isolates (n)	PCV7	PCV10non7	PCV13non10	Non-PCV13
Chiba et al. (2014)	Japan	302	34.1	1.0	19.9	45.0
Suga et al. (2015)	Japan	308	36.4	0.6	31.8	31.2
Average			*23.9*	*17.5*	*30.6*	*27.9*
Notes: n=isolates serotyped, serotypes categories=: PCV7: 4, 6B, 9V, 14, 18C, 19F, 23F, PCV10not7: 1, 5, 7F, PCV13not10: 3, 6A, 19A. *= proportion of IPD due to PCV10 specific serotypes is larger than PCV13 specific serotypes.						

Meta-analysis

The proportional contribution of serotypes after PCV7 implementation/pre highly valent PCVs computed by meta-analysis are shown in Table 20 and Table 21.

PCV7

The contribution of PCV7 serotypes to IPD post-PCV7 ranged from 0% to 75% (Table 18).Considering data from five world regions, except Africa and South East Asia for which no data were identified, serotypes included in PCV7 accounted for approximately a quarter of IPD in young children but there was high heterogeneity [I^2=98%] in this pooled estimate which reduces its reliability. Meta-analysis of the data available which represented different lengths of PCV7 implementation also showed there was high heterogeneity across settings when analysed by region. Data from Latin America and Eastern Mediterranean regions, serotypes included in the heptavalent conjugate vaccine accounted for over 50% (52.1% [I^2=84%] and 58.4% [I^2=94%], respectively) of total serotyped IPD in young children, ten times the contribution in North America (5.7%) [I^2=92%]. The proportion was between 20 [I^2=96%] and 35% [I^2=90%] of IPD cases, in Europe and Western Pacific regions. The pooled results are reported in Table 20 for reference

PCV10 non PCV7

Combined, the proportional contribution of PCV10-specific types (1, 5, 7F) showed a high level of heterogeneity [I^2=96%]. The pooled estimate is reported in Table 20 for reference. PCV10-specific serotypes contributed from 0.6% to 30.2% of the reported childhood IPD cases in the settings reporting data from post-PCV7 (Table 18). Predominant PCV10-specific serotypes were identified by region with varying degrees of heterogeneity in the pooled regional assessment. 7F predominated in North America and Europe, but its estimated contribution is affected high levels of heterogeneity (I^2=73% and 91%,

respectively). 7F's contribution to IPD was less than three per cent of childhood IPD in other world regions, with less heterogeneity present in these settings [I^2=49–69%]). Europe was the region with the highest prevalence of PCV10-specific types followed by North America but, the analysis by region did not reduce the high heterogeneity observed in the overall estimate. The contribution of PCV10-specific types ranged between 4.8%-28.7% in North America (eight studies) and between 7.1%-30% in Europe (17 studies). For the other regions, the estimated contribution of PCV10-specific serotypes was based on results from few studies: in the Eastern Mediterranean, these serotypes contributed to 10.4% 95% CI: 2.6–28.6% of childhood IPD. There was moderate heterogeneity in the meta-analysis (I^2=61%) but evidence was only available from two studies. Similarly, two studies reported data for Latin America and three for the Western Pacific region. The proportional contribution was lower than 10% in both settings 9.6% (95% CI: 2.3–20.9%) [I^2=0%] and 1.4% (95% CI: 0.1–3.6) [I^2=32%] respectively.

PCV13 non PCV10

When data from different settings and length of PCV7 use were pooled, serotypes unique to PCV13 accounted for more IPD cases than any other category. The high levels of heterogeneity [I^2=94%] reduced the reliability of this summary estimate (36.6% 95% CI: 27.6–46.6). The proportional contribution of these serotypes to IPD cases in individual settings ranged from 11.1% to 59.7%. The ranking of PCV13-specific types in terms of frequency based on pooled data indicated that 19A predominated followed by 3, and then 6A. The estimated overall contribution of these serotypes should be interpreted with caution given the high heterogeneity when pooling the data. (Table 20). For serotype 3, the heterogeneity decreased to moderate and low in most regional analyses, increasing the reliability of the result. For serotypes 6A and 19A, heterogeneity did not decrease when data were stratified and pooled by regions. Serotype 19A was the most frequently isolated serotype in individual regions, except in Latin America where serotype 3 predominanted.

Non-PCV13 serotypes

The number of non-PCV13 serotypes isolated varied in individual studies. At least one case was reported for 66 different serotypes identified during post-PCV7 study periods and 95 during study periods of post-highly valent PCVs implementation. The estimated contribution of non-PCV13 serotypes to IPD post-PCV7/Pre PCV10 or PCV13 ranged from 2.8% to 65.5% (Table 18). High levels of heterogeneity [I^2=91%] reduce the reliability of the pooled estimate of 20.6% (95% CI: 9.8–35.7%) as a summary estimate (Table 21). The contribution of non-PCV13 serotypes was similar across regions (range: 15.7–29.8%) and this subgroup analysis did not reduce the high heterogeneity observed in the overall meta-analysis. The ranking of non-PCV13 serotypes post-PCV7 presented in Table 21. Overall, the top non-PCV13 types were 15BC, 22F, 10A, 33F, 15A, 23B, 38, 24F, and 12F. These serotypes and the category reported as "other", accounted for at least 1% of childhood IPD individually and combined represented 77% of non-PCV13 IPD.

Leading serotypes by region

Based on the data from years of PCV7 implementation, the number of serotypes that accounted for 80% of childhood IPD was 11, overall, but this number varied by region (Table 19): nine in North America, 10 in Europe, 11 in Latin America and the Western Pacific. In the Eastern Mediterranean and Western Pacific regions, non-PCV13 serotypes in a category reported as "other" were among the leading serotypes contributing to the 80% of IPD cases.

After PCV7 introduction, one to two non-PCV13 serotypes featured among the leading serotypes in most regions, except in North America and Western Pacific. In these two latter regions, five and four non-PCV13 serotypes featured among the leading serotypes.

Table 19 Ranking of leading serotypes accounting for 80% of IPD post-PCV7 by world region

Rank	Overall	North America	Europe	Western Pacific	Latin America	Eastern Mediterranean
1	19A	19A	19A	19A	14	19F
2	7F	7F	1	6B	3	23F
3	1	3	7F	23F	19F	Other*
4	14	22F*	14	14	23F	9V
5	3	15BC*	3	19F	6B	19A
6	19F	33F*	19F	15BC*	19A	6A

7	15BC*	38*	15BC*	22F*	1	5
8	6B	23B*	6A	Other*	18C	
9	6A	6A	6B	15A*	9V	
10	22F*		5	6A	11A*	
11	23F			3	10A*	

Table 20 Serotype-specific contributions (%) to paediatric IPD cases post-PCV7 implementation, by region

	Overall (n=32)		North America (n=8)		Europe (n=17)		Western Pacific (n=3)		Latin America (n=2)		E Mediterranean (n=2)	
	% (95% CI)	I^2 (%)	% (95% CI)	I^2 (%)	% (95% CI)	I^2 (%)	% (95% CI)	I^2 (%)	% (95% CI) (%)	I^2	% (95% CI) (%)	I^2
Post-PCV7 implementation												
PCV7	23.4 (13.7-35.2)	97.6	5.7 (1.1-13.5)	92.3	22.7 (12-36.2)	96.4	32.3 (13.4-59.5)	90.4	52.1 (19.7-107.1)	84.1	58.4 (24.5-141.7)	94.4
4	1 (0.4-1.7)	64.0	0.6 (0-1.7)	56.3	0.9 (0.2-2)	72.9	2 (1-3.2)	0.0	0.6 (0-3.4)	0.0	0.8 (0-2.7)	0.0
6B	4.1 (2.4-6.2)	88.2	0.9 (0.1-2.2)	65.7	3.5 (1.8-5.6)	79.9	10.5 (3.9-19.8)	91.5	8 (2.7-15.6)	38.8	5.2 (2.5-8.7)	0.0
9V	1.7 (0.9-2.7)	72.5	0.6 (0-1.8)	61.3	1.2 (0.6-2)	44.1	1.4 (0.2-3.4)	66.2	2.4 (0.2-6.2)	0.0	10.9 (7-15.5)	0.0
14	6.4 (4-9.2)	90.8	0.8 (0.1-1.8)	43.5	7.8 (4.5-11.8)	90.2	5.2 (1.2-11.7)	89.8	20 (13.3-27.7)	0.0	5.2 (0-26.4)	90.4
18C	2 (1.2-2.9)	64.6	0.6 (0.1-1.4)	39.7	2.6 (1.6-3.8)	57.4	1.8 (0.5-3.9)	62.6	4.4 (0.9-9.8)	23.5	1.2 (0-12.4)	84.5
19F	5.4 (3.5-7.7)	87.6	1.9 (0.8-3.4)	57.9	5.1 (2.6-8.2)	88.1	4.8 (3.3-6.5)	0.0	8.7 (0-28.8)	87.8	20.1 (15-25.8)	0.0
23F	2.8 (1.3-4.8)	90.2	0.3 (0-1.1)	38.8	1.6 (0.7-2.7)	62.8	6.6 (3.3-10.9)	75.5	8 (2.7-15.6)	38.8	15 (0-50.4)	93.9
PCV10non7	19.3 (11.9-28.3)	95.9	15.6 (10.1-24.1)	84.0	28.9 (19-40.8)	91.5	1.4 (0.1-3.6)	31.7	9.6 (2.3-20.9)	0.0	10.4 (2.6-28.6)	61.1
1	7.8 (4.8-11.4)	93.2	1.5 (0.2-3.7)	81.0	14.5 (10.5-19)	87.1	0.6 (0.1-1.4)	0.0	7.4 (2.1-15.1)	43.3	2.4 (0-8.9)	59.2
5	1.8 (0.7-3.3)	87.6	0.5 (0-2.7)	86.8	2.6 (0.9-5)	88.3	0 (0-0)	0.0	2.2 (0.1-5.9)	0.0	5.3 (2.6-8.8)	0.0
7F	9.7 (6.4-13.6)	93.2	13.6 (9.9-17.8)	73.1	11.8 (7.6-16.8)	91.2	0.8 (0.1-2.1)	49.1	0 (0-0)	0.0	2.7 (0-10.9)	69.0
PCV13non10	36.6 (27.6-46.6)	93.6	49.5 (35.2-65.8)	91.4	29.9 (20.5-40.8)	87.1	36.4 (20.8-55)	94.8	18 (4.6-41.1)	47.2	15.1 (5.4-29.4)	7.5
3	5.8 (4.6-7.1)	61.7	7.4 (5.7-9.3)	28.8	5.4 (4.3-6.7)	30.9	2.7 (1.1-5)	58.1	9.5 (1-24.2)	78.7	1.2 (0-3.3)	0.0
6A	3.4 (2.1-4.9)	81.0	1.9 (0.3-4.5)	83.3	3.6 (1.9-5.8)	82.2	3.2 (1.8-4.9)	21.4	0.6 (0-3.4)	0.0	6.9 (1.5-15.2)	54.2
19A	27.4 (20.9-34.5)	95.6	40.2 (29.2-52)	93.5	20.9 (14.4-28.3)	93.9	30.5 (17.9-45.1)	93.3	7.9 (3.6-13.5)	0.0	7 (3.9-10.9)	0.0

Notes: %: Estimates of proportional contributions to IPD in children and 95% confidence intervals (95% CI) reported are based on the random-effects model. PCV: pneumococcal conjugate vaccine, IPD: invasive pneumococcal disease

Table 21 Estimates of the proportional contribution of non-PCV13 serotypes post-PCV7 implementation, by region

	Overall (n= 32)			Europe (n= 17)		North America (n= 8)		Latin America (n= 2)		E. Mediterranean (n= 2)		Western Pacific (n= 3)	
	x	(95% CI)	I^2 (%)	(95% CI)	I^2 (%)	(95% CI)	I^2 (%)	(95% CI)	I^2 (%)	(95% CI)	I^2 (%)	(95% CI)	I^2 (%)
Meta-estimate		20.6 (9.7-35.7)	91.0	18.4 (7.8-35.8)	84.5	28.8 (10.9-62.6)	84.5	21 (0.2-111.9)	22.2	15.7 (0-106)	97.2	29.8 (3.9-99.9)	85.9
15BC*	26	4.5 (3.3-5.9)	72.5	4.7 (3.6-6)	36.7	4.2 (2.5-6.3)	59.9	2.3 (0-12.7)	80.0	1.2 (0-12.4)	84.5	4.4 (0.1-13.5)	94.6
22F*	24	3.1 (2.1-4.3)	69.6	1.8 (0.8-3.1)	68.3	5.4 (4.2-6.7)	1.9	0.6 (0-3.4)	0.0	0.1 (0-1.2)	0.0	4.2 (2.5-6.3)	35.0
10A*	19	1.8 (0.9-2.9)	78.1	1.8 (0.6-3.4)	79.6	1.8 (0.3-4.1)	80.0	2.3 (0-15.5)	85.9	0 (0-0)	0.0	1.1 (0-3.6)	79.6
33F*	17	1.6 (0.7-2.8)	81.2	1.2 (0.3-2.6)	80.2	3.2 (0.6-7.3)	89.9	0 (0-0)	0.0	0 (0-0)	0.0	2.1 (1.1-3.3)	0.0
Other*	19	1.4 (0.2-3.2)	92.4	0.7 (0-3.1)	93.7	1.1 (0-3)	80.3	0 (0-0)	0.0	11 (0-72)	97.8	3.9 (0-16)	96.8
15A*	17	1 (0.5-1.7)	63.8	0.6 (0.3-1)	0.0	1.1 (0.5-1.8)	6.3	1.1 (0-5.3)	34.5	0.5 (0-2.3)	0.0	3.6 (0.1-10.9)	93.2
23B*	17	1 (0.5-1.7)	68.4	0.9 (0.3-1.7)	65.0	2 (1.3-2.9)	67.0	1.6 (0-5)	33.6	0 (0-0)	0.0	0 (0-0)	68.2
38*	12	1 (0.4-1.8)	84.0	0.5 (0-1.4)	78.8	2.6 (1.1-4.6)	0.0	0.5 (0-4.1)	0.0	0 (0-0)	0.0	1 (0-2.8)	93.1
24F*	20	1 (0.2-2.1)	55.0	2.2 (0.9-3.9)	46.7	0 (0-0)	0.0	0.6 (0-3.4)	0.0	0 (0-0)	0.0	0.9 (0-5.9)	0.0
12F*	16	0.9 (0.3-1.6)	68.7	1.3 (0.7-2)	26.8	1.6 (0.1-4.4)	87.1	0.5 (0-4.1)	33.6	0 (0-0)	0.0	0.1 (0-0.8)	0.0
NT	22	0.7 (0.1-1.6)	80.3	0.3 (0-0.9)	63.7	1.3 (0-4)	87.5	0 (0-0)	0.0	0 (0-0)	0.0	2 (0-10.3)	95.7
6C	10	0.4 (0-1)	72.4	0.2 (0-0.6)	26.7	0.6 (0-2.5)	83.2	0 (0-0)	0.0	0 (0-0)	0.0	2.4 (0-7.7)	90.4
11A	15	0.4 (0.1-0.8)	44.5	0.2 (0-0.6)	22.5	0.5 (0-1.4)	53.7	2.4 (0.2-6.2)	0.0	1.2 (0-3.3)	0.0	0.9 (0-3.5)	82.0
16F	18	0.4 (0.1-0.8)	31.3	0.4 (0.1-0.8)	1.2	0.7 (0-2)	68.3	1.1 (0-5.3)	34.5	0 (0-0)	0.0	0.2 (0-0.7)	0.0
23A	13	0.4 (0.1-0.8)	43.0	0.2 (0-0.5)	0.0	0.6 (0.1-1.5)	47.1	0.5 (0-4.1)	33.6	0 (0-0)	0.0	1 (0-4.4)	87.1
8	14	0.3 (0-0.7)	50.6	0.5 (0.1-1.2)	52.5	0.1 (0-0.5)	16.6	1.1 (0-5.3)	34.5	1.2 (0-12.4)	84.5	0 (0-0)	0.0
35B	13	0.2 (0-0.5)	16.3	0.1 (0-0.4)	0.0	0.4 (0-1.3)	49.6	1.1 (0-5.3)	34.5	0 (0-0)	0.0	0.8 (0-2.5)	67.5
24	7	0.1 (0-0.5)	58.0	0 (0-0)	31.5	0 (0-0)	0.0	0 (0-0)	0.0	0.5 (0-2.3)	0.0	1 (0-6.6)	94.1
17F	11	0.1 (0-0.4)	12.9	0.2 (0-0.5)	0.0	0.1 (0-0.8)	51.5	0 (0-0)	33.6	0 (0-0)	0.0	0 (0-0)	0.0
21	9	0.1 (0-0.3)	9.9	0.2 (0-0.5)	0.0	0.2 (0-1)	52.8	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0
35F	9	0.1 (0-0.3)	0.0	0.2 (0-0.5)	0.0	0.3 (0-1.2)	0.0	0.5 (0-4.1)	0.0	0 (0-0)	0.0	0 (0-0)	0.0
9N	9	0.1 (0-0.3)	0.0	0.1 (0-0.3)	0.0	0.4 (0.1-0.9)	23.2	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0
2	3	0 (0-0)	52.4	0 (0-0)	67.7	0 (0-0)	0.0	0 (0-0)	61.6	0 (0-0)	0.0	0 (0-0)	0.0
10	4	0 (0-0)	27.6	0 (0-0)	0.0	0.1 (0-1)	61.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0
11	3	0 (0-0)	19.5	0 (0-0)	0.0	0 (0-0)	68.9	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0
12†	7	0 (0-0)	0.0	0 (0-0)	0.0	0.1 (0-1)	0.0	0.6 (0-3.4)	33.6	0 (0-0)	0.0	0 (0-0)	55.0
13	5	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0
15†	4	0 (0-0)	14.2	0 (0-0)	0.0	0 (0-0)	61.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0
16	4	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0
17	4	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	33.6	0 (0-0)	0.0	0 (0-0)	0.0
20	3	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0.6 (0-3.4)	0.0	0 (0-0)	0.0	0 (0-0)	0.0
22†	3	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0
27	3	0 (0-0)	8.1	0 (0-0)	48.4	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0
28	3	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0
29	3	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0

	Overall (n= 32)			Europe (n= 17)		North America (n= 8)		Latin America (n= 2)		E. Mediterranean (n= 2)		Western Pacific (n= 3)	
	x	(95% CI)	I^2 (%)	(95% CI)	I^2 (%)	(95% CI)	I^2 (%)	(95% CI)	I^2 (%)	(95% CI)	I^2 (%)	(95% CI)	I^2 (%)
31	3	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0
33†	3	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0
34	2	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	31.7	0.5 (0-4.1)	0.0	0 (0-0)	0.0	0.2 (0-1.2)	0.0
35	2	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0
37	2	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0
39	2	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0
42	2	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0
46	2	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	34.5	0 (0-0)	0.0	0 (0-0)	0.0
47	2	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	1.6	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0
48	2	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0
10B	2	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0
10F	2	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0
10FC33C	1	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0
11AD	1	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0
11B	1	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0
11BC	1	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0
11F	1	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0
12A	1	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0
12B	1	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0
12FB	1	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0
13/28	1	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0
15AF	1	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0
15CF	1	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0
15F	1	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0
18A	1	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0
18B	1	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0
18F	1	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0
19B	1	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0
19C	1	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0
22A	1	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0
22F/A	1	0 (0-0)	27.8	0 (0-0)	0.0	0 (0-0)	75.3	0 (0-0)	0.0	0 (0-0)	0.0	0 (0-0)	0.0

Notes: Estimates of proportional contributions to IPD in children and 95 confidence intervals (95 CI) reported are based on the random-effects model. PCV: pneumococcal conjugate vaccine, IPD: invasive pneumococcal disease, n= number of data points included in the meta-analysis, x=number of studies that reported at least one case. (95 CI) I^2: the measure of heterogeneity, *top 10 serotypes, †serogroup related to one of the serotypes in the top 10.

After highly valent PCVs introduction

The contribution of serotypes to IPD by categories in individual studies are shown in Table 22.

Table 22 Distribution of serotypes by categories among IPD in children after post-highly valent PCVs

Reference / Vaccine used	Country	Isolates serotyped	PCV7 serotypes (%)	PCV10 serotypes (%)	PCV13 serotypes (%)	Non-PCV13 serotypes (%)
PCV10/PCV13						
Diawara et al. (2015)	Morocco	45	33.3	13.3	8.9	44.4
del Amo et al. (2014)	Spain	159	13.8	42.1	28.9	15.1
Average			*23.6*	*27.7*	*18.9*	*29.8*
PCV10						
Knol et al. (2015)	Netherlands	57	0.0	1.8	19.3	78.9
SIREVA II	Brazil	841	26.0	3.7	30.0	40.3
SIREVA II	Chile	633	25.8	7.4	29.4	37.4
SIREVA II	Colombia	473	30.0	8.5	31.3	30.2
SIREVA II	Ecuador	113	35.4	4.4	34.5	25.7
SIREVA II	Peru	86	24.4	1.2	32.6	41.9
Average			*23.6*	*4.5*	*29.5*	*42.4*
PCV13						
Kambire et al. (2008)	Burkina Faso	173	17.3	27.7	15.6	39.3
von Gottberg et al. (2013)	South Africa	843	25.5	9.8	21.9	42.7
Cohen (2017) et al., [HIV +]	South Africa	240	10.0	2.5	9.2	78.3
Cohen (2017) et al., [HIV -]	South Africa	75	10.7	1.3	16.0	72.0
Mokaddas et al. (2018)	Kuwait	27	11.1	3.7	14.8	70.4
Al-Sheikh et al. (2014)	Saudi Arabia	78	73.1	2.6	10.3	14.1
Shibl et al. (2012)	Saudi Arabia	108	53.7	25.0	15.7	5.6
Varon et al. (2015)	France	181	5.5	0.0	12.2	82.3
van der Linden et al. (2015)	Germany	567	4.9	12.3	18.2	64.6
Steens et al. (2013)	Norway	47	2.1	25.5	27.7	44.7
Guevara et al. (2014)	Spain	25	4.0	12.0	36.0	48.0
Fennoll et al. (2015)	Spain	584	19.2	11.6	29.1	40.1
Ceyhan et al. (2016)	Turkey	69	42.0	5.8	17.4	34.8
Waight et al. (2015)	UK	247	2.8	5.3	6.1	85.8
Ladhani et al. (2018)	UK	237	1.3	0.8	13.1	84.8
Scotland surveillance	UK	206	1.9	8.3	9.7	80.1
Demczuk (2013)	Canada	886	3.3	9.8	42.4	44.5
Bruce (2015)	USA	52	3.8	3.8	17.3	75.0
Kaplan (2013)	USA	283	3.2	15.2	38.2	43.5
Moore (2015)	USA	177	4.0	2.3	13.0	80.8
SIREVA II	Argentina	519	12.7	21.6	12.3	53.4
SIREVA II	Costa Rica	57	31.6	14.0	24.6	29.8
SIREVA II	El Salvador	50	40.0	4.0	12.0	44.0
SIREVA II	Mexico	266	16.9	3.0	40.2	39.8
SIREVA II	Panama	113	11.5	37.2	22.1	29.2
SIREVA II	Paraguay	94	34.0	2.1	25.5	38.3
SIREVA II	Dominican Rep	58	51.7	15.5	15.5	17.2
SIREVA II	Uruguay	138	9.4	18.1	18.1	54.3
(Australian DoH, 2012-17)	Australia	1021	8.2	3.0	31.5	57.2
(Nakano et al., 2016)	Japan	126	0.8	2.4	25.4	71.4
(New Zealand Ministry of Health, 2015)	New Zealand	193	5.2	2.1	33.2	59.6
(Ministry of Health Singapore, 2012-14)	Singapore	109	21.1	0.0	55.0	23.9
(Su et al., 2015)	Taiwan	24	20.8	0.0	70.8	8.3
Average	…	…	*9.3*	*23.3*	*50.2*	*17.1*
Notes: For Cohen (2017) et al., data HIV positive (+) and negative (-) were extracted separately.						

Meta-analysis

The results from the meta-analysis of studies post highly valent PCVs are shown in Table 24.

PCV7

In studies reporting data from years when highly valent PCVs were being implemented, the proportional contribution of PCV7 serotypes to IPD in young children ranged between 0 to 73% (Table 22). All countries included in the analysis, except the Netherlands, still identified PCV7 serotypes and the predominant PCV7 serotype varied by region. The pooled analysis indicated almost a fifth of IPD cases in young children were associated with PCV7 serotypes, but high levels of heterogeneity [I^2=97%] reduced the reliability of this summary estimate (17.4% 95% CI 10.1–26.3, Table 24). Though it was possible to determine the leading serotype by region based on meta-analysis, the summary estimates should be interpreted with caution as heterogeneity varies for different serotypes. For instance, from negligible for North America to high in Latin America. The leading PCV7 serotypes were: 14 in Latin America (12.1% 95% CI 7.8–17.2 [I^2=91%]), 19F in North America (1.9% 95% CI 1.1–2.9 [I^2=0%]) and Europe (2.5% 95% CI 0.8–4.8 [I^2=78%]), 23F in Eastern Mediterranean (13.5% (95% CI 1.3–34.3 [I^2=89%]), and 6B in Western Pacific (2.9% (95% CI 0.3–7.6 [I^2=86%]). Furthermore, serotypes targeted by PCV7, combined as a category, were most frequently isolated from studies reporting on childhood IPD cases in the Eastern Mediterranean, Latin America, and Africa regions. There is high heterogeneity in the results from these regions (49.7% [I^2=93%], 29.3% [I^2=91%], and 20.8% [I^2=92%] of IPD cases, respectively). Conversely, PCV7 serotypes accounted for lower proportions of IPD in North America, Europe, and the Western Pacific after PCV10 or PCV13 introduction (range: 3.0– 6.5). Despite this consistent lower contribution, high levels of heterogeneity were also observed in the pooled estimate for Europe and Western Pacific [I^2=89-95%] but not in North America .

PCV10 non PCV7

Serotypes 1, 5, and 7F were identified in all studies with periods of highly valent PCVs implementation. These serotypes were reported in most settings, except

France, Singapore, and Taiwan. Their proportional contribution to childhood IPD across studies ranged from 0% to 42% (Table 22). The high levels of heterogeneity [I^2=94%] reduced the reliability of the summary estimate for the contribution of PCV10-specific serotypes overall (9.1% 95% CI: 4.8−14.4). The contribution to paediatric IPD cases due to PCV10-specific serotypes was similar in all world regions, except in the Western Pacific where it was lower. Analysing data by region did not decrease the high heterogeneity (I^2 = ranging between 88 to 96%), except in Western Pacific, where it was moderate (I^2 = 43.0%). Though individual serotypes appear to be most common in a particular region, these results should be interpreted with caution due to the presence of high levels of heterogeneity. For instance, serotype 1 was the most common PCV10non7 serotype in Latin America and Africa (point estimates 4.4% and 6.6% with high heterogeneity [I^2>93%], serotype 5 in the Eastern Mediterranean (4.6% [I^2=96%]), while in Europe, Western Pacific, and North America 7F was the most predominant (point estimates ranging from 0.7% to 8.2%, with high heterogeneity in North American and Europe but moderate in Western Pacific).The results are reported in Table 24 for reference.

PCV13 non PCV10

The contribution of PCV13-specific serotypes in individual settings ranged from 6.1% to 70.8% (Table 22). While the most frequent PCV13-specific type was 19A, followed by 3, and then 6A, the reliability of the pooled estimates for their contribution are limited given the high levels of heterogeneity (Table 24). The high levels of heterogeneity for serotype 19A did not decrease when analysed by world region but some similarities across settings were noticeable. 19A's proportional contribution was over 15% in Western Pacific, North America, Latin America, and Europe (range: 17–41%), and below 10 but higher than 5% in Eastern Mediterranean and African regions (range: 6.1–7.7). The proportional contribution of serotype 3 was between 6–9% overall and in most world regions, except Africa and the Eastern Mediterranean region where it was lower than three per cent. High levels of heterogeneity remained in regional estimates for serotype 3 in Western Pacific and Latin America, but in other regions these levels were moderate or low (Table 24). Conversely, 6A

was associated with approximately 5–6% of IPD cases in Eastern Mediterranean, Africa, and Latin America, but its contribution to IPD in other world regions was negligible. The reliability of 6A's summary estimates is affected by high levels of heterogeneity overall [I^2=87%], but heterogeneity decreased when analyses were conducted by region, except in Africa.

Non-PCV13 serotypes

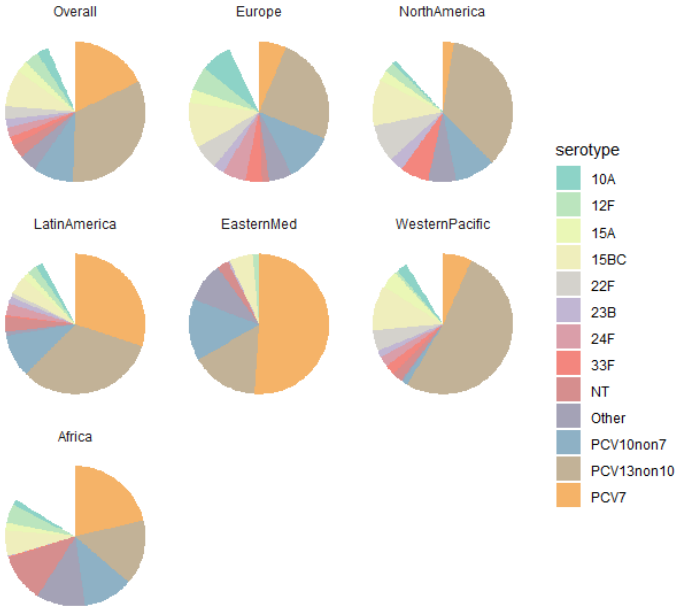
The proportion of childhood IPD cases associated with non-PCV13 types ranged from 5.60% to 85.8% in the studies analysed (Table 22). The pooled estimates indicate that less than half of IPD cases in studies reporting periods of highly valent PCV implementation were associated with non-PCV13 serotypes. The high heterogeneity [I^2=97%] reduces the reliability of the pooled estimate with data from 41 studies (41.6% 95% CI: 22.5−66.3%). As shown in Table 25, the leading non-PCV13 types included 15BC, 12F, isolates for which no type was identified (NT), 22F, 15A, 10A, 24F, 33F, and 23B. Their contribution is estimated to be to at least 2% of IPD individually. Additionally, serotypes 6C, 8, 11A, 23A, and 35B contributed to 1% of IPD individually. This estimated overall individual contribution should be interpreted with caution as there are high levels of heterogeneity and variations across regions (Table 25). Figure 18 shows the top ten non-PCV13 serotypes contribution to childhood IPD in the study periods of highly valent PCV implementation, in addition to serotypes included in current vaccine formulations, by regions. The differences and similarities in the proportional contribution of some serotypes between regions are worth highlighting. For instance, 15BC was the leading non-PCV13 serotype in all regions. Also, notably, the prevalence of serotypes 24F and 10A was low or not explicitly reported in studies from North America, Eastern Mediterranean or Africa. However, these serotypes were prevalent in other world regions, especially in Europe.

Leading serotypes by region

Overall, 80% of childhood IPD was associated with 15 serotypes (and the category reported as "others" in individual studies) (Table 23). Regionally, 80% of childhood IPD in North America was associated with the fewest number of serotypes (nine, of which six were non-PCV13 serotypes). One in four cases

of IPD in this region was due to 19A (Table 24). Contrary, Latin America was the region with the greatest number of serotypes needed to account for 80% of IPD (15, of which 4 are non-PCV13 serotypes). In this region, the only two serotypes included in PCV formulations that were not among the leading serotypes were 4 and 18C. Europe was the region with a greater diversity of non-PCV13 serotypes among the leading serotypes (in decreasing ranking: 15BC, 10A, 12F, 22F, 24F, 33F, 15A).

Figure 18 Proportional contribution of vaccine serotypes (by category) and the top ten non-PCV13 serotypes to childhood IPD after highly valent PCVs implementation by world region



Notes: NT – not typable isolates

Table 23 Ranking of leading serotypes accounting for 80% of IPD post-highly valent PCVs by world region

Rank	Overall	North America	Europe	Western Pacific	Latin America	Eastern Mediterranean	Africa
1	19A	19A	19A	19A	19A	23F	Other*
2	15BC*	15BC*	15BC*	15BC*	14	6B	NT*
3	3	22F*	10A*	3	3	14	19A
4	14	7F	3	22F*	6B	Other	23F
5	1	3	7F	15A*	6A	19F	1
6	19F	33F*	12F*	6B	19F	6A	19F
7	Other	Other*	22F*	10A*	1	5	15BC*
8	6B	35B*	24F*	23A	15BC*	19A	6A
9	12F*	23B*	Other*	6C*	NT	15BC*	5
10	7F		1	33F*	5	1	12F*
11	NT		33F*		24F*		8*
12	22F*		15A*		23F		6B
13	10A*				7F		35B*
14	15A*				12F*		14
15	6A				9V		
16	23F*						

Table 24 Serotype-specific contributions (%) to paediatric IPD cases by region after highly valent PCVs implementation

	Overall (n=41)		North America (n=4)		Europe (n=11)		Western Pacific (n=5)		Latin America (n=13)		E Mediterranean (n=4)		Africa (n=4)	
	% (95% CI)	I^2 (%)	% (95% CI)	I^2 (%)	% (95% CI)	I^2 (%)	% (95% CI)	I^2 (%)	(95% CI)	I^2 (%)	(95% CI)	I^2 (%)	(95% CI)	I^2 (%)
PCV7	17.4 (10.1-26.3)	96.8	2.5 (1.2-4.5)	0	6.1 (0.9-16.3)	95	6.5 (0-23.4)	89.7	29.3 (18.1-42.8)	91.2	49.7 (10.4-123.4)	93	20.8 (7.8-42.8)	92.2
4	0.5 (0.2-0.9)	45.6	0.5 (0.1-1.1)	0.0	0.2 (0-1)	42.7	0.1 (0-1.4)	55.0	0.4 (0.1-0.8)	3.8	3.2 (0-10)	63.6	1.3 (0.6-2.2)	0.0
6B	3.6 (2.2-5.3)	88.4	0 (0-0)	0.0	0.6 (0-2)	73.3	3 (0-9.5)	90.8	6.3 (4.4-8.6)	71.2	11.6 (4.1-21.9)	64.7	2.9 (0.3-7.6)	85.9
9V	0.7 (0.3-1.3)	67.9	0 (0-0)	0.0	0.1 (0-0.7)	52.6	0 (0-0)	0.0	2 (1.1-3.1)	49.7	2 (0-7.5)	58.0	0.4 (0-1.5)	41.8
14	5.4 (3.2-8.1)	93.6	0.1 (0-0.5)	0.0	1.8 (0.1-4.9)	88.8	1.1 (0-3.3)	67.0	12.1 (7.8-17.2)	90.8	11.1 (4.8-19.3)	49.2	2.6 (0.1-7.5)	88.0
18C	0.7 (0.3-1.2)	59.7	0 (0-0)	0.0	0.3 (0-0.9)	10.5	0 (0-0)	0.0	1.6 (0.9-2.5)	38.9	1.6 (0-10.6)	81.8	0.6 (0-2.5)	72.4
19F	4.2 (2.9-5.6)	80.7	1.9 (1.1-2.9)	0.0	2.5 (0.8-4.8)	78.0	2 (0-7.4)	89.5	4.5 (2.6-6.8)	79.1	6.7 (0.1-19.8)	82.3	6.2 (4.5-8.1)	9.4
23F	2.3 (1.1-3.8)	88.7	0 (0-0)	0.0	0.6 (0-2)	70.5	0.3 (0-1.7)	57.6	2.4 (1.3-3.8)	66.0	13.5 (1.3-34.3)	89.0	6.8 (2.3-13.3)	86.9
PCV10 non7	9.1 (4.8-14.4)	94.2	9 (3.4-16.7)	89.2	10.9 (4.1-21)	95.6	1.3 (0.1-3.8)	43.0	9.6 (3.2-18.9)	94.5	13.9 (2.5-35.4)	87.7	11.2 (2.2-27)	95.8
1	4.3 (2.4-6.6)	92.2	0.8 (0.3-1.5)	0.0	5 (1.5-10.2)	92.2	0.6 (0.1-1.3)	0.0	4.4 (1.3-8.9)	94.2	5.2 (0.7-12.5)	58.7	6.6 (0.4-18.6)	95.6
5	1.7 (0.7-3)	88.9	0 (0-0)	0.0	0.5 (0-1.9)	79.1	0 (0-0)	0.0	3.1 (0.8-6.5)	92.2	6.1 (1.8-12.1)	38.3	4.6 (1.8-8.4)	73.7
7F	3.1 (1.7-4.8)	89.4	8.2 (3.2-15.2)	88.9	5.4 (2.7-8.9)	82.8	0.7 (0-2.5)	55.5	2.1 (1-3.5)	67.8	2.6 (0-10.8)	74.5	0 (0-0)	0.0
PCV13 non10	31.8 (24-40.5)	93.8	34.2 (16.9-55.7)	96.1	24.2 (15.2-35.3)	91.2	50.5 (30.1-75)	90.0	31.5 (21.1-43.6)	90.5	15.1 (4.4-30.8)	0	14.5 (3.2-33.3)	87.9
3	7.5 (5.7-9.6)	85.3	7.1 (4.3-10.5)	62.2	6.7 (4.7-8.9)	52.9	9.5 (3.2-18.4)	90.0	7.9 (5.6-10.6)	75.5	2.8 (0.5-6.2)	0.0	2 (1-3.2)	8.8
6A	2.3 (1.2-3.7)	87.1	0.5 (0-1.3)	19.0	0.5 (0-1.6)	58.9	0 (0-0)	0.0	4.8 (3-7)	74.8	6.2 (2.8-10.6)	0.0	4.8 (0.4-13)	92.9
19A	22 (17.2-27.3)	94.9	26.6 (12.6-44)	95.9	17 (10.5-24.8)	91.7	41 (26.9-56.6)	92.3	18.8 (12.6-26)	93.6	6.1 (1.1-14)	60.6	7.7 (1.7-17.2)	92.7

Notes: %: Estimates of proportional contributions to IPD in children and 95% confidence intervals (95% CI) reported are based on the random-effects model. PCV: pneumococcal conjugate vaccine, IPD: invasive pneumococcal disease

Table 25 Estimates of the proportional contribution of non-PCV13 serotypes post-highly valent PCVs implementation, by region

	Overall (n= 41)			Europe n= (11)		North America n= (4)		Latin America n=13		E Mediterranean n= (4)		Western Pacific n= 5)		Africa n= (4)	
	x	% (95% CI)	I² (%)	% (95% CI)	I² (%)	% (95% CI)	I² (%)	% (95% CI)	I² (%)	% (95% CI)	I² (%)	% (95% CI)	I² (%)	% (95% CI)	I² (%)
Non-PCV13	41	41.6 (22.6-66.3)	97.2	58.8 (22.6-116.5)	98.1	54.3 (17.6-133.4)	97.2	29.6 (12.8-56.1)	88.4	21.1 (0.5-94.2)	95.4	41.9 (14.4-105.3)	95.5	53.3 (5.2-171.5)	97.6
15BC*	34	8.4 (6.6-10.4)	79.70	10.1 (6.9-13.9)	69.40	10.4 (5.6-16.5)	82.80	4.1 (3-5.4)	38.70	5.4 (0.5-13.9)	20.20	10.3 (8.5-12.2)	0.00	5.7 (1.8-11.5)	85.60
Other*	22	4 (1.5-7.4)	96.50	5.2 (0.2-14.7)	97.30	6.3 (0.3-17.8)	96.10	0.9 (0-2.8)	87.80	8.9 (0-32.9)	92.70	0.3 (0-3.2)	87.30	11 (0.9-29.8)	97.30
12F*	28	3.2 (1.9-4.7)	85.70	5.4 (2.3-9.6)	87.50	2.3 (0.2-6.2)	85.80	2.1 (0.7-4)	83.00	1.4 (0-7.2)	66.70	0.7 (0-2.9)	68.20	4.3 (0.8-9.9)	87.10
NT*	19	3.1 (1.3-5.5)	94.30	1.6 (0-6.4)	94.90	0 (0-0)	62.80	3.3 (1-6.7)	92.40	2.6 (0-16)	88.50	2.3 (0.1-6.5)	83.10	10.7 (0-35.7)	98.40
22F*	25	2.9 (1.7-4.4)	86.30	5.4 (3.5-7.7)	61.90	8.3 (5.2-12.1)	64.60	1 (0.4-1.8)	51.50	0 (0-0)	0.00	4.6 (1.2-9.8)	83.00	0 (0-0)	0.00
15A*	28	2.6 (1.6-3.8)	80.00	3.2 (1.3-5.8)	78.50	2.4 (0.2-6.5)	86.20	1.6 (1-2.3)	15.60	0 (0-0)	0.00	3.9 (0.6-9.3)	85.70	1.8 (0-7.8)	92.70
10A*	26	2.6 (1.5-4)	85.00	6.9 (3.6-11.1)	85.50	0.9 (0-3.9)	86.20	1.5 (1-2.1)	6.20	0 (0-0)	0.00	2.4 (0.8-4.6)	48.30	1.3 (0-5.7)	89.10
24F*	20	2.2 (0.8-4.1)	92.90	5.3 (1.6-10.8)	92.70	0 (0-0)	0.00	2.7 (0.9-5.2)	87.80	0 (0-0)	0.00	2.2 (0-11.4)	95.40	0 (0-0)	0.00
33F*	25	1.9 (0.9-3.2)	85.00	3.8 (1.1-7.7)	88.40	6.4 (2.2-12.5)	10.50	0.4 (0-1.4)	12.60	0 (0-0)	0.00	2.3 (0.3-5.6)	91.20	0.3 (0-1.9)	50.50
23B*	21	1.9 (0.9-3.1)	87.10	2.4 (0.4-5.6)	89.20	3.2 (2.1-4.5)	87.80	1.6 (1-2.3)	76.70	0.4 (0-2.4)	0.00	1.6 (0-7.2)	75.20	0.1 (0-1.2)	72.20
6C	26	1.6 (0.9-2.5)	73.00	1.5 (0.6-2.6)	38.30	2.4 (1.3-3.8)	22.50	2 (0.8-3.5)	74.40	0 (0-0)	0.00	2.4 (1.2-3.9)	19.30	0 (0-0)	0.00
8	25	1.6 (0.8-2.7)	82.50	2.5 (0.5-5.6)	86.50	0.5 (0-1.8)	59.80	1.2 (0.7-1.9)	21.30	0.4 (0-2.4)	0.00	0.6 (0-1.9)	37.90	3.3 (0-11.2)	93.70
11A	26	1.1 (0.6-1.8)	61.00	1.1 (0.6-1.8)	58.00	0.7 (0-3.4)	64.60	1.8 (1.1-2.7)	18.60	0 (0-0)	6.20	0.5 (0-2.7)	45.20	0.2 (0-1.9)	72.20
23A	23	1.1 (0.6-1.7)	64.40	0.6 (0-1.7)	0.70	1.6 (0.3-3.6)	85.10	0.9 (0.4-1.5)	34.60	0.3 (0-2.4)	2.60	2.4 (0.9-4.5)	73.40	0.3 (0-1.9)	72.20
35B	19	1 (0.4-1.8)	78.50	0.4 (0-1.3)	55.90	3.3 (0.2-9)	90.80	0.5 (0-1.4)	71.40	0 (0-0)	0.00	1.4 (0.4-2.8)	27.30	2.9 (0-11.4)	94.80
9N	20	0.7 (0.3-1.2)	47.50	0.3 (0-1.3)	66.10	0.5 (0.1-1.1)	0.00	0.9 (0.4-1.6)	31.20	0 (0-0)	0.00	0.9 (0-2.6)	50.80	1.8 (1-2.8)	0.00
38	14	0.6 (0.1-1.4)	84.90	1.3 (0-4)	88.00	2.3 (0-7.8)	91.90	0.1 (0-0.8)	80.00	0 (0-0)	0.00	1.6 (0.5-3.1)	29.30	0 (0-0)	0.00
16F	19	0.5 (0.1-1)	64.50	0.4 (0-1.2)	51.50	0.4 (0-1.9)	67.70	0.6 (0.1-1.4)	51.40	0 (0-0)	0.00	0.1 (0-0.7)	31.90	2.4 (0-9.5)	93.70
7C	14	0.2 (0-0.6)	36.40	0 (0-0)	65.90	0.1 (0-2)	30.20	0.4 (0.1-0.8)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	2 (0.4-4.5)	28.30
34	14	0.1 (0-0.4)	46.50	0 (0-0)	0.00	0.1 (0-2)	61.50	0.1 (0-0.4)	16.30	0 (0-0)	0.00	0.1 (0-0.8)	0.00	0.9 (0.1-2.2)	66.00
17F	13	0.1 (0-0.3)	14.80	0 (0-0)	18.80	0.1 (0-0.5)	0.00	0.3 (0.1-0.6)	0.00	0 (0-0)	0.00	0.1 (0-0.6)	0.00	0.7 (0-3.4)	84.00
21	13	0.1 (0-0.3)	39.80	0.4 (0-1.3)	57.80	0.1 (0-1.3)	71.20	0 (0-0)	0.00	0 (0-0)	0.00	0.3 (0-0.9)	0.00	0.5 (0-2.7)	78.10
35F	14	0.1 (0-0.3)	20.00	1 (0.1-2.4)	0.00	0.2 (0-1.1)	0.00	0 (0-0)	25.40	0 (0-0)	2.60	0.2 (0-0.7)	0.00	0 (0-0)	0.00
10	14	0 (0-0)	21.70	0 (0-0)	0.00	0.2 (0-2.2)	61.50	0 (0-0)	25.10	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	34.40
10B	11	0 (0-0)	23.30	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	43.90
10F	9	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	2.50	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
10FC33C	7	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	25.80	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	45.00
11	7	0 (0-0)	25.00	0 (0-0)	0.00	0.2 (0-2)	0.00	0 (0-0)	33.80	0.1 (0-2)	0.00	0.1 (0-1.5)	0.00	0 (0-0)	0.00
11AD	7	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	62.90	0 (0-0)	0.00
11B	7	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
11BC	5	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	37.80	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
11F	5	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
12	5	0 (0-0)	0.00	0 (0-0)	0.00	0.3 (0-2.8)	0.00	0 (0-0)	0.00	0 (0-0)	60.40	0 (0-0)	0.00	0 (0-0)	80.20
12A	5	0 (0-0)	3.20	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	40.10	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
12B	5	0 (0-0)	0.00	0 (0-0)	26.10	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
12FB	5	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	1.3 (0-8.3)	0.00
13	4	0 (0-0)	17.90	0 (0-0)	0.00	0 (0-0)	81.00	0.3 (0.1-0.6)	0.00	0 (0-0)	0.00	0 (0-0)	77.50	1.1 (0.2-2.5)	0.00
13/28	4	0 (0-0)	32.90	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	6.20	0 (0-0)	85.90	0 (0-0)	77.90

	Overall (n= 41)			Europe n= (11)		North America n= (4)		Latin America n=13		E Mediterranean n= (4)		Western Pacific n= 5)		Africa n= (4)	
	x	% (95% CI)	I² (%)	% (95% CI)	I² (%)	% (95% CI)	I² (%)	% (95% CI)	I² (%)	% (95% CI)	I² (%)	% (95% CI)	I² (%)	% (95% CI)	I² (%)
15	4	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	4.30	0.3 (0-2.4)	38.80	0.4 (0-3.6)	0.00	0.2 (0-1.7)	0.00
15AF	4	0 (0-0)	41.60	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	73.60	0 (0-0)	6.20	0 (0-0)	0.00	0 (0-0)	0.00
15CF	4	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	22.20	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
15F	3	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
16	3	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
17	3	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
18A	3	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0.4 (0.1-0.9)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
18B	3	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	1.50	0 (0-0)	0.00
18F	3	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0.3 (0-3.3)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
19B	3	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	33.30	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
19C	3	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
2	2	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	77.10	0 (0-0)	0.00	0.6 (0-4.9)	0.00	0 (0-0)	14.10	0.3 (0-2.4)	0.00
20	2	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0.4 (0.1-0.9)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	11.80
22	2	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	83.90	0 (0-0)	0.00	0.1 (0-2)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
22A	2	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	43.20	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	41.20	0 (0-0)	0.00
22F/A	2	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	43.20	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	14.10	0 (0-0)	0.00
23AB	2	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
24	2	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	45.10	0.3 (0-2.4)	0.00	0.1 (0-0.7)	0.00	0 (0-0)	0.00
24A	2	0 (0-0)	44.20	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	80.10	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
24ABF	2	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0.1 (0-1.6)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
24B	2	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0.1 (0-1.3)	0.00	0 (0-0)	0.00
24C	2	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	67.30
25A	2	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	71.20	0.2 (0-0.7)	0.00	0 (0-0)	0.00	0 (0-0)	1.50	0 (0-0)	0.00
25F38	2	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
27	2	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
27B	2	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
28	2	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
28A	2	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0.1 (0-0.3)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
28F	2	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
28FA	2	0 (0-0)	34.10	0 (0-0)	0.00	0 (0-0)	90.90	0 (0-0)	31.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
29	2	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0.1 (0-0.4)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
3/16F	2	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	51.10	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
31	1	0 (0-0)	0.00	0 (0-0)	0.00	0.1 (0-0.5)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
32F	1	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
33	1	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
33/35	1	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
33A	1	0 (0-0)	44.50	0 (0-0)	0.00	0.4 (0-1)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	94.90
33B	1	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
33C	1	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
33D	1	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	14.10	0 (0-0)	0.00
33FA	1	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0.2 (0-1.5)	0.00

	Overall (n= 41)			Europe n= (11)		North America n= (4)		Latin America n=13		E Mediterranean n= (4)		Western Pacific n= 5)		Africa n= (4)	
	x	% (95% CI)	I² (%)	% (95% CI)	I² (%)	% (95% CI)	I² (%)	% (95% CI)	I² (%)	% (95% CI)	I² (%)	% (95% CI)	I² (%)	% (95% CI)	I² (%)
33FA37	1	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
35	1	0 (0-0)	0.00	0 (0-0)	0.00	0.1 (0-1.3)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
35A	1	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
35AC42	1	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
35BF	1	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
35C	1	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
35F47F	1	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
37	1	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
39	1	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
42	1	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
46	1	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
47	1	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
48	1	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
6D	1	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00
7A	1	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	11.80
7B	1	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00	0 (0-0)	0.00

3.5.3.3 Quality assessment

The quality of 50 peer-reviewed studies was assessed (Table 26). The majority of publications (n=43, 86%) were of high quality. However, the quality of ten of these was borderline medium as there were three categories for which the answer was "No" or "unclear". Most studies (n=45, 90%) did not describe the study subjects or study setting in detail. This question (#4) was assessed separately to highlight the limitations of the data. Another common shortcoming identified among studies is that it was unclear if the analysis had been conducted with sufficient coverage (e.g., information on the percentage of IPD isolates that were serotyped or information on coverage of the surveillance).

Table 26 Quality assessment of studies reporting proportion-based data for serotypes in the study periods after PCV implementation

Reference	1. Was the sample frame appropriate to address the target population?	2. Were study participants sampled appropriately ?	3. Was the sample size adequate?	4.1 Were the study subjects described in detail?	4.2 Was the study setting described in detail?	5. Was the data analysis conducted with sufficient coverage of the identified sample?	6. Were valid methods used for the identification of the condition?	7. Was the condition measured in a standard, reliable way?	8. Was the statistical analysis appropriate?	9. Was the response rate adequate?	Overall appraisal of quality
Post-PCV7											
Mokaddas (2018)	Yes	Yes	Yes	No	No	Yes	Yes	Unclear	Yes	Yes	High
Rendi-Wagner (2009)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	High
Lepoutre (2015)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	High
Varon (2015)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	High
van der Linden (2015)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	High
Knol (2015)	Yes	Yes	Yes	No	No	No	Yes	Unclear	Yes	Yes	High
Steens (2013)	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	High
Aguiar (2008)	Unclear	Unclear	NA	Unclear	Unclear	Unclear	Yes	Yes	No	Unclear	Low
Aristegui (2007)	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	No	High
Barricarte (2007)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	High
Calbo (2006)	Unclear	Yes	Unclear	No	Yes	Yes	Yes	Unclear	No	Yes	Medium
Guevara (2014)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Munoz-Almagro (2011)	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	High
Perez-Trallero (2009)	Yes	Yes	NA	No	No	Unclear	Yes	Yes	Yes	Yes	Medium
Rodriguez (2011)	Yes	Yes	Yes	No	No	Unclear	Yes	Yes	No	Unclear	Medium
Salleras (2009)	Yes	Yes	Yes	No	No	Unclear	Unclear	Yes	Yes	Yes	High

Reference	1. Was the sample frame appropriate to address the target population?	2. Were study participants sampled appropriately ?	3. Was the sample size adequate?	4.1 Were the study subjects described in detail?	4.2 Was the study setting described in detail?	5. Was the data analysis conducted with sufficient coverage of the identified sample?	6. Were valid methods used for the identification of the condition?	7. Was the condition measured in a standard, reliable way?	8. Was the statistical analysis appropriate?	9. Was the response rate adequate?	Overall appraisal of quality
Ceyhan (2016)	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	No	High
Miller (2011)	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	High
Parra (2013)	Unclear	Unclear	Unclear	No	Yes	Unclear	Unclear	Unclear	Yes	Unclear	Low
Luna-Muschi (2019)	Yes	Yes	No	No	No	No	Yes	Yes	Yes	Yes	High
Bettinger (2010)	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	High
De Wals (2012)	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	High
Black (2007)	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	High
Bruce (2015)	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	High
Kaplan (2013)	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	High
Pilishvili (2010)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	High
Sharma (2013)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	High
Weatherholtz (2010)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	High
Williams (2011)	Yes	Yes	Yes	Yes	No	Yes	Unclear	Unclear	Yes	Yes	High
Chiba (2014)	Yes	Yes	Yes	No	No	No	Yes	Yes	No	Unclear	Medium
Suga (2015)	Yes	Yes	Yes	Yes	No	Unclear	Yes	Yes	Yes	Yes	High
Post-highly valent PCV											
Diawara (2015)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	High
del Amo (2014)	Yes	Yes	Yes	No	Unclear	No	Yes	Yes	Yes	Yes	High
Kambire (2008)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
von Gottberg (2013)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes		High
Cohen (2017)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	High
Al-Sheikh (2014)	Yes	Yes	NA	Unclear	Unclear	Unclear	Yes	Yes	No	Unclear	Medium
Shibl (2012)	Yes	Yes	Yes	No	Yes	Unclear	Yes	Yes	Yes	No	High
Fennoll (2015)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Unclear	High
Ceyhan (2016)	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	No	High
Waight (2015)	Yes	Yes	Yes	No	Yes	Yes	Yes	Unclear	Yes	Yes	High
Ladhani (2018)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	High
Demczuk (2013)	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	High
Moore (2015)	Yes	Yes	Yes	No	Yes	Unclear	Yes	Yes	Yes	Yes	High
Nakano (2015)	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	High
Su (2015)	Yes	Yes	Yes	No	Yes	Unclear	Yes	Yes	Yes	Yes	High
Lepoutre (2008)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	High

Reference	1. Was the sample frame appropriate to address the target population?	2. Were study participants sampled appropriately ?	3. Was the sample size adequa te?	4.1 Were the study subjects described in detail?	4.2 Was the study setting describe d in detail?	5. Was the data analysis conducted with sufficient coverage of the identified sample?	6. Were valid methods used for the identification of the condition?	7. Was the condition measured in a standard, reliable way?	8. Was the statistica l analysis appropri ate?	9. Was the respon se rate adequa te?	Overall appraisal of quality
Levy (2011)	Yes	Yes	Yes	No	Yes	Unclear	Yes	Yes	Yes	Yes	High
Hernandez-Bou (2018)	No	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	Medium
del Amo (2015)	Yes	Yes	Yes	No	Unclear	No	Yes	Yes	Yes	Yes	High

3.6 Discussion

In this chapter, I examined the impact of highly valent PCVs on childhood IPD with a focus on the role and contribution of serotypes. I found that the introduction of PCV13 and/or PCV10 has resulted in a consistent and considerable reduction of IPD among young children. The decreases in the incidence of IPD have been driven by declines of cases due to targeted serotypes. Less consistently, there was evidence on a potential lag between PCV introduction and increases of non-PCV13. Based on data from various settings implementing highly valent PCVs it is possible to obtain pooled estimates of the contribution of serotypes categories to IPD. However, in its majority, these estimates should be interpreted with caution as their reliability is limited due to the high heterogeneity. Thus the proportion from individual settings is also reported. Approximately less than half of childhood IPD cases (42%) are caused by non-PCV13 serotypes, but in the included studies their proportional contribution ranged widely (from 5.6% to 85.8%). These results respond directly to a gap in the global health literature by pooling data from different settings to document the impact of highly valent PCVs and emerging challenges associated with the available formulations.

3.6.1 Impact of highly valent PCVs on the incidence of childhood IPD

I first aimed to estimate the impact of highly valent PCVs on the incidence of childhood IPD. To present the results, I initially focused on the evidence from settings that implemented PCV13, followed by a discussion on the evidence for PCV10-implementing settings.

PCV13

Introduction of PCV13 into national immunisation programmes, between 2010 and 2011 in the settings analysed, resulted in a greater than 40% overall reduction in IPD incidence in both children under two and under five years old. This estimate did not change when the analysis was restricted to studies from similar settings (HIC) evaluating similar post-PCV13 follow-up period (from the year of introduction up to three or four years of introduction) for children under five years of age (Figure 15). However, the pooled estimate for children under

two years indicated a lower reduction in the overall incidence (33%). It included the possibility of no overall protective effect as confidence intervals included the null value (95% CI: -1 to 56%) (Figure 10). As the studies included in each meta-analysis differed in terms of populations and study periods, it is not possible to conclude the estimates from this meta-analysis suggest age-related differences. Additionally, considering that the direction and magnitude of the effect are similar, the discrepancy in results by age groups may be due to the low number of studies included in the meta-analysis for children under two years (n=4) and resulting in large confidence intervals. Other findings associated with the role of age on the impact of PCV13 is discussed later in this section.

For children under five years, the overall pooled reduction of IPD was within the range of the reductions seen post-PCV7 and post-highly valent PCVs in other analyses. For instance, the 40% reduction is within the range of the reductions of childhood IPD in HIC estimated in post-PCV7 years one through seven compared to pre-PCV years (range point estimates of rate ratios: 0.33–0.55) (Feikin et al., 2013). The estimate presented here is also within the range of the pooled IRR for the years after PCV7 introduction compared to four years after the introduction of highly valent PCVs in seven European countries (IRR: 0.53 [95% CI: 0.43–0.65]) (Savulescu et al., 2017). It is worth noting that heterogeneity in terms of I^2 was high in the estimates in this review, similar to the heterogeneity in other meta-analyses of PCV impact (Feikin et al., 2013, Savulescu et al., 2017).

When assessed by serotype categories, the declines in the incidence of childhood IPD were mainly associated with the impact on PCV13-type IPD. A decline of over 70% in both age groups analysed (73% and 75% in children under two years and five years, respectively) was consistently reported across individual settings (as shown in Figure 7 and Figure 12). However, it is worth highlighting the disproportionate burden of preventable IPD in resource-limited settings despite PCV implementation. For instance, for children under five, in seven settings (out of 13 analysed), the average incidence rate of PCV13-IPD was ≤5 per 100,000 children. In the remaining six, including the three resource-

limited settings identified, incidence rates of preventable IPD were 2 to 15 times higher. The comparable protective effect of PCV13 across settings is valuable information to support the introduction and continuation of the immunisation programmes for the prevention of IPD in children. Furthermore, this review underscores the need for population-based research in resource-limited settings and from PCV7-naïve settings to inform public health policy in relation to PCVs. Without data from these settings, the impact of PCV13 may be underestimated (depending on the serotype distribution in the absence of prior use of PCV7) or overestimated (if only data from settings with high PCV uptake are considered).

In this review, I found evidence of increases of IPD due to non-PCV13 types when data from all settings are pooled together, even though increases were not reported consistently in individual settings. The summary estimates for the change of non-PCV13 IPD indicate there was evidence in support of an increase among children under two (of 32% [95% CI: 14–53]). Though direct comparisons between age groups were not possible, because different studies were included, a smaller effect in the same direction for children under five years than for children under two years was estimated, and the confidence interval included the possibility of no effect (14% [95%CI: -5–37]). There are two aspects to consider when interpreting these results: the likely lag between vaccine introduction and replacement in IPD and the interaction between host-related factors and vaccine uptake (dependent on age).

The lag between PCV introduction and increases in IPD due to non-PCV13 serotypes were also noticed after PCV7 use. After PCV7 it was suggested the lag was most likely related to the time it took the prevalence of serotypes in carriage to reach a steady-state as non-PCV7 serotypes replaced targeted serotypes by the vaccine (Weinberger et al., 2011). It was estimated that it would take approximately 14 years to reach a 90% reduction of PCV13non10 serotypes among young children (Shiri et al., 2017). Settings where increases of non-PCV13 IPD have occurred after highly valent PCVs are implemented concur with the observations regarding serotype replacement after PCV7 implementation (Feikin et al., 2013). The increases in incidence started to

occur after ~4 to 5 years after the vaccine's implementation, their magnitude varied by site. However, in all sites, these were not sufficient to offset overall IPD reductions. In this review, the sensitivity analysis indicated there was no evidence of serotype replacement within the initial three years of PCV13 use as the estimate included the possibility no effect of the vaccine on incidence of non-PCV13-IPD. Furthermore, of the studies included reporting data for after the fourth year post-PCV10/13 (n=5), the lag was evidenced in the UK and Sweden, the two studies for which comparison of pre- and post-highly valent PCVs incidence rates were possible. Data on the change of incidence of non-PCV13 in Germany, Canada, or the USA could not be evaluated analytically but are discussed below.

Serotype replacement in IPD due to non-PCV13 has been hypothesised to be driven by different factors, including vaccine uptake (which is age-dependent). Wijayasri and colleagues (2019) assessed changes in trends for the categories: unique PPV23 and remaining non-preventable serotypes among infants (<1 year) and older children (1–4 years). They reported a significant increasing trend (based on p-value <0.001) of IPD due to unique PPV23-type IPD in children under one year in Ontario, Canada over the eight years of PCV implementation. Conversely, no significant trend of PPV23-type IPD was identified among those 1–4 years old. For the remaining non-PCV13 serotypes, they found the opposite: a significant increase among 1–4 years old but not significant among infants (p=0.58). The increases in incidence for non-PCV13 serotypes in Ontario was greatest in older adults. In Germany, Weinberger et al. (2018) describe a steep increase of non-PCV13 IPD among infants and fluctuations for other age groups. Ladhani et al. (2018) found increases of similar magnitude of non-PCV13 IPD in both children under two and those aged two to four years in the UK when comparing the incidence rate of the sixth year post-PCV13 to the pre-PCV13 average annual rate.

Given that vaccine uptake is dependent on age, it is difficult to assess the role of age alone, mostly from aggregated data. Nonetheless, as PCV programmes mature globally, findings from this review illustrate the need to develop robust estimates of the impact of PCV13 on childhood IPD and to monitor serotype

replacement in different countries. There are a few considerations and recommendations which are presented in the general discussion of the thesis to achieve this goal.

PCV10

Only three studies reporting at least three years of incidence rate data, by serotypes categories, were identified. The fourth study only reported data for the first two years of post-PCV10 vaccination. In the three studies from Europe, the incidence of all-type IPD decreased by over 70% by the end of the study period assessed. A particular concern in settings implementing PCV10 is the potential for an increase in the incidence of serotype 19A-IPD, as this serotype is unique to PCV13 and has, in some settings, quickly increased after PCV7 implementation. In the three studies from Europe, after long-term use of PCV10, the incidence of 19A-IPD in children has fluctuated without an apparent increase or decrease.

Furthermore, there was no evidence of an increase of non-PCV10 serotypes in the study periods reported. As discussed for post-PCV13 settings, more data – disaggregated by important host-related factors - are valuable to understand better the impact of PCVs and the potential for serotype replacement to occur in different populations. For instance, in a PCV10 setting (Austria), there was a reduction of PCV10-IPD in children under two (IRR 0.23; 95% CI: 0.11–0.47), but for children 2–4 years, the estimate included the possibility of no effect as the CI for the IRR included the null value (IRR 0.96; 95% CI 0.44–2.08) (Richter et al., 2019). The consistent and high percentage of decrease in incidence rates in PCV10-implementing settings without a clear predominant serotype is useful information which can support decision making in terms of vaccine choice in different countries.

The other study reporting incidence rates of IPD after PCV10 introduction was conducted in Morocco. Morocco is the only country in the Eastern Mediterranean region that has introduced this formulation (WHO, 2019a). The short period of PCV10 implementation in this study limits the conclusions that can be drawn regarding vaccine impact. It will be essential to consider that

specificity of Morocco in the future to assess the impact of PCV10. Moreover, the synthesis of the impact of PCV10 in this review mainly reflects the experience in HIC with high vaccine uptake. Countries in Africa and Latin America that introduced PCV10 did so between 2010 and 2013 (IVAC, 2018). High-quality studies from PCV10-implementing countries in these regions (6 countries in each) are needed to understand the long-term impact of this formulation, to monitor serotype replacement in IPD by 19A or other non-PCV10 serotypes, and to assess vaccination strategies.

3.6.2 The proportional contribution of serotypes to childhood IPD

The second question I aimed to explore in this Chapter was regarding the proportional contribution of serotypes to childhood IPD after widespread implementation of PCV programmes globally. The most important finding of this review for global health is the evidence and estimates of increasing differences in the serotype epidemiology post-PCV across world regions among children.

Before any PCV was introduced, it was estimated that PCV7-targeted serotypes accounted for 49−82% of childhood IPD (Johnson et al., 2010). In this analysis, I found that, after PCV7 introduction, the proportional contribution of PCV-targeted serotypes was 23% (with confidence intervals from 14 to 35%). This estimate, though affected by high heterogeneity, is consistent with other regional estimates; for instance, prior to the introduction of highly valent PCVs in Europe PCV7-type IPD was approximately 19% among children based on data from 26 countries (Navarro Torne et al., 2014). The estimate is higher than the previous estimate by the author of this thesis, yet within the same range (14.8%; 95% CI: 11.4–19.1) (Balsells et al., 2017). It is important to note several differences exist between the present analysis and the prior iteration of this work that have strengthened the validity of studies (which are summarised in section 3.6.4 of this discussion).

Subsequent to the introduction of higher valent PCVs, the estimated proportional contribution of serotypes targeted by PCVs was 17% (95% CI:

10.1–26.3), but this pooled estimate should be interpreted with caution due to high levels of heterogeneity. Direct comparisons are not possible between this and the estimate from the post-PCV7 period as different studies were included. The estimate for post-highly valent PCVs included more data points (41 data points vs 32). Regional meta-estimates show that the burden of PCV7-IPD is disproportionately concentrated in regions with LMIC (Latin America, Eastern Mediterranean, and Africa) which have in common shorter post-vaccine follow-up periods than in other regions with mainly HIC. The post-highly valent PCVs settings represented in this review had implemented PCV7 prior to introducing PCV10 or PCV13 introduction (only three were PCV7 naïve). More information, which was not available from all studies, is needed to determine the extent to which these PCV7-IPD cases are due to vaccine failures or associated with low vaccine coverage during the years reported.

Concerns exist about optimum prevention of PCV13-types 3 and 19A−IPD in young children. I estimated that serotype 3−specific contribution to childhood IPD was approximately 6−7% in both the post-PCV7 and post-highly valent PCV periods analysed. These estimates remained unchanged from previous results, despite differences in approaches (Balsells et al., 2017). This result is noteworthy, as serotype 3 has been associated with cases of vaccine failure (Oligbu et al., 2016a). Additionally, studies about PCV13 effectiveness against serotype 3 have produced inconsistent results, which is likely associated with the physical properties that enable it to evade the host's immune response effectively and rapidly waning antibody response following vaccination (Sings et al., 2019, Linley et al., 2019). I found that serotype 3 is among the top five serotypes causing childhood IPD in North America, Europe, Western Pacific (the regions with the most extended history of PCV programmes) and Latin America (but not Eastern Mediterranean region or Africa) (Table 23). In light of its global role in IPD and other pneumococcal diseases, this review provides evidence for the need for research on the lack of vaccine efficacy against serotype 3 so that future vaccine formulations can be improved and decrease the burden of disease associated with this serotype.

The meta-estimates presented in this thesis also show the extent of 19A's predominant contribution to childhood IPD in different world regions after the introduction of PCVs. After the introduction of PCV7, 19A was consistently identified as the most frequent serotype associated with childhood IPD cases in North America, Europe, and Western Pacific regions (causing 20% to 40% of cases). Serotype 19A remained the leading serotype in these regions, and Latin America, when data for post-highly valent PCVs periods introduced were pooled. Taken together, the estimates on the impact of PCV13 and proportional contribution of individual serotypes are in line with reports from other studies. In the USA, significant reductions of IPD after five years of use of PCV13 have been driven by decreases in 19A (Pilishvili et al., 2016). However, in other settings in Europe, this serotype continues to pose challenges as a disease-causing strain despite widespread use of PCVs (Fry et al., 2016, Corcoran et al., 2016). Differences in vaccine schedules and catch-up campaigns between settings, as well as time required to observe a decrease in disease due to vaccine-targeted strains, are key factors that will influence the epidemiology of *S. pneumoniae* types (Weinberger et al., 2011). The estimated contributions of serotypes to childhood IPD in this study emphasise the need for a better understanding of factors associated with disease due to vaccine types, especially as PCV10 and PCV13 continue to be administered worldwide.

Knowledge of the serotypes that are associated with IPD among the target population is important to assess the need for the development of new vaccines that extend protection against non-PCV13 serotypes. I found that after the introduction of higher valent PCVs in North America, Western Pacific, Europe, and Latin America between 25%–50% of childhood IPD cases were due to serotypes for which there is no protection via PCVs. The serotypes likely to provide further reductions in disease in the two regions with greatest representation of non-PCV13 IPD are 15BC, 22F, 33F, 35B, and 23B (31% combined) in North America and 15BC, 10A, 12F, 22F, 24F, 33F, and 15A (accounting for 40% of IPD) in Europe. Some of these serotypes are included in PPSV23 (10A, 12F, 15BC, 22F, and 33F). Thus, to some extent, these

cases are vaccine-preventable, if the disease is mostly happening among high-risk children for whom this vaccine is recommended. However, there is evidence to suggest that these serotypes are likely to affect previously healthy children. For instance, 12F, 22F, 24F, and 33F have been identified to have high invasive disease potential (Varon et al., 2015, Yildirim et al., 2010). Studies have also shown that 15B/C/A, 23B, 24F, and 35B are not only important causes of IPD but also are common nasopharyngeal colonisers and have a high prevalence of antibiotic resistance (Camilli et al., 2013, Kim et al., 2016, Lee et al., 2014, Metcalf et al., 2016, van Hoek et al., 2014). Next-generation PCVs with either an expanded serotype coverage or with a different formulation for dominant serotypes in different regions will be needed to reduce the remaining burden of IPD considering the contribution of non-PCV13 serotypes estimated in this analysis.

Though there were no studies reporting incidence data at the population level from Latin America, I analysed proportion-based data from 13 countries in this region. All data are from SIREVA surveillance systems, of which five currently use PCV10. In Latin American countries, 1,500,000 cases and 28,000 deaths of IPD were estimated to occur annually in children less than five years of age in Latin America prior to PCV introduction (Valenzuela et al., 2009). A large proportion, over half, of IPD cases in the region was associated with a serotype included in the current formulations of PCVs. Given the predominant role of vaccine types in IPD, the expansion of immunisation programmes with PCVs and surveillance of epidemiological changes is critical to reduce the burden of preventable IPD and to monitor potential serotype replacement in Latin American countries.

Before and after PCVs became available, the highest proportion of deaths associated with childhood IPD were estimated to occur in Africa and South-East Asia (O'Brien et al., 2009, Wahl et al., 2018). To date, the majority of African countries have introduced PCVs into their national immunisation programme. However, issues regarding achieving high uptake by two years post-introduction were identified and, worryingly, over half of the countries were found to experience declines in coverage between years two and four

post-introduction (Olayinka et al., 2017). I only identified serotype data suitable for inclusion for two countries from this region –South Africa and Burkina Faso. Notably, serotype 8, which contributed to approximately 3% of childhood IPD was among the leading serotypes in this region, but not in others. In South-East Asia, progress in introducing PCVs has been slow, and a limited number of countries are implementing vaccination programmes. In this review, I did not identify studies from this region that met the inclusion criteria. A recent systematic review of serotypes associated with IPD found that 1, 14, and 19F were common in South Asian countries in the pre-PCV era (Jaiswal et al., 2014a). Evidence of the effects of PCV in countries in Asia, Africa, and Eastern Mediterranean is needed to understand and monitor the role of serotypes following PCV10 and PCV13 introduction globally, especially in settings with a high burden of *S. pneumoniae* disease.

3.6.3 Limitations

This study has some limitations that are quite typical of systematic reviews and meta-analyses. Although I sought to include large studies, datasets were heterogeneous, reported different sample sizes, observed diverse populations with varying rates of PCV coverage, immunisation schedules, and methods for case detection of IPD (either by clinical or testing practices). Estimates of IPD incidence in all of the included studies are observational studies based on data from surveillance systems. Thus, the possibility of bias due to changes in clinical practices, case reporting over time, antibiotic use or serotypes' secular trends cannot be excluded, either. These non-vaccine factors can influence the recorded rates, the number of serotype-specific infections, and confound interpretation of the relationship between PCV and serotype changes. Another limitation of this review is that I was only able to explore some evidence on the role of age (which is associated with vaccine uptake) as a factor influencing the impact of PCVs. There is evidence that immunocompromised populations appear to be at greater risk of IPD in the years after PCV was implemented, particularly due to non-PCV13 serotypes (Yildirim et al., 2015). Although this host-related factor may influence vaccine impact, studies did not report information on immunocompromised populations or provided much

information about the study population (e.g., sex, ethnicity). This absence was a consistent issue, as noted in the quality assessment. Thus, the ability to comment on host-related factors that may influence vaccine impact is limited.

Issues related to extraction of data also need to be considered. In some studies, incidence rates and numbers of cases by serotype may not be exact because some data needed to be extracted from images or calculated from proportions. In other instances, serotype data were only available in a grouped format (e.g., “other”), or not all IPD cases were serotyped. Missing information is likely to affect serotypes considered “rare” or “infrequent”, which will vary in each setting, but are more likely to be non-PCV13 serotypes. These issues can potentially introduce biases to our results since not all serotypes could be assessed individually. The meta-estimates for individual serotypes are thus not exempt from the risk of under- or over-estimation. Considering that most data are from laboratory surveillance systems or from hospital-based studies, which are prone to selection bias, the results from this meta-analysis are likely to represent an underestimate of the burden associated with individual serotypes. The external validity of the results is limited by the nature of the data in terms of sources, and the reliability of the pooled results is reduced by the high heterogeneity in the results, and the geographical distribution of the studies identified.

3.6.4 Strengths

Limitations withstanding, the analyses using incidence and proportion-based data are supported by strengths in the synthesis and analyses of data. First, analyses on the impact of first and second generation of PCVs were conducted by formulation in order to differentiate between their effects. I aimed to address issues of heterogeneity by analysing the most comparable data and case definitions. I also stratified analysis by age groups, income level, and restricted the analysis to studies with the most comparable post-PCV follow-up periods wherever possible. Second, a large number of isolates from different countries were analysed. This is a strength of the estimates of the proportional contribution of serotypes to IPD. Furthermore, estimates are strengthened by analytical choices such as computing estimates individually per serotype using

a statistical approach that allowed the inclusion of data from all settings, including where the case count was zero. In such a way, potential biases were minimised. An additional strength is presentation of normalised estimates, so that the sum of all serotypes is 100%.

3.7 Conclusion

In the post-PCV era, childhood IPD is associated with a large number of serotypes globally. A large protective impact of highly valent PCVs on childhood IPD has been consistently noted across settings. There is no evidence to rule out the possibility of serotype replacement by non-PCV13 serotypes yet. This lack of evidence is an important finding keeping in mind that non-PCV13 serotypes caused a considerable proportion of childhood IPD. Potential candidate serotypes can be identified through the results of this review, though other factors will need to be considered. Data on serotypes causing IPD from the regions with the highest burden were not available to develop estimates. The geographic diversity of serotypes and changing epidemiology of *S. pneumoniae* underscores the importance of continued surveillance of pneumococcal serotypes to guide vaccine recommendations.

4 The relative invasive disease potential of serotypes in children after the introduction of PCVs

4.1 Background

The previous chapter detailed the results of the systematic review, which summarises the evidence on the impact of highly valent PCVs on childhood IPD and provides estimates of the proportional contribution of individual serotypes by region and globally. The overall decreases in IPD after highly valent PCV use in individual settings, despite circulation and disease due to non-vaccine serotypes, would suggest that non-vaccine types have a relatively low invasive disease potential. However, the emergence of non-PCV13 IPD in some, but not all, settings after PCV13 use emphasises the need to characterise the role of non-vaccine serotypes better to inform strategies and priorities against these serotypes.

4.2 Objective

In this chapter, I aimed to estimate the invasive disease potential of *S. pneumoniae* serotypes in young children, by age and syndrome, by pooling data from different countries with routine use of PCV.

4.3 Research questions

- What is the invasive disease potential of *S. pneumoniae* serotypes in young children compared to 19A?
- What is the invasive disease potential of serotypes currently not included in PCVs compared to other non-PCV serotypes?

4.4 Methods

4.4.1 Sources of data and search methods

I identified *S. pneumoniae* serotype data from childhood carriage and IPD studies from two primary sources: published studies identified through systematic searches of electronic databases: Medline, Embase, and Global Health (Ovid), Global Health Library (WPRO, EMRO, and SEA), Web of

Science, and LILACs and data obtained via email, upon request, from investigators in different settings.

Original searches were conducted independently between October and November 2015 by the author of this thesis. A second reviewer (Struan Ducker) performed the same search independently, in accordance with PRISMA guidelines for publication of an earlier iteration of the research presented in this chapter (Balsells et al., 2018). Search strategies are available in Appendix 4. I used Datathief (http://www.datathief.org/) to extract serotype data from figures in published studies. I collected the data requested from investigators between October 2015 and May 2016. I asked for re-analysed or an extension of previously published serotype specific IPD/carriage data for the years when PCV was available in each setting, up to the year 2015 from investigators in 20 locations (3 in North America, 12 in Europe, 4 in Africa and 1 in Latin America). I invited researchers from these locations to be authors of any publication resulting from analyses performed for the study of invasive disease potential. I developed a data collection template and piloted before its final use. I maintained files and communication with investigators providing additional data.

Eligibility criteria to select studies and dataset are available in Box 2.

Box 2 Eligibility criteria to identify datasets with S. pneumoniae carriage or IPD serotype data suitable for analysis of invasive disease potential

Inclusion criteria
• Observational studies (prospective, retrospective) published between 2000−2015 • *S. pneumoniae* serotypes' data are available from carriage *and* invasive disease studies among children 0−59 months from a similar population during similar periods • The study population included children vaccinated with PCVs or from settings with wide-spread routine use of PCVs. For carriage, data had to be from healthy or not exclusively from severely sick children • IPD was defined as the identification of pneumococcus in an isolate from a normally sterile site (e.g., blood, cerebrospinal, pleural effusions, or joint fluid)
Exclusion criteria:
• The study does not report data on *S. pneumoniae* serotypes, or serotype-specific data are not reported for all carriage or IPD cases • Serotype data for either IPD or carriage are not available specifically for a period after PCV introduction • Serotype data are from study populations exclusively of immunocompromised populations or data include adults • If data overlap with other publications exists, studies with the longest study period or larger sample size are to be included • Isolates were recovered to address a specific question and high risk of bias (e.g., rates of antimicrobial resistance, severe cases) • IPD and carriage serotype data are not from similar paediatric populations • Pneumococcus recovered from nasopharynx with a diagnosis of invasive disease used as a surrogate from a normally sterile site (IPD)

4.4.2 Definitions

PCV coverage was defined as the percentage of children from carriage studies who received their age-specific PCV recommended dose. Other definitions of PCV coverage were accepted, e.g., the percentage of children who received their primary immunisation series by 12 months of age, in settings where these were the only data available.

Post-PCV years were defined as follows: in each setting, I considered the year following the introduction of PCV for which data on isolates in both IPD and carriage was available as the first year eligible for analysis. It was expected that the annual number of IPD isolates would be low in some settings, yet available for all eligible years in all settings, and carriage data would mostly be available for short periods and from cross-sectional studies. As a consequence, I included all available data from eligible years after the initial year even if carriage data were not available for every year in this period.

Serotypes' overall contributions to IPD or carriage in the combined dataset were estimated as described in the following equation:

$$IPD_i = \frac{\sum_{i=1}^{j} x_{ij}}{N} \times 100(\%)$$

; **w**here x_{ij} is the number of isolates in serotype *i* in study *j*, *j* is the index of settings, *N* is the total number of isolates serotyped in the combined dataset.

If sites evaluated multiple serotypes for morphologically distinct colonies, investigators were asked to report each serotype for which individual children tested positive separately.

Invasive disease potential (OR) was estimated using the following formulas:

$$\boldsymbol{OR} = \left(\frac{a \times d}{b \times c}\right) = \frac{\textbf{number of invasive serotype X isolates} \times \textbf{number of carriage reference isolates}}{\textbf{number of carriage serotype X isolates} \times \textbf{number of invasive reference isolates}}$$

$$\boldsymbol{OR} = \frac{number\ of\ invasive\ isolates\ due\ to\ \text{non-PCV13}\ serotype\ \text{x} \times carriage\ \text{isolates of other non-PCV13 types}}{number\ of\ \text{non-PCV13 serotype}\ x\ \text{in}\ carriage\ \times\ isolates\ of\ \text{other non-PCV13 serotypes}\ in\ IPD}$$

4.4.3 Data analysis

The primary objective was to develop overall estimates of the invasive disease potential of individual serotypes compared to a reference serotype, following

the same logic as the multi-site study in the pre-PCV era (Brueggemann et al., 2004). Before PCV7 implementation, serotype 14 was most commonly identified in childhood IPD. A higher invasive disease potential than for this type would indicate the serotype/serogroup was highly invasive (Brueggemann et al., 2004). For the present analysis, the reference serotype was selected based on the same criteria used in the previous study: a) the serotype was represented in both IPD and carriage studies for all datasets, b) the serotype contributed among the largest overall proportion in both IPD and carriage datasets, c) the serotype was among the top 5 in individual datasets.

PCV13-type 19A was selected as the reference as it met the criteria for selection. However, estimating the invasive disease potential using 19A as the reference can be problematic because 1) PCV10 does not include serotype 19A and 2) since 19A is included in PCV13, it is important to consider the effectiveness and the impact of PCVs against IPD and carriage. After routine use of PCV7, 19A emerged as the most frequent serotype in childhood IPD across industrialised settings (Weinberger et al., 2011). Since most of the datasets available were from settings where PCV13 had been implemented, the choice of 19A was suitable to identify highly invasive serotypes in periods after PCV was introduced. The effectiveness of PCV ranges between 65–95% against PCV13 types IPD and ~50% against PCV13 types carriage (Cohen et al., 2017b). As both carriage and IPD due to serotypes included in the vaccine decrease over time, the role of the reference serotype will be minimised as it is directly affected by vaccine pressure. Thus, for vaccine serotypes, the invasive disease potential represents the ability of vaccine types to have breakthrough disease (or cause vaccine failure). For non-vaccine types, for which all children are unimmunised, the invasive disease potential in relation to other non-vaccine types represents the actual ability to cause disease compared to other circulating non-vaccine types in that setting. To explore these issues, I conducted the sensitivity analyses described below.

Since not all settings had IPD and carriage data for two key age groups (0–23 and 0–59 months), I developed two sets of data with strict criteria by age. The individual contribution of each serotype to IPD or carriage in each combined

dataset was estimated as described in the previous section. I restricted the meta-analyses to serotypes representing at least 1% of IPD in the combined dataset for 0–59 months.

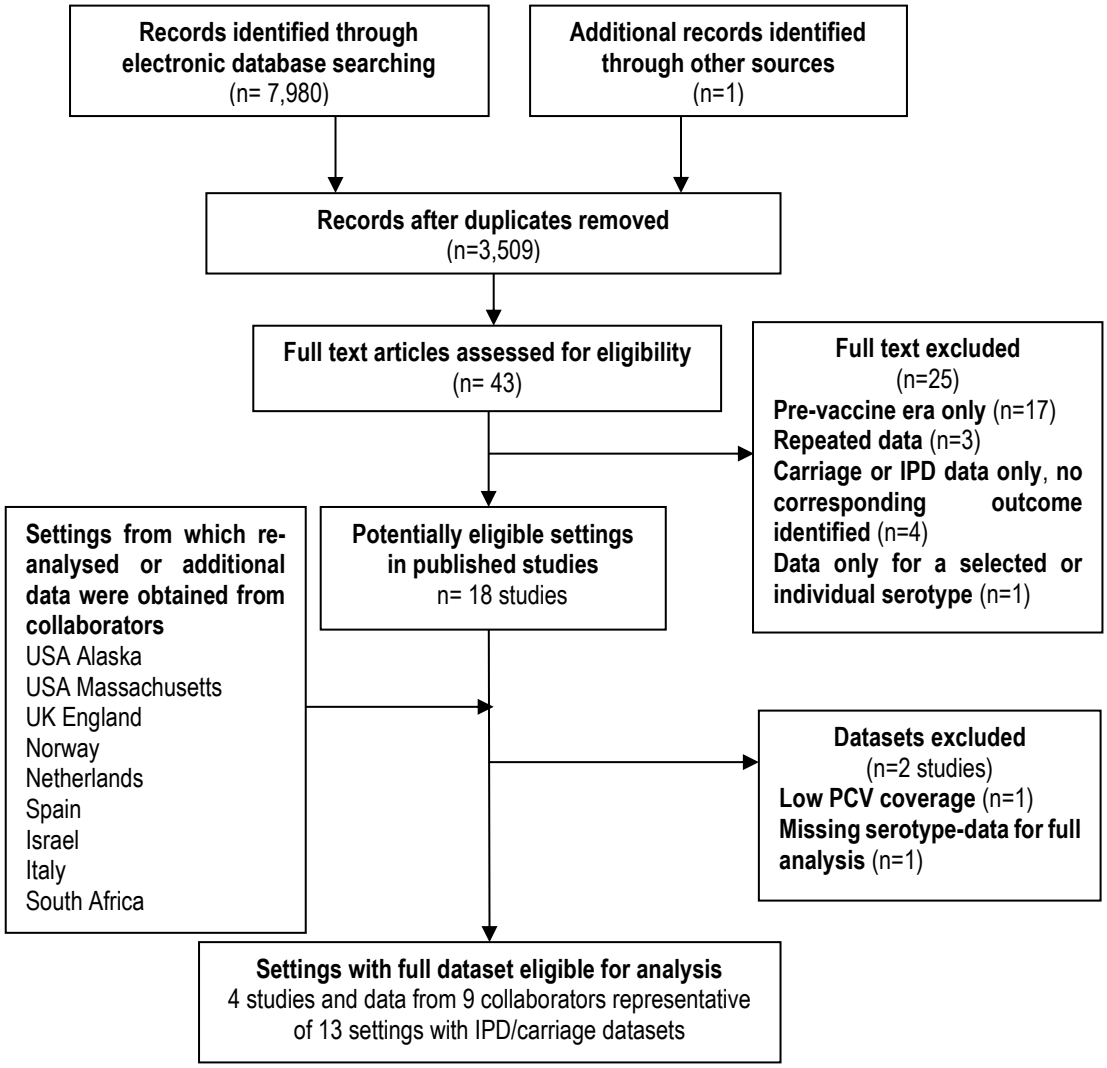
The "*metan*" command in Stata Version 13 (College Station, TX: StataCorp LP) was used to estimate serotype-specific invasive disease potential OR and 95% CI. Overall serotype-specific meta-estimates are reported if carriage or IPD data for a specific serotype were reported in at least three datasets. For a comparative analysis between narrower age groups (0–23 and 24–59 months) and across syndromes, I only included datasets that reported data for all categories.

For the main analysis of invasive disease potential in relation to a reference serotype, I conducted sensitivity analyses to explore the effect of differences on overall meta-estimates by restricting the analysis to datasets with the following characteristics: a) ≥70% PCV coverage, b) setting with a low prevalence of HIV, c) industrialised country settings, d) case counts from years after the introduction of a higher valent PCV (10/13), e) implementation of PCV10 or PCV13. In order to explore issues associated with estimating the invasive disease potential of vaccine vs non-vaccine serotypes, I use the datasets where PCV13 was implemented and compare the invasive disease potential of non-PCV13 types to each other. I excluded serotype 6C from this analysis because of cross-protection with 6A included in PCV13 (Naucler et al., 2017).

4.5 Results

The PRISMA flowchart depicts the process to identify datasets eligible for analysis. I included 13 datasets: nine included data provided by collaborators and four from published studies (Parra et al., 2013, Scott et al., 2012, Sharma et al., 2013, Varon et al., 2015).

Figure 19 Process to identify dataset to estimate S. pneumoniae serotypes invasive disease potential



The datasets included were from settings with routine use of PCVs from Europe (n=7, 53.8%), North America (4, 30.8%), Latin America (1, 7.7%), and Africa (1, 7.7%). There were no eligible datasets from South East Asia or the Western Pacific. The characteristics of IPD and carriage studies are shown in Table 27. While age groups were harmonised for the IPD and carriage data, there are differences across sites as well as within individual settings. Carriage studies included cross-sectional surveys among children in the community or different health facilities. Within individual sites, the geographical/racial overlay of carriage data (e.g., individual cities) and IPD data (entire countries) are not exact. In these cases, I aimed to obtain the carriage and IPD data that best correlated in each site and assumed that the carriage data are representative of the entire country.

Table 27 Characteristics of datasets included in the meta-analysis

	Carriage			IPD			
Setting, year PCV7 and PCV10-13 introduction	**Study design**	**Study population**	**Study period in meta-analysis**	**Study design**	**Case ascertainment**	**Study period in meta-analysis**	**Analyses dataset included**
USA Alaska†, PCV7 2001, PCV13 2009/10	Cross-sectional annual surveys	Children at urban paediatric clinics and households in rural Alaska villages. ≥80% vaccination coverage estimated from study population in carriage studies.	2002, 2003, 2004, 2008, 2009, 2010, 2011, 2012, 2013, 2014	State-wide surveillance by clinical laboratories. IPD is a reportable condition in Alaska	A positive culture from a normally sterile site from Alaska residents. IPD cases from south-east Alaska were excluded, so IPD data correlated with carriage data	2002-14, inclusive	0–59 months, 0-23 months, age groups, syndromes
USA Atlanta ABCs PCV7 2001, PCV13 2010‡	Cross-sectional survey	Children 6–59 months of age residents of the study area and who sought medical care, regardless of presenting symptom at the emergency department	2009 Jan/Aug	Continuous active population-based surveillance	A positive culture from a normally sterile site from the residents of the study area	2008Jun/09May	0–59 months,
USA Massachusetts † PCV7 2000, PCV13 2010	Cross-sectional surveys	Children attending well-child or sick visits at primary care practices in 16 (2003/04) and 8 (other study periods) communities during respiratory virus season	2003Nov/04Apr, 2006Oct/07Apr, 2008OCt/09Apr, 2010OCt/11Apr, 2013Oct/14Apr	Passive, prospective surveillance	A positive culture from a normally sterile site in Massachusetts	Oct-Sep in years 2003/04, 2006/07, 2008/09, 2010/11, 2013/14	0–23 months
USA Navajo PCV7 2000, PCV13 2010‡	Prospective longitudinal observational cohort	A representative selection of nasopharyngeal samples from the 861 first acquisition isolates from a prospective longitudinal observational cohort study of children <5 years	2006Mar-08Mar	Active surveillance of clinical microbiology laboratories	Children under five years of age who resided in the carriage cohort study communities, and who had an incident episode of IPD identified through active surveillance	2006March-08March	0–59 months,
Colombia PCV7: 2009; PCV13 ‡	Cross-sectional survey	Nasopharyngeal samples recovered at six urban areas of Bogotá from healthy children of 12 to 18 months who were vaccinated with PCV7.	2011Jun/Nov	Passive, prospective surveillance	Children ≤2 years of age diagnosed with IPD who were living in Bogotá through National Surveillance*	2010-2011	0–23 months
France PCV7: 2006; PCV13 2010	Cross-sectional surveys	Three hundred healthy children aged 6–24 months for well-baby visits among 90 paediatricians.	2008/09 and 2012/13	Prospective surveillance	Cases reported from 400 laboratories located in the 22 regions of France	2008/09 and 2012/13	0–23 months
Israel† PCV7: 2009; PCV13 2010	Prospective health-facility based surveillance.	Collection of NP among healthy children visiting the paediatric emergency or maternal and child	2010, 2011, 2012, 2013, 2014, 2015	Prospective surveillance	A positive culture from blood or cerebrospinal fluid from the entire country	2010, 2011, 2012, 2013, 2014, 2015	0–59 months, 0–23 months, age groups, syndromes

	Carriage			IPD			
Setting, year PCV7 and PCV10-13 introduction	**Study design**	**Study population**	**Study period in meta-analysis**	**Study design**	**Case ascertainment**	**Study period in meta-analysis**	**Analyses dataset included**
		health centres for vaccination or regular check-up in Southern Israel					
Italy† PCV7: 2006; PCV13 2010	Prospective, cross-sectional surveys	PCV13-vaccinated healthy children in Milan, Lombardy, Italy evaluated by home visits	Sep/Dec 2011, Jun 2011, Sep12/Dec12	Prospective surveillance system	A positive culture from blood and/or cerebrospinal fluid Lombardy	2011-15, inclusive	0–59 months, 0–23 months
The Netherlands† PCV7: 2006; PCV13 2011	Prospective, cross-sectional surveys in two age-cohorts of healthy children vaccinated	The child had to be vaccinated according to the national immunisation schedule, and the parents have to be willing and able to participate in the trial according to the procedure. The child is either 11 or 24 months old (+/- 1-4 weeks) in the Western region evaluated by home visits	2009 Feb-Jul 2010/11 Sep-March2012/13 Sep-March	Prospective surveillance	Reference laboratory provided the IPD data from the same period and age group as carriage data, nationwide	2009−14, inclusive	0–23 months**
Norway† PCV7: 2006; PCV13 2011	Cross-sectional surveys	Children in day-care centres in and around Oslo.	2006 Autumn, 2008 Autumn, 2013 Autumn, 20015 Autumn	Prospective surveillance	A positive culture from a normally sterile site Reference Laboratory from the entire country	2008-15(Nov), inclusive	0–59 months, 0–23 months, age groups, syndromes
Spain† PCV7: 2001; PCV13 2011	Prospective surveillance University Hospital in Barcelona, Spain.	Healthy Children who attended University Hospital in Barcelona for minor surgical procedures in our hospital (i.e., phimosis or dermatologic surgery)	2004, 2005, 2006, 2007, 2008, 2009, 2010, 2014, 2015	Prospective surveillance	Presence of clinical findings of infection, together with the isolation by culture and/or DNA detection by real-time PCR of *S. pneumoniae* in any usually sterile fluid	2004-15, inclusive	0–59 months, 0–23 months, age groups, syndromes
UK† PCV7: 2006; PCV13 2010	Cross-sectional surveys	Children born between July 2006 and February 2009, recruited via the Child Health Department and/or day-care facility. Children that had received PCV13, incomplete PCV7 schedule, or with an acute respiratory infection were excluded.	2010Nov/11Sep, 2014Feb/15Aug	Prospective surveillance	IPD cases identified through 10 laboratories sending isolates to Oxfordshire surveillance program	2010–15 inclusive	0–59 months, 0–23 months, age groups
South Africa PCV7: 2009; PCV13 2011	Cross-sectional surveys	Well-baby clinics and ART clinics as part of a mother-infant pair study with concordant HIV status. Excluded from the study: Underlying illness that contraindicated a	2010May/11Feb, 2012May/13Apr	Passive, Population-based surveillance	IPD cases were identified through the laboratory at Chris Hani Baragwanath Hospital, Soweto	2010-13, inclusive	0–59 months, 0–23 months, age groups, syndromes

	Carriage			IPD			
Setting, year PCV7 and PCV10-13 introduction	**Study design**	**Study population**	**Study period in meta-analysis**	**Study design**	**Case ascertainment**	**Study period in meta-analysis**	**Analyses dataset included**
		nasopharyngeal swab or discordant HIV status with mother					

Notes: †Re-analysed or unpublished data from researchers included. ‡Setting has now introduced a highly valent PCV, but data were only available for PCV7 implementation years

4.5.1 Serotype distribution in IPD and carriage in individual sites

As datasets from individual sites included different years after the introduction of PCVs, there were variations across sites as evidenced by the range in the proportional contribution of serotypes for different categories in individual sites (Table 28).

Table 28 Range of the number of carriage and IPD isolates by age group

Age (n sites)	0-23m (11 sites)		0-59m (9 sites)	
Outcome	**Carriage**	**IPD**	**Carriage**	**IPD**
All (number of isolates)	94–4784	65–746	139–6451	47–1070
PCV7 (%)	0.56-26.59	3.16-38.1	0.66-27.32	0-18.91
PCV10-PCV7 (%)	0-3.30	2.65-18.46	0-2.42	5.97-27.78
PCV13-PCV10 (%)	4.44-24.61	13.25-40.94	5.28-22.3	12.34-51.06
Non-PCV13	61.02-95.00	29.76-69.47	58.5-89.77	33.51-69.29

In children 0–23 months (11 datasets), non-PCV13 represented over 50% of carriage isolates in all datasets. These serotypes were more commonly identified in carriage than in IPD isolates in most sites (by 12.3–43.6%), except in South Africa where the proportional contribution of non-PCV13 was higher in IPD than in carriage (67.5% and 61.0%, respectively). Non-PCV13 serotypes contributed to more than >50% of IPD in six datasets and to less than 50% in the remaining five datasets.

Among children aged 0–59 months (nine datasets), the distribution of non-PCV13 was similar to the younger age group, with small differences in IPD isolates. Non-PCV13 also represented over 50% of carriage isolates in all datasets. It was more prevalent in carriage (by 20.0%–36.5%) than in IPD, except in South Africa, where the contribution of non-PCV13 to childhood IPD was similar across sites (median: 48.5%, average: 50.3%).

Table 29 and Table 30 provide the number of isolates from carriage and IPD by category in each of the settings for children 0–23 months and 0–59 months, respectively. Figure 20 and Figure 21 depict the proportional contribution of serotypes by categories in these two age groups.

Table 29 Number of carriage and IPD isolates for different categories by setting in children 0–23 months

	USA Alaska		USA Massachusetts		Colombia		Spain		France		Israel		Italy		Netherlands		Norway		UK England		South Africa	
	Carr	IPD	Carr	IPD	Carr	IPD	Carr	IPD	Carr	IPD	Carr	IPD	Carr	IPD	Carr	IPD	Carr	IPD	Carr	IPD	Carr	IPD
PCV7	92	9	25	5	15	32	28	40	25	36	531	47	22	9	69	10	16	6	1	3	251	25
PCV10	14	24	10	21	0	9	6	34	5	87	28	111	0	9	14	48	2	20	0	10	4	4
PCV13	264	67	132	61	10	18	25	86	48	171	541	105	22	11	267	64	13	38	8	16	113	20
non-PCV13	1468	80	624	62	69	25	123	77	277	275	3684	483	347	36	735	138	255	79	171	66	576	102
Carr: carriage, IPD: invasive pneumococcal disease																						

Figure 20 Proportional contribution of serotypes, by categories, to carriage and IPD in children 0–23 month in different settings

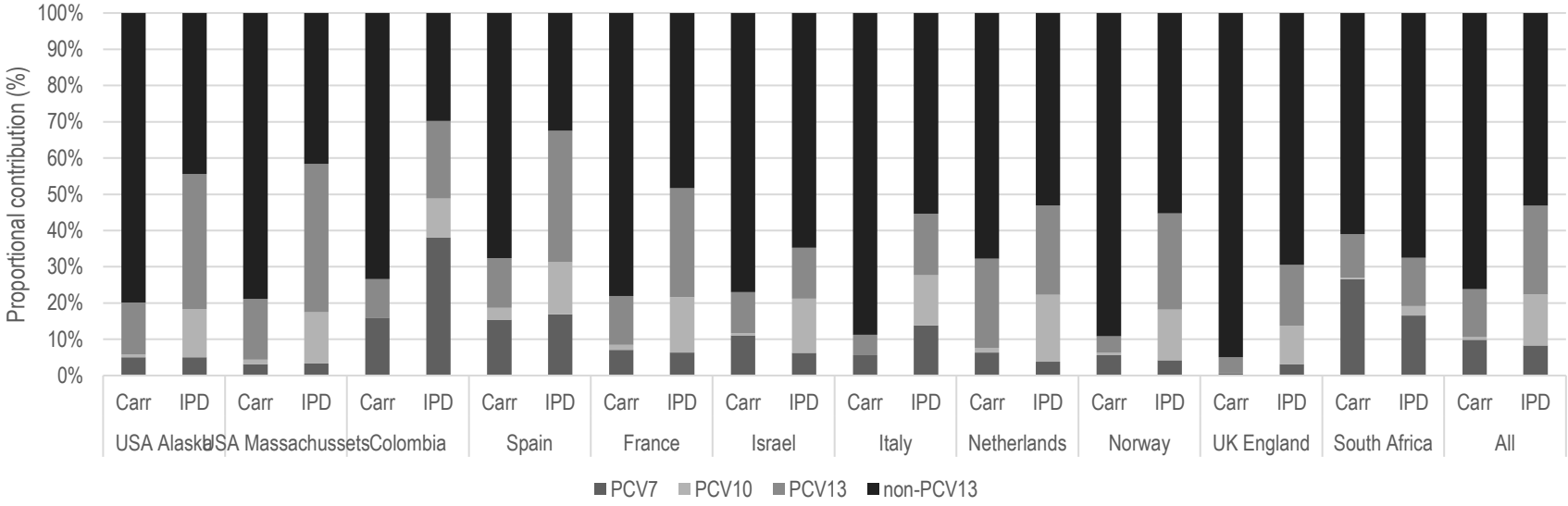
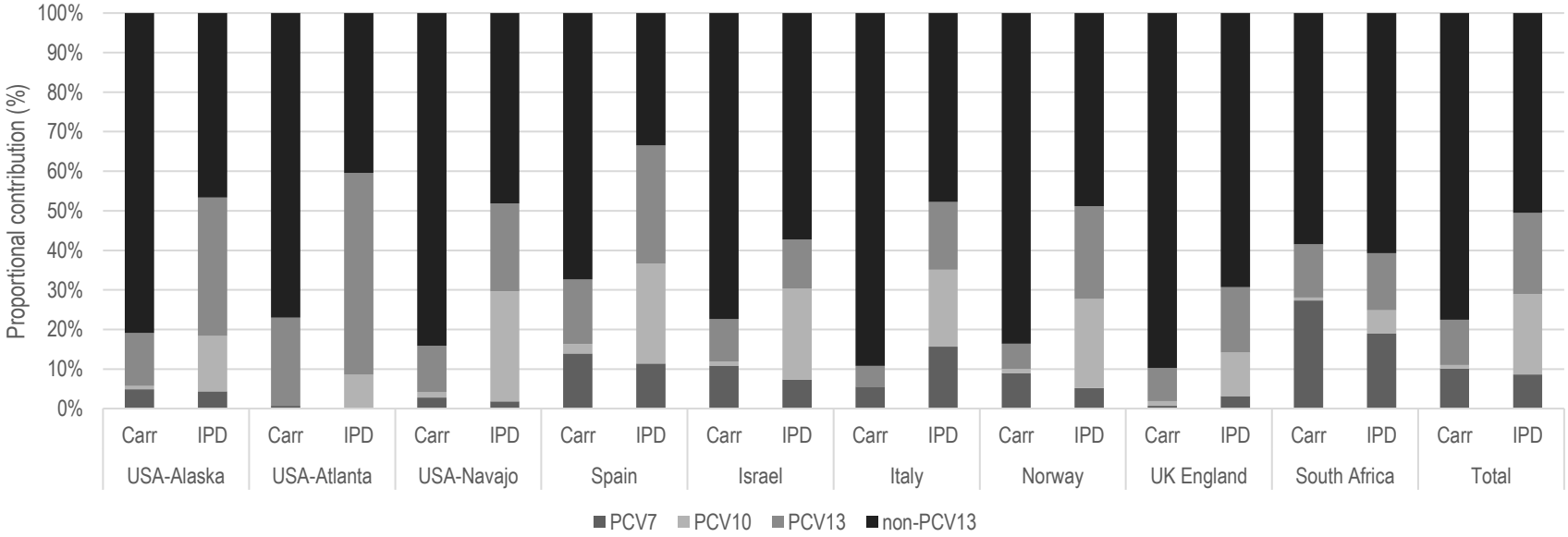


Table 30 Number of carriage and IPD isolates for different categories by setting in children 0–59 months

	USA-Alaska		USA-Atlanta		USA-Navajo		Spain		Israel		Italy		Norway		UK England		South Africa	
	Carr	IPD	Carr	IPD	Carr	IPD	Carr	IPD	Carr	IPD	Carr	IPD	Carr	IPD	Carr	IPD	Carr	IPD
PCV7	214	11	1	0	6	1	69	63	701	79	23	21	121	11	5	4	466	38
PCV10	38	35	0	4	3	15	12	139	61	246	0	26	14	48	9	14	13	12
PCV13	590	88	31	24	25	12	81	165	698	132	22	23	86	50	63	21	229	29
non-PCV13	3568	117	107	19	180	26	334	185	4991	613	372	64	1124	104	676	88	998	122

Figure 21 Proportional contribution of serotypes, by categories, to carriage and IPD in children 0–59 month in different settings



4.5.2 Serotype distribution in IPD and carriage in the combined dataset

Table 31 shows the overall distribution of serotypes in the different datasets included in the meta-analyses. The combined dataset for after PCV was introduced for children 0–59 months included 2,648 IPD isolates and 15,931 pneumococci isolates from carriers. The leading IPD-causing serotypes in the combined datasets included PCV10 and PCV13 serotypes, except for 4 and 9V. Serotypes included in meta-analysis represented 85.3% of all IPD cases in the combined dataset (48.6% were PCV13 and 36.8% non-PCV13) and 69.6% of carriers (21.7% PCV13 and 48.1% non-PCV13). Among children, 0–23 months, 2,677 IPD and 10,930 carriage isolates were examined. Serotypes analysed were associated with 86.8% (46.0% PCV13 and 40.7% non-PCV13) of IPD and 70.2% (23.2% PCV13 and 47.1% non-PCV13) of carriers. The distribution of other serotypes in IPD and carriers in the combined datasets (not included in the meta-analysis) is provided in Appendix 7.

Table 31 Serotype distribution and number of isolates included in meta-analyses

Analysis	**Overall**				**By age**		**By clinical syndromes**		
Clinical outcome	Any IPD				Any IPD		Meningitis	Bacteraemia/Sepsis	Pneumonia
Age (months)	**0–23**		**0–59**		**0–23**	**24–59**	**0–59**	**0–59**	**0–59**
Number of settings	11		9		6	6	5	5	5
	Number of (n) IPD/Carriage Isolates (%)								
Total	2677/10930		2648/15931		1552/8214	862/6947	323/14408	719/14408	1133/14408
PCV10	599/1158	(22.4/10.6)	767/1756	(29.0/11.0)	(21.5/11.8)	(42.6/10.8)	(25.1/11.7)	(23.4/11.7)	(37.2/11.7)
PCV13 not 10	657/1443	(24.5/13.5)	545/1825	(20.6/11.7)	(21.4/11.7)	(17.7/11.3)	(13.3/11.6)	(17.5/11.6)	(23.9/11.6)
NVT	1421/8329	(53.1/75.9)	1336/12350	(50.5/76.9)	(57.1/76.4)	(39.7/77.9)	(61.7/78.4)	(59.1/76.4)	(38.8/76.4)
1*	111/23	(4.1/0.2)	255/41	(9.6/0.3)	65/15	165/25	7/39	27/39	186/39
3†	134/129	(5/1.2)	146/299	(5.5/1.9)	79/90	56/195	9/258	25/258	89/258
5*	77/15	(2.9/0.1)	160/26	(6/0.2)	68/14	86/11	19/25	30/25	103/25
6A†	48/358	(1.8/3.3)	52/434	(2/2.7)	31/267	21/159	9/426	18/426	26/426
6B*	29/201	(1.1/1.8)	33/294	(1.2/1.8)	18/162	14/129	6/289	12/289	14/289
6C	20/397	(0.7/3.6)	20/559	(0.8/3.5)	10/224	7/272	4/468	5/468	7/468
7F*	189/45	(7.1/0.4)	124/83	(4.7/0.5)	70/25	40/57	12/74	32/74	53/74
8	40/52	(1.5/0.5)	33/75	(1.2/0.5)	23/41	6/30	13/70	5/70	6/70
10A	105/278	(3.9/2.5)	51/377	(1.9/2.4)	45/170	5/177	10/310	22/310	5/310
10B	20/115	(0.7/1.1)	25/166	(0.9/1)	19/114	6/52	2/166	10/166	7/166
12F	202/55	(7.5/0.5)	239/94	(9/0.6)	169/52	54/37	32/80	101/80	65/80
14*	57/130	(2.1/1.2)	69/180	(2.6/1.1)	33/115	26/59	4/174	19/174	35/174
15A	55/482	(2.1/4.4)	43/681	(1.6/4.3)	28/374	10/245	9/587	7/587	16/587
15BC	154/1107	(5.7/10.1)	131/1503	(4.9/9.4)	93/844	31/613	22/1372	55/1372	25/1372
16F	31/509	(1.2/4.7)	32/813	(1.2/5.1)	20/446	11/353	5/779	12/779	12/779
18C*	21/41	(0.8/0.4)	19/66	(0.7/0.4)	7/34	11/32	4/66	11/66	3/66
19A†	475/956	(17.7/8.7)	346/1092	(13.1/6.9)	222/607	76/429	25/1000	83/1000	156/1000
19F*	63/404	(2.4/3.7)	47/602	(1.8/3.8)	38/340	4/248	13/586	19/586	9/586
22F	87/238	(3.2/2.2)	76/401	(2.9/2.5)	46/174	17/207	8/350	19/350	17/350
23B	34/562	(1.3/5.1)	42/873	(1.6/5.5)	21/411	15/421	9/756	13/756	5/756
23F*	29/229	(1.1/2.1)	36/350	(1.4/2.2)	20/205	12/141	12/345	12/345	8/345
24F	107/98	(4/0.9)	58/173	(2.2/1.1)	34/73	14/93	9/148	14/148	14/148
33F	113/197	(4.2/1.8)	94/305	(3.5/1.9)	72/157	11/137	13/278	31/278	34/278
35B	39/520	(1.5/4.8)	35/711	(1.3/4.5)	30/383	2/304	5/660	13/660	9/660
38	36/103	(1.3/0.9)	39/202	(1.5/1.3)	28/86	7/109	1/181	18/181	8/181
NT	48/431	(1.8/3.9)	56/727	(2.1/4.6)	42/356	14/328	9/663	6/663	37/663

Notes: IPD: Invasive pneumococcal disease. n: number of cases, NVT: non-PCV13, *PCV10/13 and †PCV13 serotype. Data reported for "Other" clinical syndromes are not shown

4.5.3 Invasive disease potential by age group

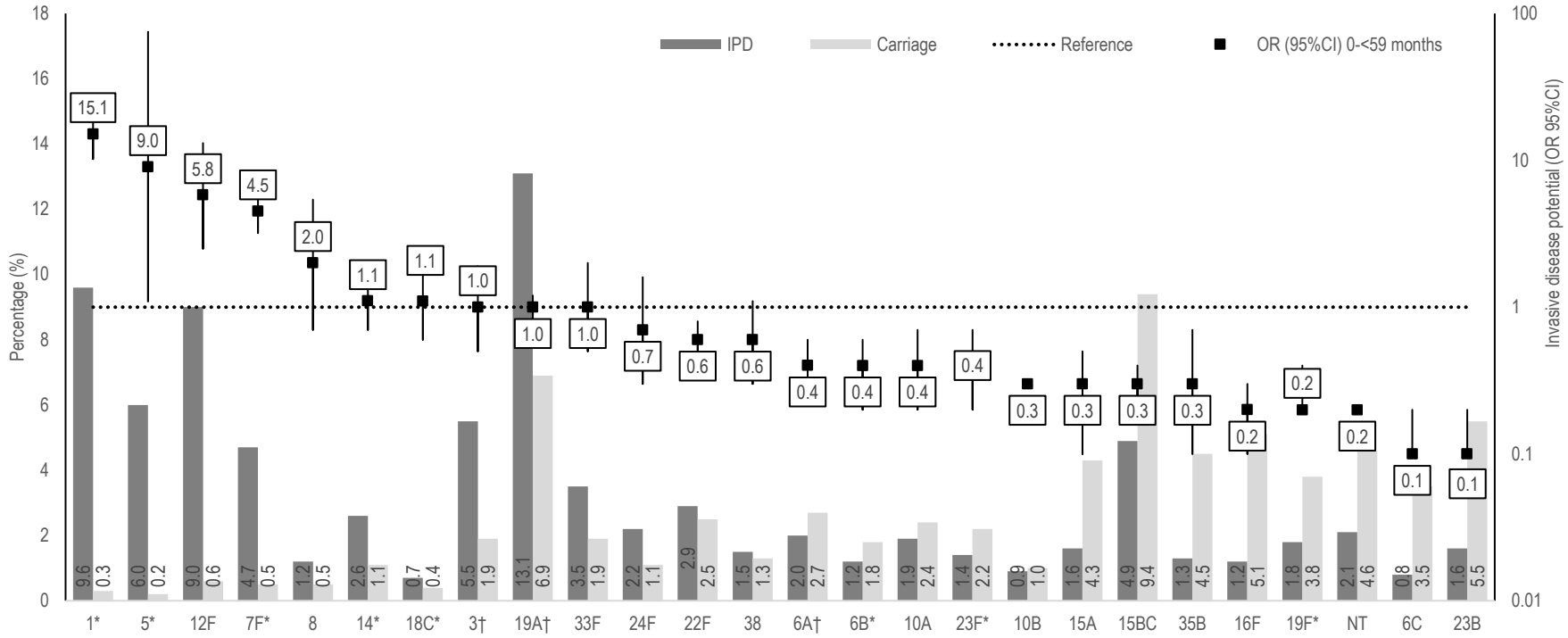
Children 0–59 months

Nine settings were included in the analyses for children aged 0−59 months. Figure 22 shows results from meta-analyses of the invasive disease potential (OR) as a continuum of invasive disease potential. It also shows the proportional contribution to IPD and carriage in the combined dataset. Overall, significant differences in the meta-estimates of the invasive disease potential of serotypes were found. Among serotypes included in the vaccines, 1 and 7F were significantly more invasive than 19A (OR between 5−15). Conversely, the invasive disease potential for 6A, 6B, 19F, and 23F was significantly lower (OR between 0.3−0.4). The invasive disease potential of other vaccine serotypes (3, 5, 14, and 18C) was not significantly different from 19A. The invasive disease potential of non-vaccine serotypes, 12F was higher than 19A, 5.8 times higher in relation to 19A while for other non-vaccine serotypes (6C, 15A, 15BC, 16F, 22F, 23B), the invasive disease potential was significantly lower than 19A (ORs ranged between 0.1−0.6). Estimates for the remaining non-vaccine serotypes (8, 10B, 24F, 33F, 35B, 38, NT) were not significantly different from that of 19A. Based on meta-estimates, the invasive disease potential of non-vaccine serotypes 12F, 8, 33F, 24F, 22F, and 38 ranked higher than other non-vaccine serotypes in this age group relative to 19A.

In sensitivity analyses, the point-estimates from the overall analysis for children 0−59 months remained similar for serotypes with high or low invasive disease potential in relation to 19A. However, some differences in terms of significance and heterogeneity of meta-estimates for serotypes were noted (7). Heterogeneity was negligible to moderate for serotypes with a higher or lower invasive disease potential than 19A, except for 12F (I^2 >75%). For this serotype, no sensitivity analyses showed to influence the heterogeneity. The invasive disease potential of serotype 5 was no longer significantly higher than 19A when the analysis was restricted to data from settings with low HIV prevalence or industrialised settings. However, it remained significantly more invasive than 19A, and the heterogeneity for this serotype was low or negligible in settings with 70% PCV coverage. The homogeneity of the invasive disease

potential for 35B increased when analyses were restricted to settings with low HIV prevalence of industrialised settings with low heterogeneity. Restricting the analysis to data for the period with current higher valent PCV did not change the point estimate for serotypes with lower invasive disease potential (6A, 6B, 22F, and 23F). However, results were no longer significantly different from 19A.

Figure 22 Serotype-specific contribution to IPD, carriage, and invasive disease potential in children 0–59 months

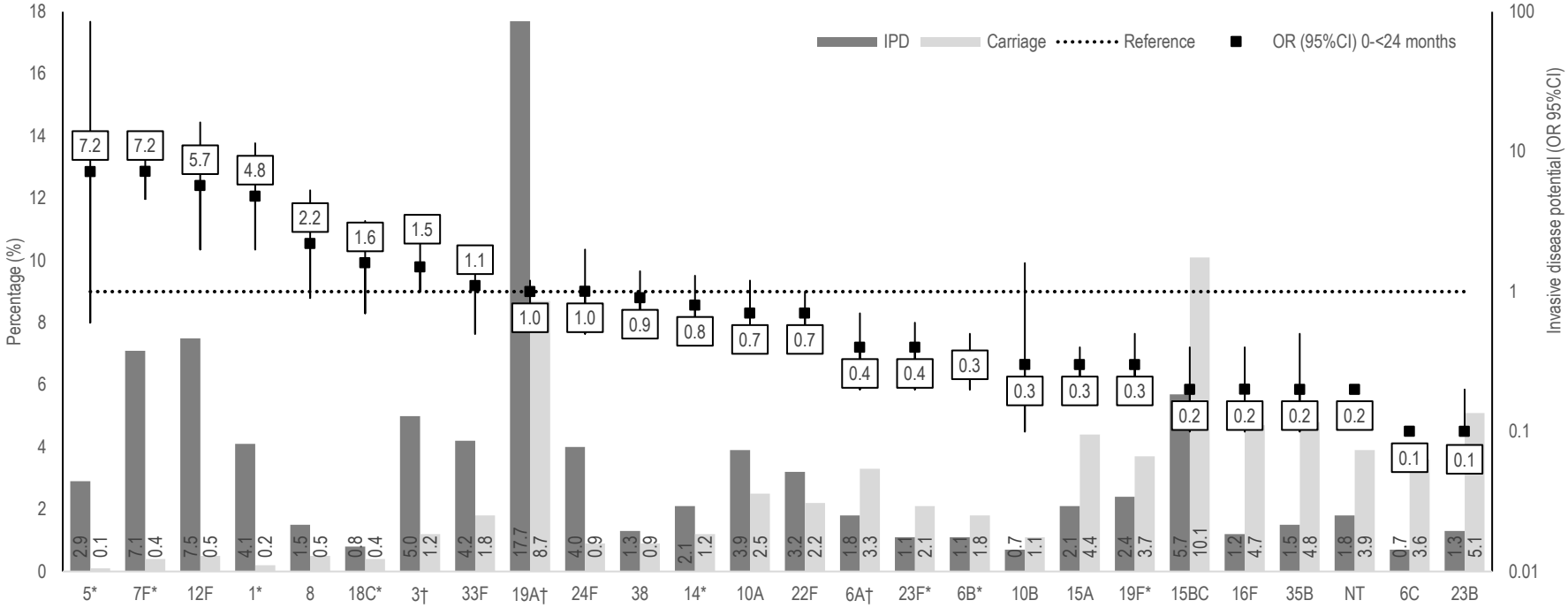


Serotypes are ranked from the highest to the lowest estimate of invasive disease potential. Bars depict the overall contribution of each serotype to IPD and carriage in the combined dataset (%, left axis, N=9 settings). Dots show meta-estimates of serotype-specific invasive disease potential (OR 95% CI, the right axis on a log-scale, point estimate shown in boxes). Dotted black line: Reference line for invasive disease potential (19A; right axis). *PCV10/13 and †PCV13 serotype

Children 0–23 months

The analyses of data for 0−23 months olds (11 settings) showed similar results as for the 0−59 months old children (Figure 23). Vaccine serotypes 1 and 7F were more invasive (5 to 7-fold) compared to 19A, while 6A, 6B, 19F, and 23F were significantly less invasive than 19A (OR ranged between 0.3−0.4). The invasive disease potential of other vaccine serotypes (3, 5, 14, and 18C) was not significantly different from 19A. Non-PCV13 serotype 12F was significantly more invasive than 19A in this age group while estimates for 15A, 15BC, 16F, 35B, 6C, and 23B were significantly lower compared to 19A. The sensitivity analyses in this age group demonstrated similar patterns as in the 0−59 months. There was considerable heterogeneity in the invasive disease potential for all serotypes with a higher or lower estimate than 19A, for which sensitivity analyses showed no influence on I^2 except for serotype 5. When the analysis was restricted to low HIV prevalence or industrialised settings, the homogeneity of the estimate for 35B increased. Inclusion of data from a country implanting PCV10 in this age group did not impact the overall conclusion as results were similar to those when all datasets were considered (Appendix 7).

Figure 23 Serotype-specific contribution to IPD, carriage, and invasive disease potential in children 0–23 months



Serotypes are ranked by highest to the lowest estimate of invasive disease potential. Bars depict the overall contribution of each serotype to IPD and carriage in the combined dataset (%, left axis, N=11 settings). Squares depict meta-estimates of serotype-specific invasive disease potential (OR 95% CI, the right axis on a log-scale, point estimate shown in boxes). Dotted black line: Reference line for invasive disease potential (19A; right axis). *PCV10/13 and †PCV13 serotype

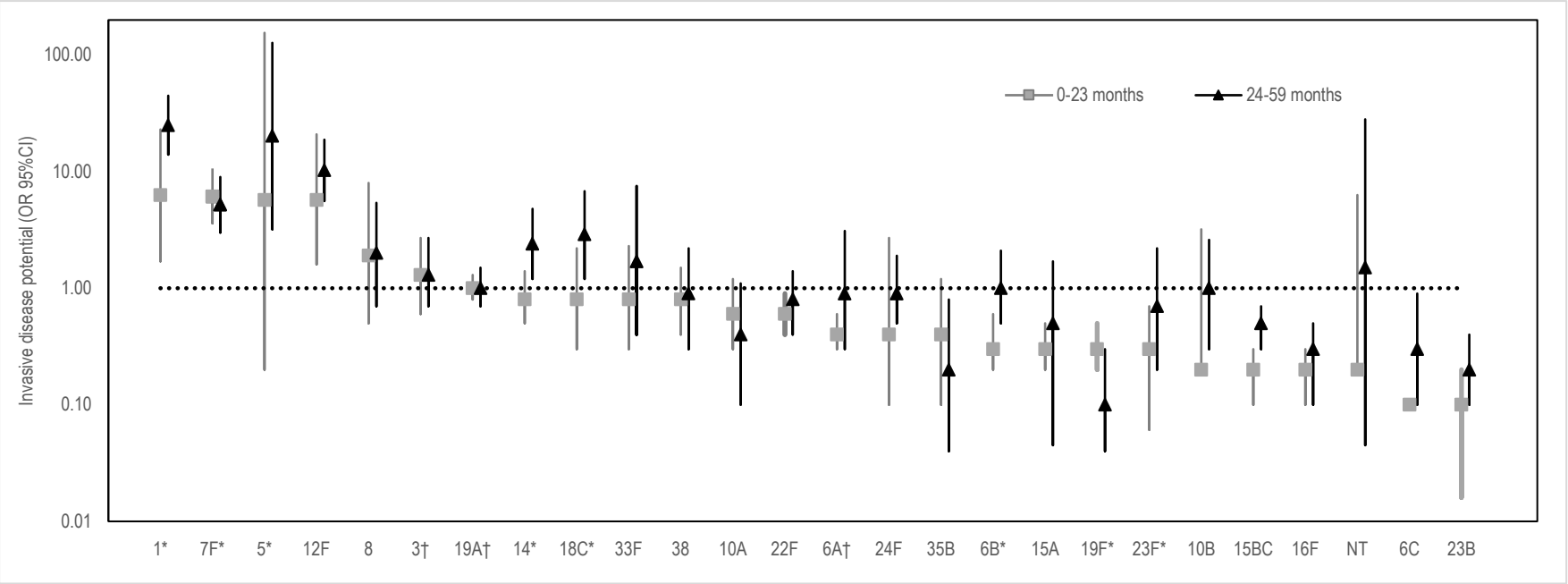
4.5.4 Invasive disease potential by narrow age groups

For six settings, the serotype-specific invasive disease potential could be estimated for children 0–23 and 24–59 months (Table 31). Estimates of individual serotypes for both age groups were largely in agreement in terms of magnitude, as well as in the direction of the OR, in relation to 19A. When evaluated by narrow age groups, the invasive disease potential of the serotypes can be grouped into categories based on the direction of the point estimate in relation to 19A and between age groups (Figure 24).

- higher than 19A in both age groups: *1, 7F*, 12F
- no different to 19A in both age groups: *3*, 8, 33F, 38, 10A, 24F, 10B, NT
- lower than 19A in both age groups: *19F*, 15BC, 16F, 6C, 23B
- higher than 19A in children 24-59 months but no difference to 19A in 0-23 months: *5, 14, 18C*
- no difference to 19A in children 24-59 months but lower than 19A in children 0-23 months: *6A*, *6B, 23F*, 22F, 15A
- lower than 19A in children 24-59 months but no difference in relation to 19A in children 0-23 months: 35B

Heterogeneity for these estimates of invasive disease potential was negligible to low, except for serotypes 15BC and 5 where considerable heterogeneity (I^2>75) was noted for 0–23 and 24–59 months, respectively (Appendix 11). By serotype, the largest difference (based on point estimates) between age groups were for 1 and 5, with a point estimate of serotypes' invasive disease potential was 3−4 fold higher for serotypes 1 and 5 in the 24−59 months age group, even though there was an overlap of the wide 95% CIs. Meta-analyses of invasive disease potential by age should be interpreted with caution due to a reduced number of datasets and small sample sizes per serotype.

Figure 24 Serotype-specific invasive disease potential by narrow age groups



Grey squares and black triangles depict meta-estimates of serotype-specific invasive disease potential for 0–23 months and 24–59 months, respectively. Serotypes are sorted by the rank of estimates of invasive disease potential for the 0–23 months. (OR 95% CI, left axis on a log scale). *PCV10/13 and †PCV13 serotype

4.5.5 Invasive disease potential by clinical IPD syndromes

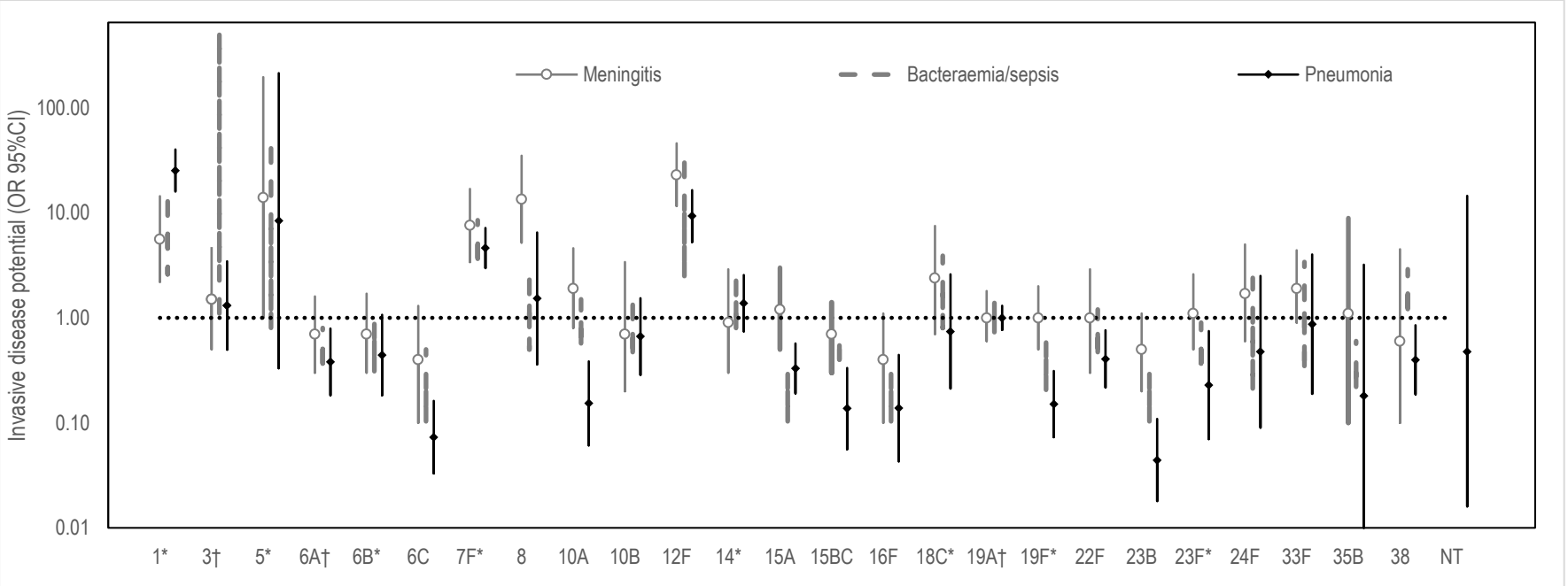
Five datasets provided serotype data from isolates for meningitis, bacteraemia/sepsis and pneumonia for children under five years (Table 31). Although the case definitions for each of the clinical syndromes varied, they were considered comparable enough to conduct sub-group analyses.

Table 32 Main characteristics of datasets with clinical syndromes

Country dataset	Meningitis	Bacteraemia	Pneumonia
USA Alaska	*S. pneumoniae* isolated from a sterile site of an Alaska resident with a clinical diagnosis of meningitis	*S. pneumoniae* isolated from a sterile site of an Alaska resident with blood culture positive with no known focus	*S. pneumoniae* isolated from a sterile site of an Alaska resident with a clinical diagnosis of pneumonia
Israel	1. Isolation of *S. pneumoniae* from cerebrospinal fluid 2. Isolation of *S. pneumoniae* from blood with Clinical diagnoses of meningitis	Positive blood for *S. pneumoniae* without focus (except Otitis)	Positive *S. pneumoniae* culture with a diagnosis of any lower respiratory tract infection reported by clinician
Norway	IPD case notified by a clinician as "Meningitis/encephalitis", or as "Sepsis + Meningitis/encephalitis."	IPD case notified by a clinician as "clinical sepsis" or as "Sepsis + Meningitis/encephalitis."	IPD case notified as a clinician as "Pneumonia / lower respiratory tract infection". All cases also have IPD, pneumococci have been isolated from an otherwise sterile site
Spain	Detection of *S. pneumoniae* by culture in cerebrospinal fluid or blood together with clinical criteria of meningitis	Sepsis or bacteraemia (cannot differentiate between)	Detection of *S. pneumoniae* by culture in blood or pleural fluid and clinical and radiological criteria of pneumonia
South Africa	Clinical diagnosis of meningitis or positive cerebrospinal fluid	Bacteraemia without focus	Clinical diagnosis of Lower Respiratory Tract Infection with positive blood or pleural fluid culture

Point estimates of invasive disease potential for individual serotypes showed consistency in the direction of invasive disease potential in relation to 19A across syndromes, with a few exceptions. For those serotypes with an invasive disease potential higher than 19A, such as for serotypes 1 and 7F, the point estimates were consistently higher (with negligible to low heterogeneity) across syndromes. However, for 12F, ORs were higher for meningitis and pneumonia (with negligible to low heterogeneity) but not for bacteraemia/sepsis. Serotypes 10A, 18C, 24F, and 33F were higher than 19A for meningitis, compared to invasive pneumonia. Serotypes 15BC, 19F, and 23B were less likely to be associated with invasive pneumonia than meningitis or bacteraemia/sepsis. These associations were mostly not statistically significant (Figure 25). Meta-analyses of invasive disease potential by syndromes should be interpreted with caution due to a reduced number of datasets and small sample sizes per serotype.

Figure 25 Serotype specific invasive disease potential by IPD clinical syndrome



Meta-estimates of serotypes' invasive disease potential (OR 95% CI left axis on a log-scale) among cases of meningitis: grey solid line and circle, bacteraemia/sepsis: grey dotted line, and pneumonia: black solid line and dots. Dotted horizontal black line: Reference line for invasive disease potential (19A). *PCV10/13 and †PCV13 serotype

4.5.6 Invasive disease potential of non-PCV13 types compared to other non-PCV13 types

The invasive disease potential of individual non-PCV13 serotypes in relation to other non-PCV13 was estimated using data from settings where PCV13 has been implemented.

The overall meta-estimates were in agreement with estimates of invasive disease in relation to 19A for children 0–59 months, in that serotypes 12F, 8, 33F, 24F, and 22F were highly invasive (OR and 95% CI>1). Although these serotypes ranked in the top five most invasive serotypes in each of the settings, there was large heterogeneity in the meta-estimate (I^2), except for serotype 33F. Serotype 16F had low invasive disease potential compared to other non-PCV13 types.

Table 33 Invasive disease potential of non-PCV13 types in comparison with other non-PCV13 types in children 0–59 months in settings where PCV13 has been implemented

	The rank of invasive disease potential in each setting						Meta-analysis			
Serotype	**Alaska**	**Israel**	**Italy**	**S Africa**	**Spain**	**UK**	**OR**	**95%LCI**	**95%HCI**	**I^2 (%)**
12F	1	1	2	1	…	2	**18.9**	**8.9**	**40.0**	**78.2**
8	5	3	3	3	3	1	**5.7**	**2.7**	**11.8**	**40.0**
33F	4	2	1	5	2	3	**3.6**	**2.7**	**4.7**	**0.0**
24F	…	4	4	…	4	5	**3.2**	**1.6**	**6.4**	**55.2**
22F	3	7	5	9	1	4	**2.4**	**1.3**	**4.3**	**58.6**
38	2	5	7	8	6	9	1.8	0.8	3.8	56.1
10A	6	6	10	6	12	6	1.3	0.8	2.0	31.9
15BC	7	9	8	11	7	7	0.8	0.6	1.2	47.1
35B	10	11	…	4	9	8	0.7	0.3	1.6	73.4
15A	8	10	9	7	11	10	0.7	0.4	1.0	25.0
NT	12	14	12	2	5	12	0.6	0.0	23.3	96.0
23B	9	13	6	13	10	13	0.4	0.2	1.0	71.3
16F	11	12	11	10	8	11	**0.4**	**0.2**	**0.5**	**0.0**
10B	…	8	13	12	…	…	..	..	..	..

Notes: Number indicates the rank of invasive disease potential in each setting, with those at the top of the spectrum of invasiveness in red/orange and those at the bottom in green. Serotypes for which the invasive disease potential was significantly different than the reference are in bold.

In children aged 0–23 months, the same serotypes than in the 0–59 months were highly invasive (12F, 8, 24F, 33F, 22F) with the addition of 10A. In this age group, the heterogeneity for serotype 8 was negligible, while it was high in the 0–59 months. Four serotypes (15BC, 15A, 16F, 23B) had low invasive disease potential compared to other non-PCV13 types.

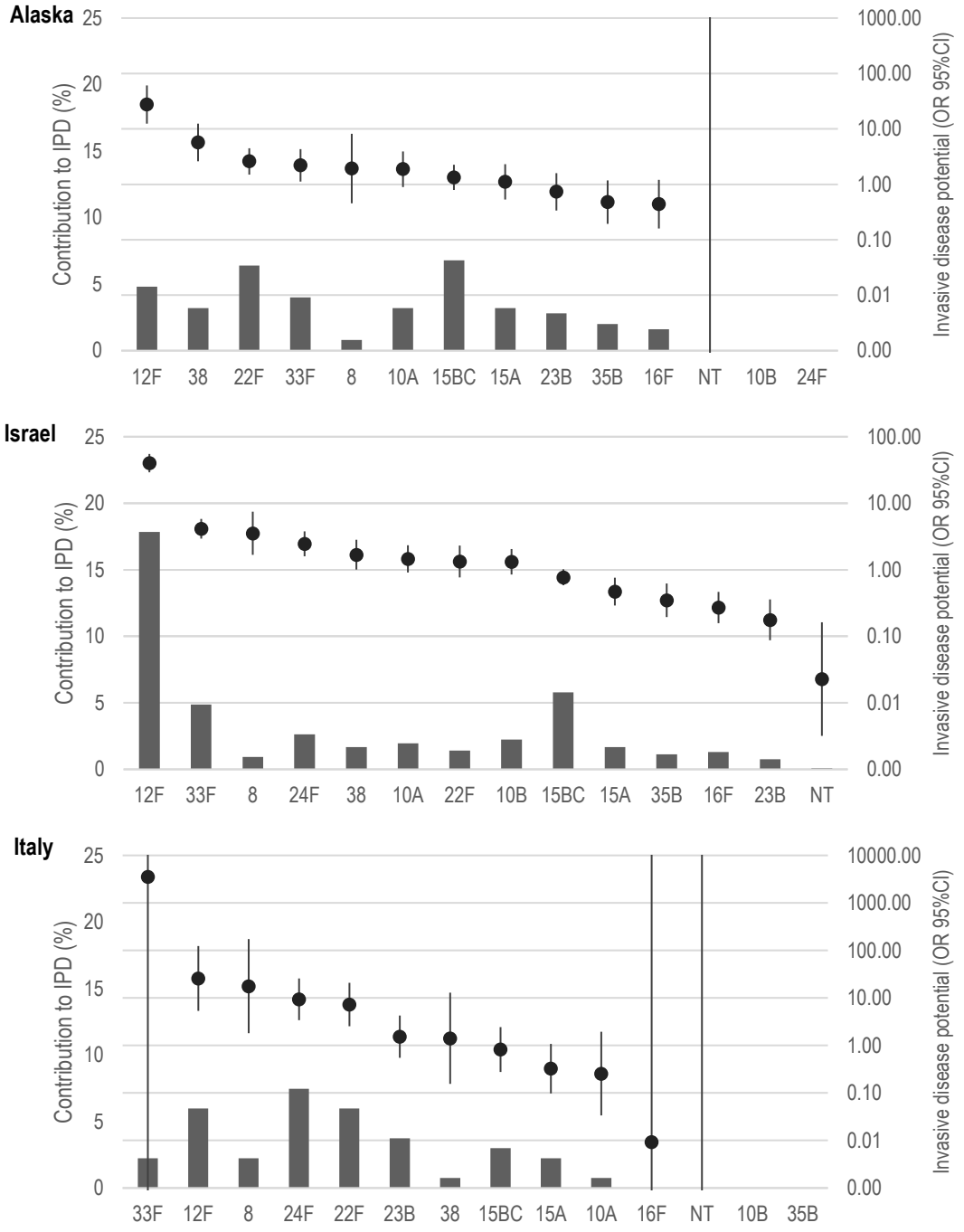
Table 34 Invasive disease potential of non-PCV13 types in comparison with other non-PCV13 types in children 0–59 months in settings where PCV13 has been implemented

	The rank of invasive disease potential in each setting								Meta-analysis			
Serotype	USA Alaska	USA Mass	France	Israel	Italy	Spain	UK	S Africa	OR	95%L CI	95% HCI	I^2 (%)
12F	1	…	1	1	2	…	4	1	**17.2**	**6.8**	**43.5**	**73.1**
8	7	…	8	3	3	3	1	3	**4.5**	**2.5**	**8.0**	**0.0**
24F	…	…	4	4	4	1	8	…	**4.3**	**1.9**	**9.9**	**63.2**
33F	3	1	6	2	1	4	5	12	**3.8**	**2.9**	**5.1**	**0.0**
38	2	3	3	5	10	10	6	8	2.5	1.0	5.8	48.5
22F	5	2	7	7	5	2	2	7	**2.5**	**1.4**	**4.3**	**55.4**
10A	4	4	5	6	11	7	3	5	**2.0**	**1.5**	**2.8**	**0.0**
10B	…	…	9	8	…	…	…	11	1.2	0.8	2.1	0.0
15BC	8	7	11	9	6	11	10	9	**0.7**	**0.6**	**0.9**	**0.0**
35B	9	9	4	11	…	6	7	4	0.7	0.3	1.6	76.2
NT	11	5	13	14	12	8	9	2	0.7	0.1	6.2	92.1
15A	6	6	10	10	8	9	12	6	**0.6**	**0.5**	**0.9**	**0.0**
16F	11	10	12	12	9	5	11	10	**0.3**	**0.2**	**0.5**	**0.0**
23B	10	8	2	13	7	12	13	13	**0.3**	**0.2**	**0.5**	**4.1**

Notes: Number indicates the rank of invasive disease potential in each setting, with those at the top of the spectrum of invasiveness in red/orange and those at the bottom in green. Serotypes for which the invasive disease potential was significantly different than the reference are in bold.

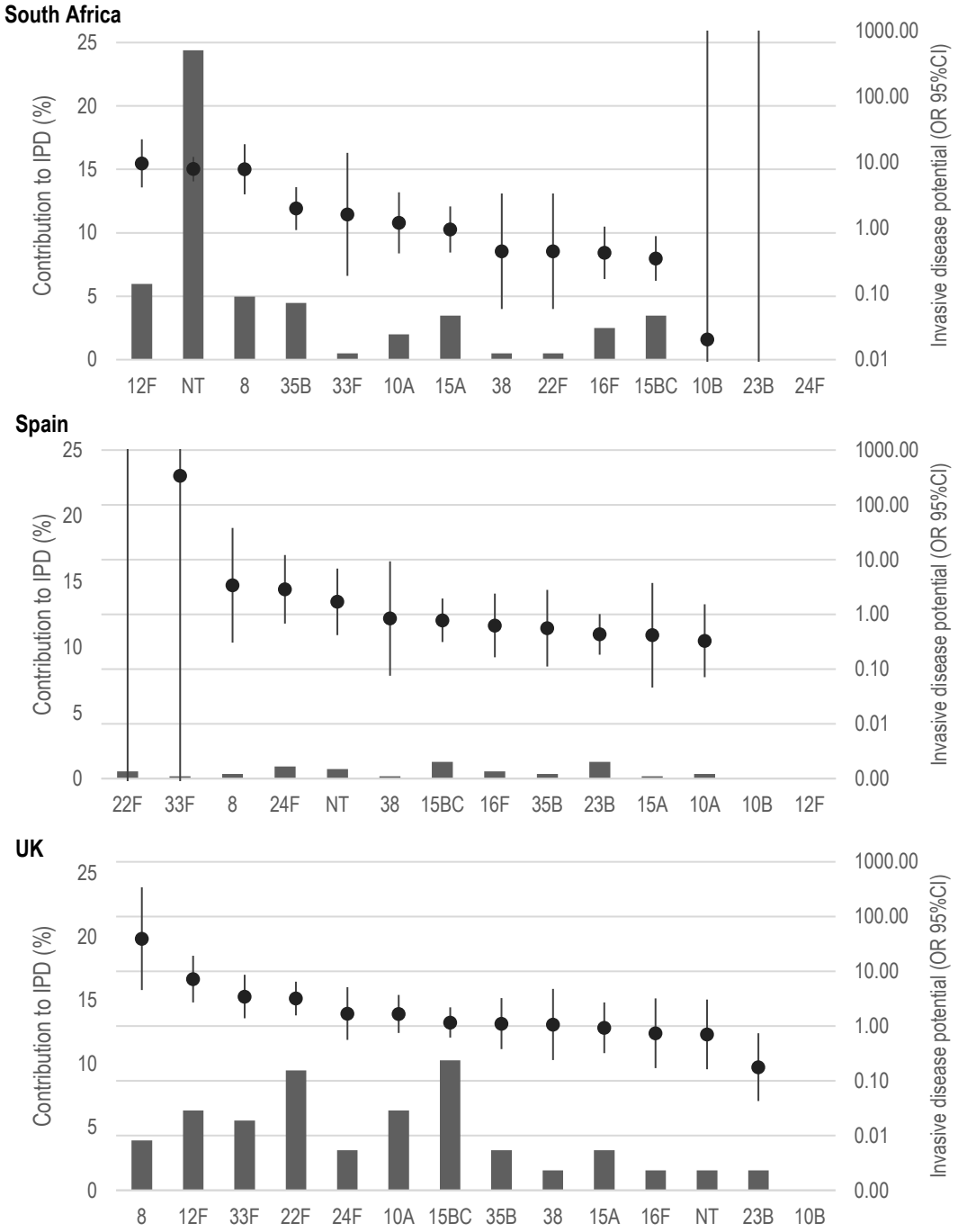
The figures below show the spectrum of invasiveness in individual settings and the proportional contribution of non-PCV13 serotypes in childhood IPD in settings where PCV13 has been implemented.

Figure 26 Invasive disease potential of non-PCV13 types and proportional contribution to IPD (%) in children 0-59 months



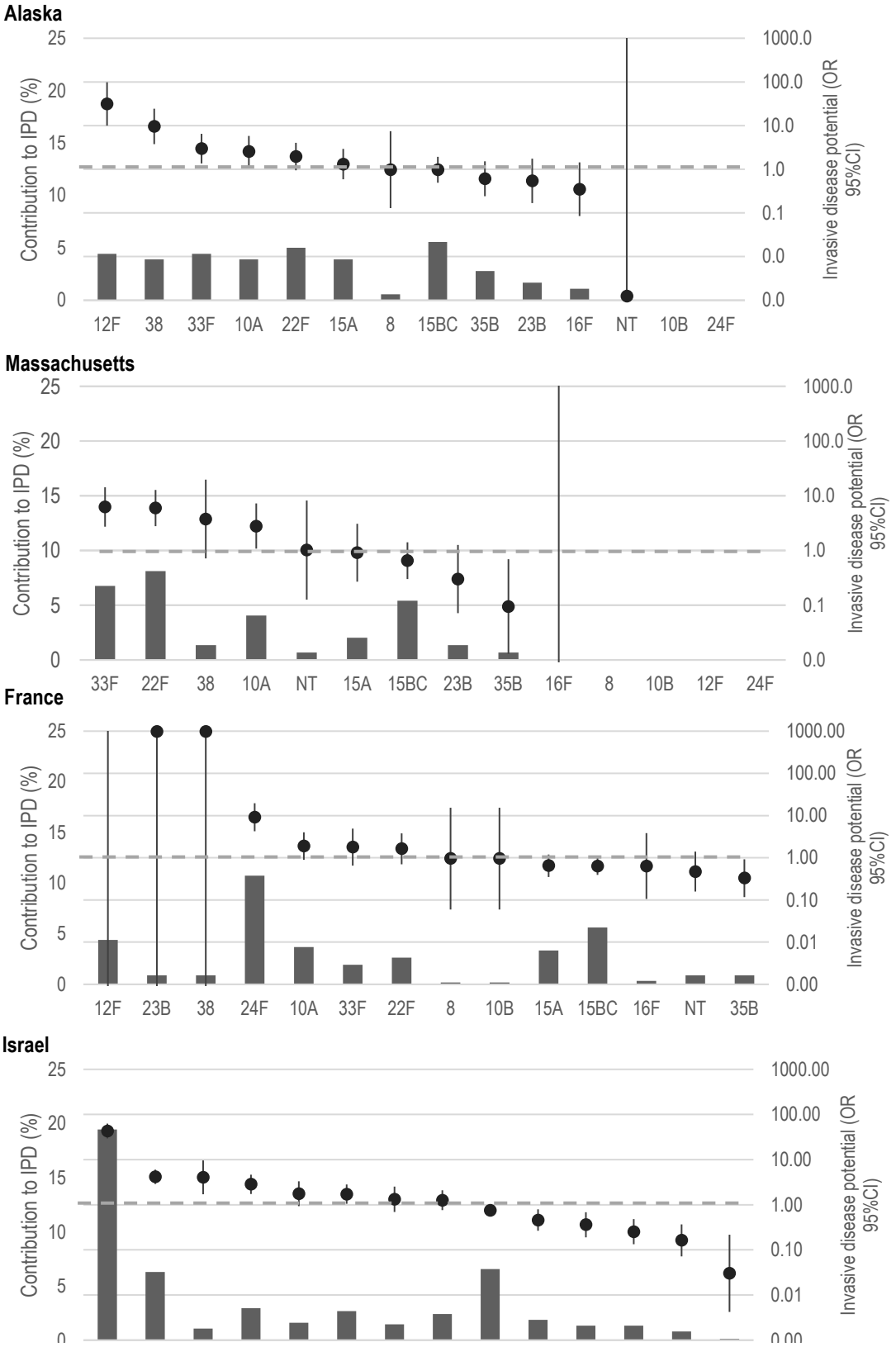
Serotypes are ranked by highest to lowest estimate of invasive disease potential. Bars depict overall contribution of each serotype to IPD. Dots show meta-estimates of serotype-specific invasive disease potential (OR 95%CI, right axis on a log-scale, point estimate shown in boxes). Dotted black line: Reference line for invasive disease potential (1; right axis)

Figure 27 Invasive disease potential of non-PCV13 types and proportional contribution to IPD (%) in children 0-59 months



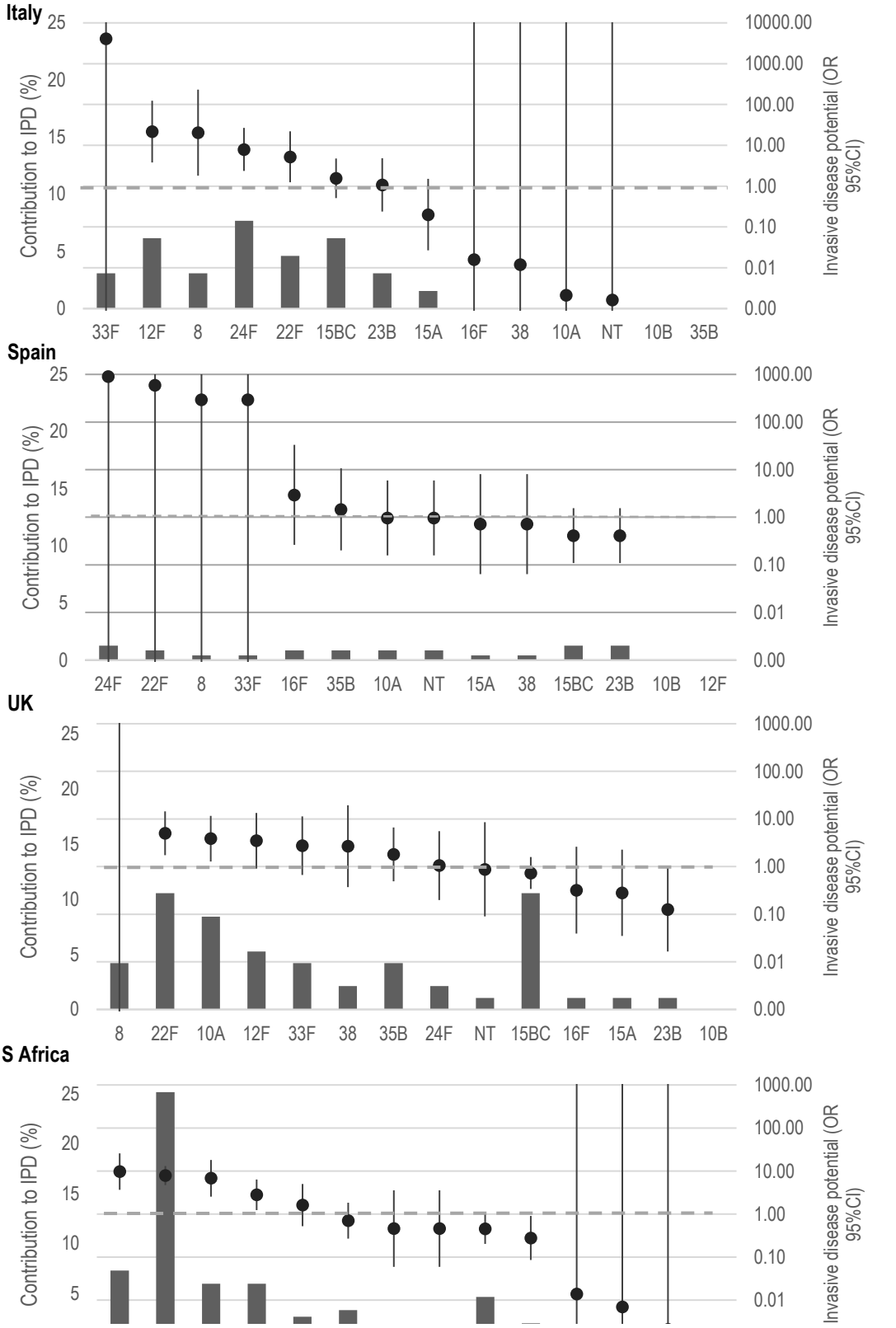
Serotypes are ranked by highest to lowest estimate of invasive disease potential. Bars depict overall contribution of each serotype to IPD. Dots show meta-estimates of serotype-specific invasive disease potential (OR 95%CI, right axis on a log-scale, point estimate shown in boxes). Dotted black line: Reference line for invasive disease potential (1; right axis)

Figure 28 Invasive disease potential of non-PCV13 types and proportional contribution to IPD (%) in children 0-23 months



Serotypes are ranked by highest to lowest estimate of invasive disease potential. Bars depict overall contribution of each serotype to IPD. Dots show meta-estimates of serotype-specific invasive disease potential (OR 95%CI, right axis on a log-scale, point estimate shown in boxes). Dotted black line: Reference line for invasive disease potential (1; right axis)

Figure 29 Invasive disease potential of non-PCV13 types and proportional contribution to IPD (%) in children 0-23 months



Serotypes are ranked by highest to lowest estimate of invasive disease potential. Bars depict overall contribution of each serotype to IPD. Dots show meta-estimates of serotype-specific invasive disease potential (OR 95%CI, right axis on a log-scale, point estimate shown in boxes). Dotted black line: Reference line for invasive disease potential (1; right axis)

4.6 Discussion

This chapter provides estimates of invasive disease potential of specific serotypes, including non-PCV13 serotypes, and shows the extent to which they vary across different settings. Overall, the invasive disease potential of non-PCV13 serotypes in children under five years was usually lower than that of 19A or other vaccine types. However, there is evidence to support some non-PCV13 serotypes are more invasive than others. The comprehensive assessment of serotype-specific disease potential across different geographic locations presented in this chapter informs our understanding of the invasive disease potential of circulating types after PCV introduction and thereby the potential of current PCVs for the prevention of IPD in the longer term. There is large heterogeneity in most estimates, thus, it is important to examine results from individual settings to gain insights into the invasiveness spectrum of non-PCV13 serotypes in the post-PCV era, mostly representative of PCV7 and early PCV13 use.

In agreement with pre-PCV findings, I found that serotypes circulating in the post-PCV era differ in their ability to cause IPD in young children (Brueggemann et al., 2004). In the combined dataset comprised of data from 13 settings for the present analysis, serotypes 1 and 7F, which are included in PCV10 and PCV13, and 12F, not included in any PCV, were more invasive than 19A in children aged 0−59 and 0−23 months. In relation to other non-PCV13 serotypes, 12F was also more highly invasive than others, followed by serotypes 8, 33F, 24F and 22F. Serotypes 15BC, 15A, 16F and 23B had a lower invasive disease potential than other non-PCV13 serotypes. These results agree to a large extent with findings by Southern and colleagues (Southern et al., 2018) who estimated case carrier ratios in 2015/16, four years after PCV13 introduction in the UK. The majority of non-PVC13 serotypes identified in this study's setting, for those aged <60 years, had a case carrier ratio (and 95%CI below 1) including 15BC, 11A, 23B, 10A,15A, 23A, 16F, 21, 24F, 35B, 17F, 31, 7C, and 37. Interestingly, serotype 24F had a low case carrier ratio in this population. While this analysis provides a range of pooled and country-level estimates, the heterogeneity in pooled estimates should be

considered. The results show clearly that it is important to describe the inherent invasiveness of *S. pneumoniae* to understand better non-PCV13 IPD to inform vaccine policies at the national level, especially as new pneumococcal vaccines become available.

Among all serotypes, 12F, a serotype currently not included in PCVs with high invasive disease potential compared with 19A and other non-PCV13 types, stands out. The estimates of high invasive disease potential are consistent with other findings of this serotype's ability to cause disease (Sleeman et al., 2006, Song et al., 2013). In 2015, 12F was identified as the leading cause of IPD due to non-PCV13 serotypes (19%) in children 0−23 months in Belgium (Verhaagen et al., 2016). Increases in the incidence of IPD associated with 12F have also been noted among adults and in association with antibiotic resistance in South Africa (du Plessis et al., 2016). Considering the observed ability of 19A to rapidly fill in the vacant niche after eradication of PCV7-types (Richter et al., 2013) and non-significant differences in IPD potential of other types like 22F, 24F, and 33F, the possibility of an emerging role in IPD for these serotypes post-introduction of PCV10 and PCV13 cannot be excluded. Highly invasive disease strains in relation to 19A, such as 1 and 12F, are rarely detected in the nasopharynx by conventional culture and serotyping methods (Varon et al., 2015, Zulz et al., 2013) or are known to have cyclical fluctuations (Normark et al., 2001, Lagos et al., 2008). Since serotype 1 is covered by PCV10 and PCV13, it is not yet possible to conclude whether serotype 12F will become dominant in the future in childhood IPD.

The meta-estimates should be interpreted considering the level of heterogeneity. The heterogeneity identified for some non-PCV13 serotypes in this meta-analysis can also be reflective of a fluctuating, by time and locality, invasive disease potential across settings included in the meta-analyses. Several factors may contribute to this heterogeneity, including factors assessed in our sensitivity analyses, but also others for which no data were available to examine, e.g., differences in blood culture rates and antibiotic susceptibility patterns. It is also important to note that differences in study

designs, populations, and study periods influence the heterogeneity (see Table 27). Moreover, the true uncertainty in estimates of invasive disease potential is wider than those reported by confidence intervals.

It is as yet unpredictable whether replacement by a particular non-PCV13 serotype will reach a similar level as with 19A replacement disease post-PCV7, e.g., 35% of all IPD cases in young children in 2005 in the USA (Moore et al., 2008). Beyond invasiveness properties, the prevalence of non-PCV13 in IPD may also be associated with increasing trends of drug resistance. For instance, high levels of drug resistance have been reported for 15A, 23B, and 35B in Europe and the USA (Sheppard et al., 2016, van der Linden et al., 2015, Kim et al., 2016). These meta-analyses indicate that the invasive disease potential of these serotypes in the settings represented in our study is at the lower end of the spectrum of invasiveness. The meta-analyses also suggest we need to await developments of these serotypes, that may also depend on the setting, antibiotic resistance, and co-morbidities, like HIV exposure.

This review also shows that there is a clear gap in the evidence base as the invasive disease potential of serotypes in low-income countries in Asia and Africa in the post-PCV era remains poorly described. In these regions, serotypes' proportional contribution to childhood IPD differed from industrialised settings before the introduction of PCV (Hausdorff et al., 2000, Hausdorff et al., 2007, Johnson et al., 2010). Following PCV10 introduction, strains with serotypes such as 2, 8, 10F, 12A, 12F, 18A, 38, and 45 have recently been found to be highly invasive in South Asia (Ahmed et al., 2016). As serotype replacement in carriage continues to take place after PCV implementation, evidence suggests that circulation of a greater number of serotypes, some with high invasive disease potential, may be found in resource-limited settings.

The risk of invasive disease by specific serotypes in different childhood age groups has not been determined. From these meta-estimates, though with overlapping confidence intervals, serotype 1 and 5 were likely to be about 3−4 times more invasive in children 24−59 months than in those less than two

years. In another study, a higher invasive disease capacity was observed for 13 out of 15 serotypes in children 0−23 months, compared with those aged 24−84 months (Yildirim et al., 2010), which suggested that the varying propensity of strains to cause IPD may contribute to a decline in incidence with increasing age. Direct comparisons between our study and this study cannot be made, as methodologies and serotypes analysed differed (e.g., methods to estimate invasiveness and geographic/temporal representation). Nonetheless, agreements in findings that serotypes vary in their capacity to cause IPD events by age groups is important for public health purposes. If replacement in carriage results in more carriage of serotypes with lower invasive disease potential, these serotypes may nevertheless act like opportunistic serotypes in individuals at high risk of IPD (e.g., elderly or with co-morbidities) and severe IPD outcomes. These groups may constitute a large part of the remaining burden of *S. pneumoniae* in the future, even though the overall IPD burden in the whole population would be lower. Data from ongoing studies in South Africa indicate that the invasiveness of serotypes is likely to differ by immune status (e.g., by HIV status). Further research in other settings is needed to explore differences in invasive disease potential by different populations.

Pneumococcal serotypes have also been shown to vary in their ability to cause particular clinical outcomes, such as case fatality or disease syndromes such as empyema or meningitis (Weinberger et al., 2010). I estimated the disease potential of strains by three IPD syndromes in children. Compared with 19A, among meningitis and pneumonia, a higher invasive disease potential was estimated for 12F. There is a paucity of reliable data describing relationships between specific serotypes and individual clinical syndromes. Nevertheless, several studies have shown that serotype 12F is associated with meningitis and has been documented indirectly from outbreaks to be hyper-invasive (Schillberg et al., 2014, Song et al., 2013). Increases in cases of overall IPD and antibiotic non-susceptible serotype 12F following PCV introduction have been recently reported in Israel and France. This increase was caused by a single clone expansion, and 89% of 12F IPD cases were penicillin non-

susceptible in Israel, suggesting the need to monitor the invasiveness of 12F (Janoir et al., 2016, Rokney et al., 2018).

Similarly, although 24F was not significantly more invasive than 19A, it appeared to be prone to cause meningitis. Serotype 24F has emerged as the leading cause of pneumococcal meningitis in France after PCV13 introduction in children 0−23 months (Levy et al., 2016). In Norway, 24F showed an increase in incidence and clinical severity (Vestrheim et al., 2016). Further studies are required to understand the epidemiology of individual serotypes on the burden of IPD from a clinical perspective to inform on new prevention strategies in the post PCV era.

This analysis has limitations. Firstly, the choice of 19A as the reference type even though it is not included in PCV10 merits discussion. This serotype is likely to be prone to selective advantages due to high genetic diversity, clonal shifts, and antibiotic resistance (Beall et al., 2011). However, it was the only serotype present in all datasets, and this enabled an estimation of ORs across multiple settings. The comparison with 19A represents 19A invasiveness mostly in populations immunised. The sensitivity analyses showed no impact on the overall conclusions when PCV10 dataset was excluded. To further explore the invasive disease potential of serotypes and address the limitation of a fixed reference type, I estimated the invasive disease potential of non-PCV13 serotypes in relation to other circulating non-PCV13 serotypes which would eventually represent the competing strains in the nasopharynx that could result in IPD.

Secondly, some of the serotype-specific estimates are affected by low numbers of cases and heterogeneity was noted. As the number of childhood IPD cases has decreased upon PCV use, estimates of invasive disease potential based on incidence rates (which were not available for this analysis), will be required. Furthermore, sampling of carriage cases differed across settings, where antibiotic use is likely to vary. As these limitations affect precision and the ability to detect significant differences, I conducted a wide range of sensitivity analyses, and I focused on describing estimates and their

plausible range of values rather than conducting significance tests to avoid issues of multiple comparisons. However, I did not assess the impact of other factors on the estimates of invasiveness, such as the role of rates of blood culturing or antibiotic use. As these factors are likely to vary across sites, their role on estimates of invasive disease potential and heterogeneity remains to be assessed.

Thirdly, biases leading to under or overestimation of invasive disease potential cannot be excluded. The IPD data came from passive surveillance systems and carriage data, usually from cross-sectional studies. These sources are vulnerable to reporting and ascertainment biases. However, it has been shown that cross-sectional data can be used reliably to examine invasive disease potential of capsular types (Sleeman et al., 2006). Changes to clinical practices and blood culturing in the post-PCV era could also lead to underestimation of the role of *S. pneumoniae* in particular in ambulatory cases of pneumonia or bacteraemia (Weinberger et al., 2011).

Additionally, the introduction of PCV would have likely changed the ratio of bacteraemic and non-bacteraemic pneumonia (the proportion of latter having increased substantially after PCV implementation) (Benfield et al., 2013). The use of post-PCV data only a few years after introduction for settings that have transitioned to PCV10/13 is also a source of bias since the development of new equilibria after PCV introduction may take time and up to 6-16 years (Shiri et al., 2017). PCV immunisation is effective on decreasing IPD and colonisation for targeted serotypes, but replacement by non-PCV13 serotypes takes time which could have led to an underestimation of the role of non-PCV13 serotypes.

This study also has several strengths, including the wide geographical spread of the included settings and the supplementation of published literature with data from collaborators, which enabled serotype-specific analyses and minimised information biases. I also included long study periods to minimise the risk of random error due to small sample sizes or outbreaks of serotypes causing IPD. I have presented analyses for many serotypes, selected by their

role in causing disease in various settings. Additionally, I report various sensitivity analyses and provide meta-estimates based on a random-effects model to highlight issues of heterogeneity across studies. Limitations withstanding, the analyses presented in this chapter provide a comprehensive view of the invasive disease potential of *S. pneumoniae* serotypes, causing childhood IPD in the post-PCV era.

4.7 Conclusion

There is substantial variation among pneumococcal serotypes in the potential to cause IPD and disease presentation, which is influenced by age and time after PCV introduction. This variation poses challenges to the design of the optimal composition of PCV in different settings. Because of the diversity of pneumococcal serotypes, surveillance of IPD and carriage is critical to understand the sustained effectiveness of current PCV products in the longer term and guide the development of future PCVs for use in specific settings.

5 Pneumococcal conjugate vaccination and paediatric IPD in Latin America: an overview of the evidence

5.1 Background

Several Latin American countries have introduced highly valent PCVs (PCV10 or PCV13) into their national immunisation programmes since 2010. Considerable protective effects these vaccines have been recorded, resulting in an overall reduction of pneumococcal disease in children <5 years, including IPD. The main driver for this reduction has been a decline of disease (Agudelo et al., 2018, de Oliveira et al., 2016) and carriage (Silva et al., 2020) associated with serotypes included in the vaccines. However, little is known about the role of non-vaccine serotypes (i.e., serotypes not included in PCVs).

Specifically, for IPD, the impact of PCVs in Latin America has been examined, but the focus of these studies has not been on non-vaccine types. In a systematic review, de Oliveira et al. (2016) found estimates of the overall effectiveness against all-type meningitis ranged from 13.3% to 62.8% for all-type meningitis and 77% to 87.7% for PCV10-serotypes. For IPD, overall reductions against all-type IPD were reported in most sites, except in one place (range: -14.7% to 66.0%). A notable finding of this review is the paucity of data for different countries of the region. Estimates for meningitis were identified in five studies, all from Brazil.

Similarly, data for IPD were from four studies, mostly representative of PCV-10 settings (Brazil and Chile). Agudelo et al. (2018) quantified the protective effect of highly valent PCVs. Researchers standardised multi-national surveillance data using population estimates for young children to conduct an interrupted time series analysis for all-type IPD and 19A. A statistically significant reduction in the trend of all-type childhood IPD after PCV10 or PCV13 introduction, compared to the expected rates if no vaccination was available, was found in some (Chile, Argentina, and Uruguay) but not all settings (five other countries). Regarding changes of serotypes, only 19A was

investigated, and no clear change was observed in any of the countries analysed. An important conclusion that can be drawn from these two recent reviews is that most of the available data on IPD and serotypes in Latin America are derived from laboratory-based surveillance systems, particularly the SIREVA II network.

Considering that no study has pooled data from several countries or examined the role of non-PCV serotypes, I aimed to quantify the effect of highly valent PCVs on the incidence of childhood IPD in Latin America to document changes in the incidence of IPD by serotype categories of interest for policymakers.

5.2 Research questions

- What are the effects of highly valent PCVs on the incidence of childhood IPD in Latin America?
- What is the role of non-PCV13 serotypes in childhood IPD in Latin America after the introduction of highly valent PCVs?

5.3 Methods

5.3.1 Data source

This analysis is based on secondary data obtained from SIREVA. Isolates of invasive pneumococcal diseases are reported by participating national laboratories and hospitals in each country. Annual reports are published by Pan American Health Organization (PAHO). I extracted the total number of cases for overall IPD and by serotype for children under five from annual reports 2008 to 2015. The data collection period for this analysis ended in November 2019. Data were extracted by serotype or serogroup, as reported, and by year for all countries available.

Serotype data were grouped into categories: PCV7, PCV10non7 (i.e., not included in PCV7: 1, 5, 7F), PCV13non10 (i.e., not included in PCV10, 3, 6, 19A), and non-PCV13 types (including non-typeable serotypes or those reported as “other”). Data provided as serogroups (instead of serotypes) that were not in groups related to PCVs (i.e., 6, 7, 9, 18, 19, or 23) were classified

as non-PCV13 types. Serotype 6C was considered non-PCV13. Data were extracted and managed in Excel.

5.3.1.1 Meta-analysis

As PCVs (whereas PCV7 and highly valent PCVs) were introduced in different years, and there were differences in reporting, countries were selected for inclusion in a meta-analysis based on data availability. Criteria for inclusion were:

- at least three years post PCV10 or PCV13
- ≥20 cases on average per year

For denominator data, I obtained the population size for children under five from United Nations (UN, 2019). PCV uptake data were obtained from The International Vaccine Access Center (IVAC, 2018). For each country, I calculated annual incidence rates by dividing the number of isolates reported per year by the midyear population. Highly valent PCVs were introduced between 2009 and 2012 in the region. I used the population estimate for 2010 as the denominator to calculate the incidence rate during the reference period. The population estimate for the year 2015 was used as the denominator to calculate the incidence rate after PCV10 or PCV13 introduction. I calculated the average annual incidence rate during the post-highly valent PCVs period by dividing the average annual number of cases reported by the mid-year population for 2015. The software R (version 3.6.0) was used to calculate incidence rate ratios (IRR) and 95% confidence intervals for each site and by year/period. The "*metainc*" command was used to conduct a meta-analysis. A random-effects model (DerSimonian-Laird estimator) was used. Subgroup analysis was conducted by PCV formulation. Heterogeneity was assessed using the I^2 statistic. I describe the heterogeneity level as low to moderate and considerable (Higgins et al., 2003), where a value below I^2 50% denotes low to moderate heterogeneity, 50%-75% as moderate to considerable, and above 75% considerable heterogeneity. The effect of PCVs on IPD are reported as IRR and as the percentage change in incidence ((1-IRR*100).

5.4 Results

5.4.1 Characteristics of serotype data from SIREVA II

Serotype data from 19 countries in Latin America were identified in the annual reports. Among countries participating in SIREVA that have introduced PCV by 2019 (n=19), four are high-income countries, and 15 are low- or middle-income countries. Of these, seven countries (36.8%) met the inclusion criteria (Table 35). Countries were not deemed eligible for inclusion if they reported a small number of isolates (<20 isolates) to SIREVA (n=7), have not included PCV in their national immunisation programme (n=1), or if data were only available for fewer than three years post PCV introduction (n=4). The distribution of isolates by serotype categories from 2008 to 2015 was similar between countries included in the meta-analysis and those excluded (PCV13 serotypes: 74.3% and 80. 9%, respectively, non-PCV13: 25.7% and 19.1%).

In 2015, around 35 million children under five were living in the seven countries included in this analysis. PCV uptake exceeded 90% in all countries, except in Argentina, where it was 82% (IVAC, 2018). PCV7 was implemented in two countries before current PCVs. PCV10 was being used in four countries included and PCV13 in three. A total of 2,812 IPD cases were considered in the post highly valent PCV period and 1,216 in the reference period across all sites (Table 35). A total of 1,064 IPD cases were reported in the year highly valent PCVs were introduced, which were excluded from the meta-analysis.

Table 35 Surveillance and data characteristics of countries included in the analysis

	Before		Highly valent PCV introduction				After		
Country	**Year**	**Isolates**	**Year**	**Isolates**	**Formulation**	**Schedule**	**Years (#)**	**Uptake**	**Isolates**
Argentina	2011	367	2012	270	PCV13	2+1	2013-15 (3)	82%	520
Brazil	2009	198	2010	215	PCV10	3+1	2011-15 (5)	94%	841
Chile	2010	282	2011	241	PCV10	3+1	2012-15 (4)	90%	636
Colombia	2010	134	2011	122	PCV10	2+1	2012-15 (4)	91%	351
Mexico	2010	124	2011	122	PCV7→ PCV10/PCV13	2+1	2012-14 (3)	94%	269
Paraguay	2011	59	2012	52	PCV10	2+1	2013-15 (3)	92%	96
Uruguay	2009	52	2010	42	PCV7 → PCV13	2+1	2011-14 (4)	94%	99

5.4.2 All-type IPD

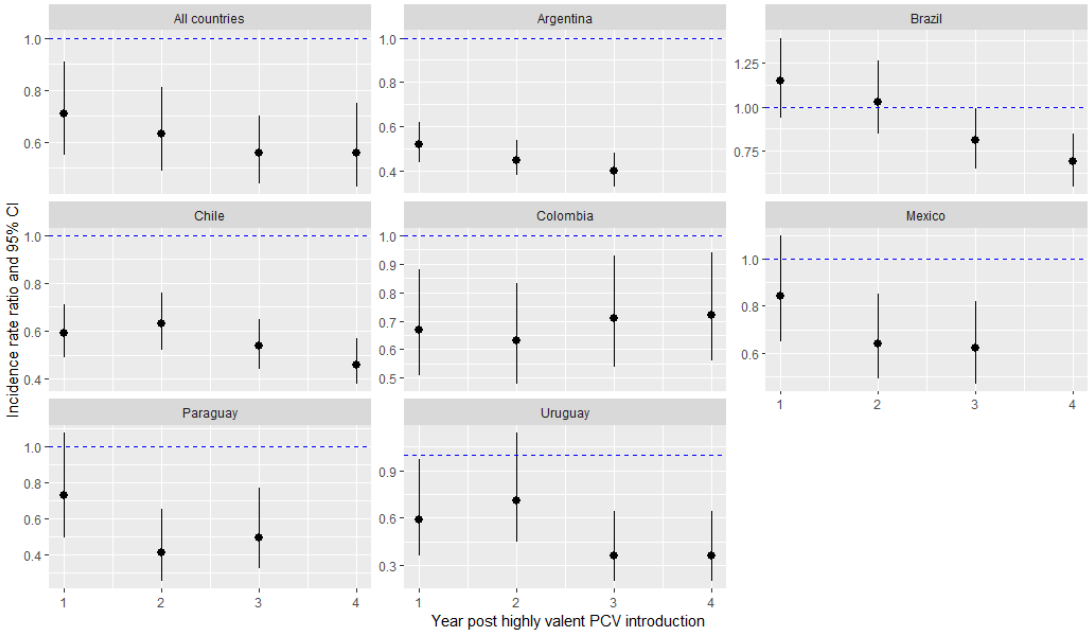
Prior to PCV13 or PCV10 introduction, the overall IPD incidence rates varied by site. For the year before the introduction, higher rates were in Chile (22.7

per 100,000 children under five per year [95% CI: 20.2–25.5]) and Uruguay (21.87 per 100,000 children under five per year [95% CI 16.7–28.7]). Lower rates were in Brazil (1.4 per 100,000 children under five per year [95% CI: 1.8–1.6]) and Mexico (1.1 per 100,000 children under five per year [95% CI 0.9–1.3]). Based on point estimates, IPD incidence rates decreased from introduction year through to the last year of data available (Figure 30). A slight increase in incidence at the end of the post-PCV10/13 period occurred in Colombia and Paraguay, but as shown in Figure 31, the 95% CIs overlapped between years in individual countries.

Figure 30 Incidence rate of all-type IPD (per 100,000 children under five years) per country

Notes: Point estimate and 95% CI showed. Blue vertical line: year introduction highly valent PCV. Countries currently implementing PCV10 are shown in red and PCV13 in blue. Black vertical line: year introduction PCV7.

Figure 31 Incidence rate ratio for all-type IPD over the highly valent PCV years compared to the year before its introduction



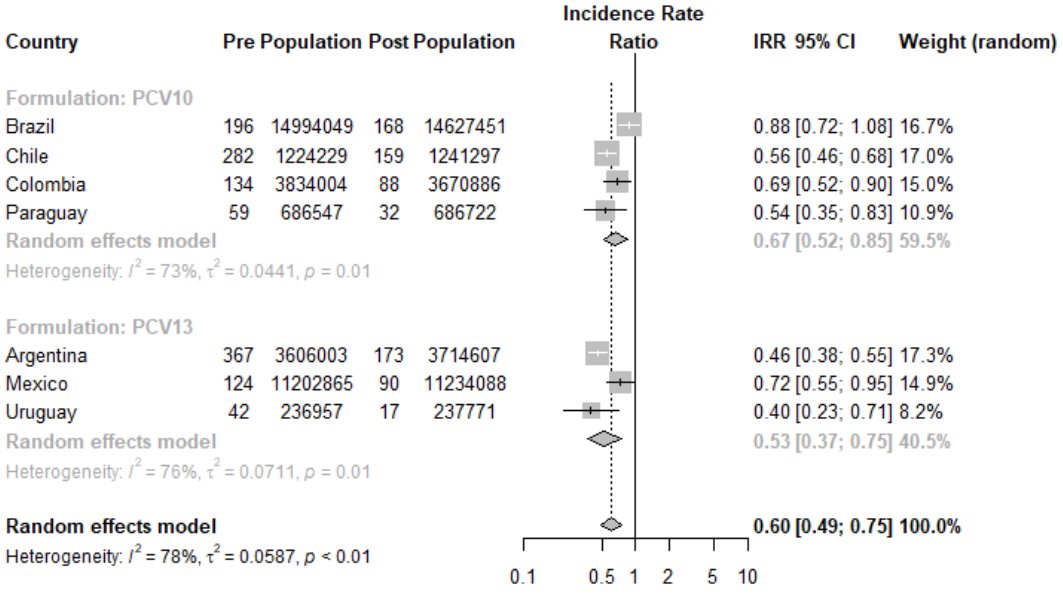
Notes: Pooled estimates of incidence rate ratio and 95% confidence intervals (CI) for all countries are included in Figure 31 for comparison. PCV: pneumococcal conjugate vaccines

Results from the meta-analysis are shown in Table 36. Data were available for three years of high valency vaccine use in all countries (n=7), while data for the fourth year was available from four countries. Pooled analysis indicated an overall decline in all-type IPD incidence during the post PCV years considered when compared to the year before highly valent PCV introduction (Table 36). The magnitude of this overall of 40% (95% CI: 25–61%) should be interpreted with caution as there is high heterogeneity of the overall result (I^2=78%) (Table 37). Additionally, the yearly data show overlapping variations in the annual decline. Based on point estimates, the rates decreased progressively from year one to four-post highly valent PCV (from a decline of 39% in the first year post-highly valent PCV compared to the year before its introduction to 64% by the fourth year of implementation), although with overlapping 95% CI around the IRR (Table 36, Figure 31). Despite variations, the reduction in IPD was consistent in all countries by the last year of data available (third or fourth year after introduction of PCV10 or PCV13) (Figure 31 and Figure 32).

Table 36 Meta-analysis of incidence rate ratios (95% confidence intervals) by year after highly valent PCV introduction

Serotype category	IRR (95% CI) by year after the introduction of PCV10 or PCV13				
	Year 1 (n=7)	Year 2 (n=7)	Year 3 (n=7)	Year 4 (n=4)	Average IR post-PCV years
All-type	0.71 (0.55-0.91)	0.63 (0.49-0.81)	0.56 (0.44-0.7)	0.56 (0.43-0.75)	0.60 (0.49-0.75)
PCV7	0.44 (0.3-0.66)	0.29 (0.2-0.41)	0.19 (0.13-0.28)	0.12 (0.06-0.25)	0.27 (0.21-0.35)
PCV10-7	0.42 (0.29-0.63)	0.28 (0.21-0.37)	0.26 (0.19-0.35)	0.2 (0.06-0.67)	0.30 (0.23-0.39)
PCV13-10	0.93 (0.6-1.43)	0.91 (0.56-1.5)	0.97 (0.56-1.69)	1.47 (0.91-2.36)	0.97 (0.60-1.56)
Non-PCV13	1.50 (1.06-2.11)	1.76 (1.3-2.39)	1.55 (1.11-2.18)	1.59 (1.04-2.41)	1.58 (1.13-2.20)
Notes: PCV: pneumococcal conjugate vaccine. IRR: Incidence rate ratio. CI: confidence interval, n: Number of countries, IR: incidence rate					

Figure 32 Forest plot pooled IRR and 95% CIs for all-type IPD in children under five



5.4.3 Changes by serotype categories

Figure 33 shows the site-specific IRRs (95% CIs) by serotype categories by year after the introduction of highly valent PCVs. Figure 34 provides the results from meta-analyses.

5.4.3.1 Serotypes included in PCVs

PCV7 serotypes progressively declined across all sites, with an overall decline of 73% (95% CI: 65–79) [I^2=49%] when comparing the average rate over the entire post-PCV years to the rate before the introduction of highly valent PCVs (Figure 34A). The pooled estimate indicated an overall decline of 70% (95% CI: 61–77%) [I^2=0%] for PCV10non7 serotypes (Figure 34B). While the average annual incidence during the post-PCV period indicated a decrease in

four countries, the 95% CI fluctuated around one in three (Brazil, Mexico, and Paraguay). Changes in PCV13 specific serotypes (3, 6A, 19A) varied by country with IRR ranging from 0.37 to 2.23 during the post-PCV years considered compared with the year before introduction in each site (Figure 34C). The high heterogeneity (I^2=79%) in the regional estimate showing no clear reduction or increase in PCV13 specific serotypes reduced its reliability. When stratified by PCV product, the meta-estimates suggested a decline in PCV13-implementing sites and an increase in PCV10 implementing settings and the heterogeneity decreased to moderate and low levels increasing the reliability of the estimates (IRR: 0.54 95% CI 0.32-0.89; I^2=50% and IRR: 1.48 95% CI 1.07-2.05; I^2= 29%, respectively).

5.4.3.2 Non-PCV13 types

The average incidence of IPD associated with non-PCV13 serotypes during the post-PCV years increased in three countries compared to the year before highly valent PCV introduction (Figure 34D). The point estimate for the IRR was above 1 for all post-PCV years in Argentina and Brazil, but the confidence intervals fluctuated around 1 in other countries (Figure 33). The pooled estimates indicate an increase of 58% (95% CI: 13-120%) and showed moderate heterogeneity [I^2=64%] in the incidence of non-PCV13 serotypes IPD during the post-PCV years. As shown in the forest plot of Figure 34D this overall conclusion was observed in the summary estimate in PCV10 settings, but not in PCV13 settings where heterogeneity was high and the possibility of no increase cannot be excluded for the available data.

Figure 35 shows the proportional contribution of each serotype to childhood IPD associated with non-PCV13 types. Serotypes 12F, not-typable strains, 24F, 15C, and 22F were the predominant non-PCV13 types, but their proportional contribution varied between PCV10 and PCV13 settings. Figure 36 comparing the distribution of the isolates for predominant non-PCV13 serotypes shows that some serotypes were predominantly reported in PCV10 settings (e.g., 38, 25A) or PCV13 settings (e.g., 24, 16F, 23A).

Figure 33 Incidence rate ratios and 95% confidence intervals by year after the introduction of highly valent PCVs, by country

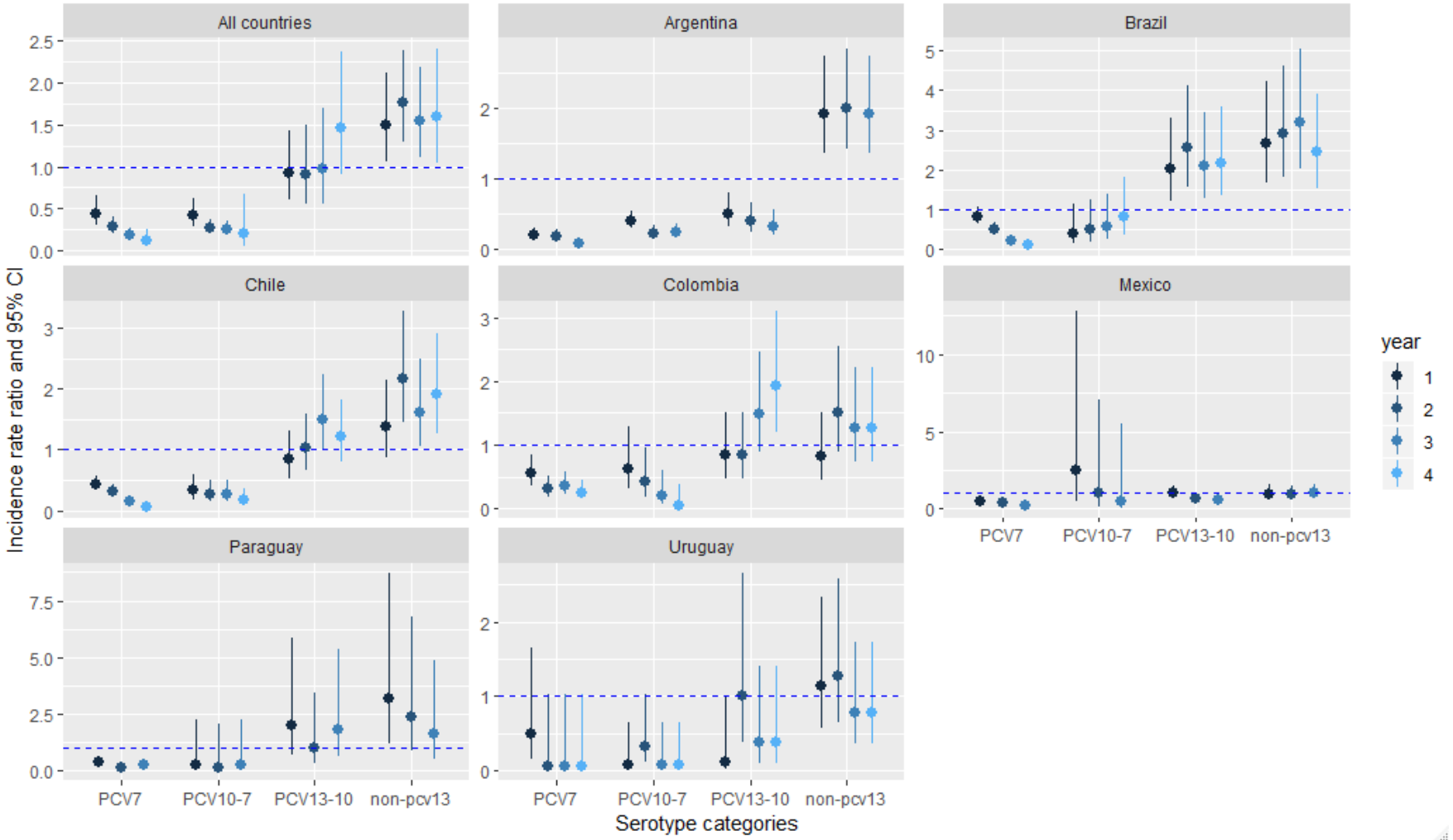
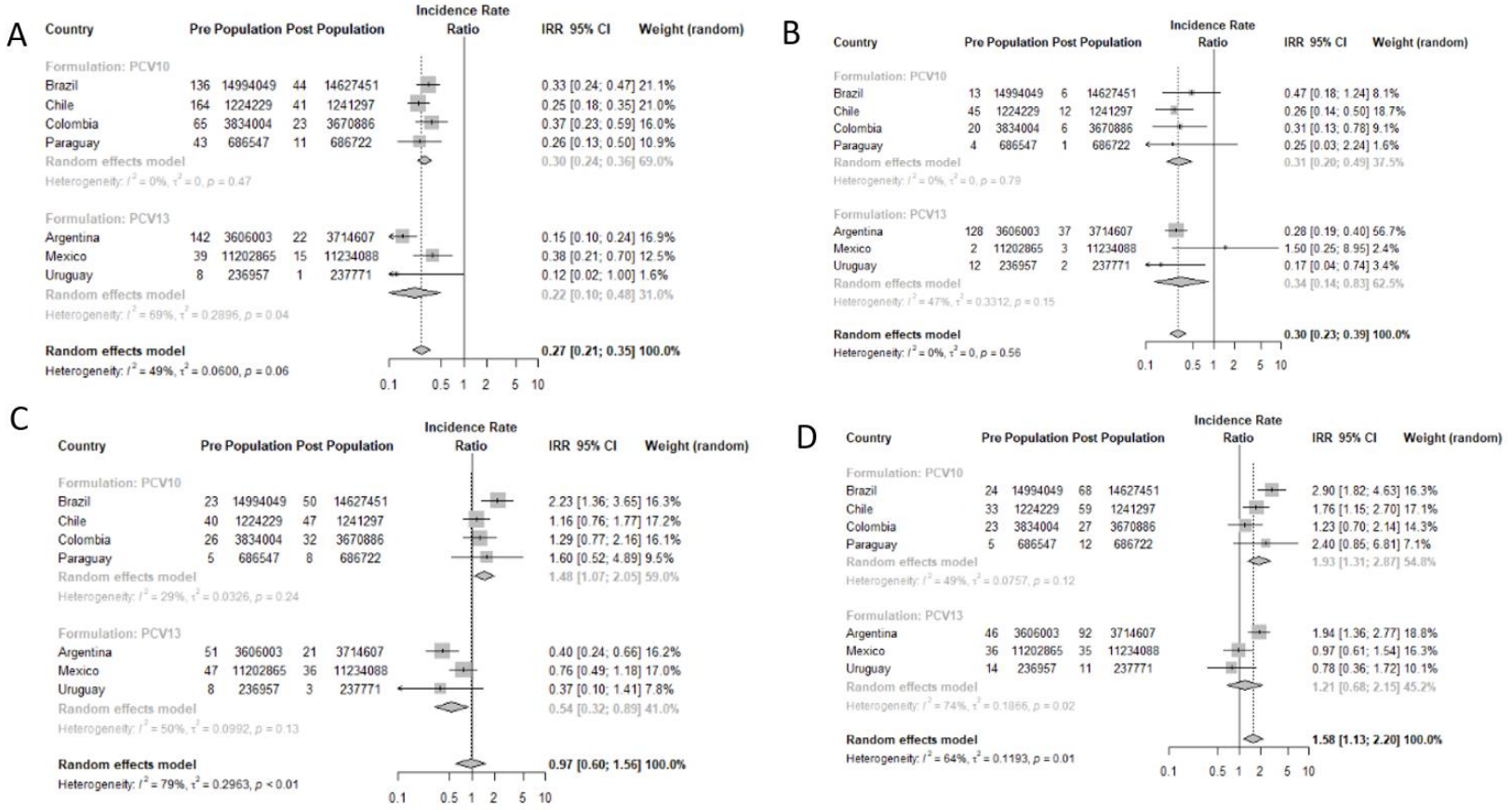
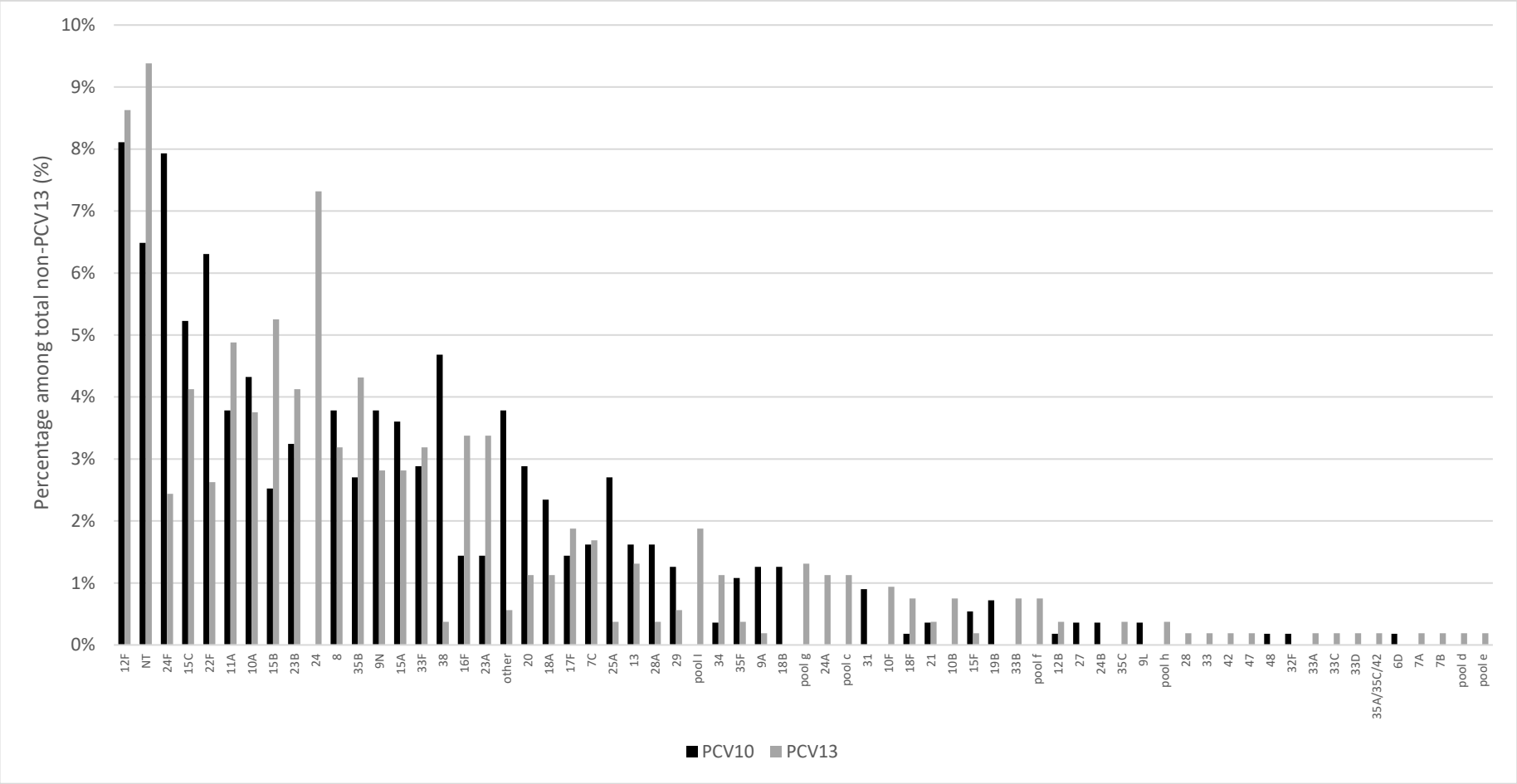


Figure 34 Forest plots showing incidence rate ratios after highly valent PCVs introduction compared with the year prior to their introduction in each country analysed by serotype category



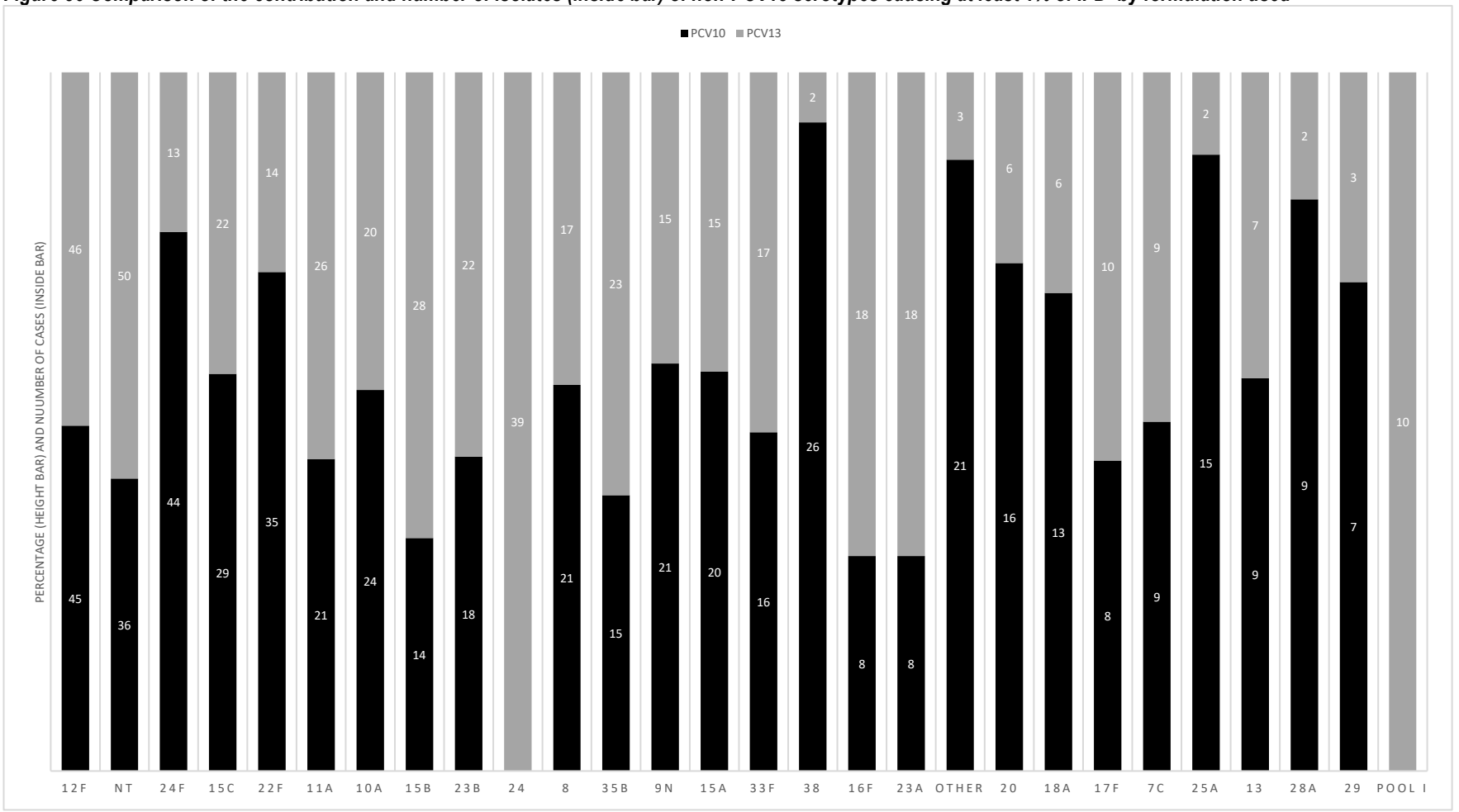
Notes: Serotype categories are as flows: A: PCV7 serotypes, B: PCV10non7, C: PCV13non10, D: non-PCV13. Forest plots show subgroup analysis by PCV formulation. The number of isolates per serotype category is shown for pre- and post-PCV years. IRR: incidence rate ratio, 95% CI: 95% confidence interval. PCV: Pneumococcal conjugate vaccine

Figure 35 Serotype-specific contribution (%) among total non-PCV13 serotype after PCV introduction in Latin America, by formulation



Notes: PCV: pneumococcal conjugate vaccine. Source: SIREVA-II

Figure 36 Comparison of the contribution and number of isolates (inside bar) of non-PCV13 serotypes causing at least 1% of IPD by formulation used



Notes: PCV: pneumococcal conjugate vaccine, IPD: invasive pneumococcal disease, non-PCV13 refers to serotypes not included in PCV13.

5.4.4 Changes in incidence of IPD by serotype category according to PCV formulation

The decline in the incidence of all-type, PCV7, and PCV10non7-IPD was similar in PCV10 and PCV13 settings. For all-type IPD the estimated decline from the year prior to the introduction of PCV10 or PCV13 and the average rate during the three or four years of implementation was higher in settings implementing PCV13 (Figure 32). However, given the presence of heterogeneity in these subgroups and overall meta-analysis, as well as overlapping confidence intervals between estimates, caution is needed to conclude any differences by PCV formulation with the data available.

For PCV7-type IPD, the reductions were above 70% for both subgroups (PCV10: 70% (95% CI 64–76%) [I^2=0%] and PCV13: 78% (95% CI 52–90%) [I^2=69%]). The heterogeneity was moderate in the PCV13 subgroup but it is worth noticing the small sample size, and associated large variability, of the average annual PCV7-IPD isolates in this group. The estimates for the reduction of PCV10non7 type IPD was similar in countries implementing PCV10 with declines of 69% (95% CI: 51–80%) [I^2=0%] and PCV13 66% (95% CI: 17–86%) [I^2=47%].

For PCV13 specific serotypes, based on point estimates, the average annual incidence post-highly valent PCVs declined in the three countries implementing PCV13 for an overall decline 46% (95% CI 11-68%) [I^2=50%], whereas it increased in all four PCV10-implementing countries 48% (95% CI 7-105%) [I^2=29%] (Figure 35C). Considering variations across countries and that there is still moderate heterogeneity in the subgroup analysis in countries implementing PCV13, the estimated increase or decrease in PCV13-targeted serotypes observed by vaccine formulation should take these two points into consideration when interpreting the results .

Overall, the meta-estimates for the change in non-PCV13 serotypes causing childhood IPD cases increased in countries using PCV10 by 93% (95% CI: 31–187%) [I^2=49%] or PCV13 by 21% (95% CI 68-115%) [I^2=74%]. Considering the moderate to high heterogeneity in the meta-estimates it is

important to note that most, but not all countries, had an IRR above 1 (Figure 33) and for four (out of seven) the low confidence intervals was below 1.

5.4.5 Heterogeneity

Based on I^2, heterogeneity was moderate or high in most pooled estimates by post-PCV year when data from both formulations were pooled (I^2 between 50 and 75%, Table 37). Heterogeneity was high (>75%) or in the high end of the moderate category in pooled analyses for all-type IPD and PCV7 IPD. For the latter, the heterogeneity appears to be arising from the PCV13-implementing sites. The heterogeneity in the analysis for PCV13non10 serotypes was lower when all data were pooled than when analysed by PCV formulation. The heterogeneity was low or negligible for estimates of PCV10non7 IPD, except when data from the four countries with data for the fourth year after PCV introduction were pooled. In general, there was more heterogeneity in the estimates for sites implementing PCV13 that in those using PCV10.

Table 37 Summary of heterogeneity (I^2) in pooled estimates of IRR

AComparison	All post-PCV years by PCV formulation			By post-PCV year (any formulation)			
Group	**PCV10**	**PCV13**	**All**	**All yr. 1**	**All yr. 2**	**All yr. 3**	**All yr. 4**
Number countries	*4*	*3*	*7*	*7*	*7*	*7*	*4*
All-type IPD	73%	76%	78%	84%	83%	77%	70%
PCV7 IPD	0%	69%	49%	84%	73%	68%	74%
PCV10non7 IPD	0%	47%	0%	35%	0%	0%	76%
PCV13non10 IPD	29%	50%	79%	73%	40%	84%	64%
Non-PCV13 IPD	49%	74%	64%	66%	60%	65%	59%

Notes: IPD: invasive pneumococcal disease, PCV: Pneumococcal conjugate vaccine, NA not applicable

5.5 Discussion

This meta-analysis of SIREVA-II data from the year of introduction of highly valent PCVs until 2015 identified a large, yet variable, protective effect of these vaccines on childhood IPD in seven countries in Latin America. The variability of the effects and the regional estimates of change in the serotype categories analysed need to be interpreted carefully and in the context of an early phase of PCV programmes. The data available for this analysis is representative of the first three to four years highly valent PCVs use. Thus, the results provide an early perspective of the changing serotype epidemiology of childhood IPD.

IPD associated with PCV7 and PCV10non7 has declined by over 70% after three years of highly valent PCV use compared to the year before their introduction. These estimates are within the range of the decline in IPD associated with PCV7 serotypes three years after the introduction of PCV13 or PCV10 in nine European countries in which the estimate was 69% [95% CI: 29–88%] and for PCV10non7 which was estimated to be 71% [95% CI: 64–77%] (Savulescu et al., 2017). In the meta-analysis conducted in this thesis, the pooled results suggested an increase of incidence of PCV13non10 serotypes in countries implementing PCV10 and a decrease in those implementing PCV13. Although the confidence intervals within each subgroup exclude one, there is moderate heterogeneity; the data do not yet support clear increases or decreases due to 3, 6, 19A in Latin America, regardless of highly valent PCV. Data from subsequent years are needed to get an updated view of the effects of highly valent PCVs in countries in the region with mature programmes and where serotype distribution and vaccine uptake is more stable than during the first few years after vaccine introduction.

The findings from the analysis in this chapter indicate that more research is needed to clarify the role of PCV13non10 serotypes in Latin America. Agudelo et al. (2018), using a similar dataset than the one used in the present meta-analysis, did not identify an increase of incidence of 19A IPD by 2015 compared to expected rates in the absence of PCV. In the Netherlands, a country that introduced PCV10 after PCV7, serotypes 19A and 3 are the predominant serotypes causing IPD after six years of PCV10 use (Vissers et al., 2018). However, the incidence of IPD is low, and while the 19A-IPD incidence in children increased after PCV7, it has returned to pre-PCV levels. Data beyond 2015, as well as from the other country in the region currently using PCV10 (Ecuador), are needed to overcome issues of small numbers and be able to reach robust conclusions of the changes, supported by analyses that allow to explore sources of heterogeneity. These data combined would be useful to both monitor the potential serotype replacement in the region and to inform analyses regarding PCV policies. For instance, as countries consider switching from PCV13 to PCV10 or from PCV10 to PCV13. For countries

considering switching to PCV10, the data available have produced inconsistent results on the potential implications (Wasserman et al., 2019, Gomez et al., 2016, Marti et al., 2013). However, more countries in the region are opting for increasing protection against the three additional serotypes in PCV13 (e.g. Chile, Paraguay). As of 2020, the majority of countries were implementing PCV13 (IVAC, 2021) with only four SIREVA-II participating countries using PCV10.

In this meta-analysis, I found that the incidence of IPD due to non-PCV13 serotypes increased in PCV10-settings by 93%, which can be interpreted as evidence of potential serotype replacement (Savulescu et al., 2017, Hanquet et al., 2019). The pooled IRR in PCV-13 settings also suggested an increase (IRR point estimates over one) but considering the 95% CIs, the possibility of no overall change cannot be excluded. Additionally, the heterogeneity of the pooled estimate is high (I^2= 74%).The estimated magnitude of the increase in non-PCV13 serotypes is similar to the increase estimated in Europe by the third year post highly valent PCVs. Notably, there was a little variation on the year-on-year change of non-PCV13 IPD IRR in individual countries or all pooled estimates. The lack of a measurable progressive increase in the incidence of non-PCV13 IPD over the years may be explained by the lack of the emergence of dominant serotypes in the period assessed (i.e., early years of highly valent PCVs). However, the pooled yearly estimates and wide confidence intervals may also be impacted by small sample sizes. With regards to predominant serotypes in the post-PCV periods, such as 12F, 24F, 15C, 22F, and those not typed, it is important to note that their proportional contribution varied between PCV10 and PCV13 settings. The role of specific non-PCV13 serotypes could not be compared to the reference pre-PCV period because data in SIREVA-II were not available for individual serotypes before 2010. As PCV programmes continue to mature in Latin America, it remains important to obtain serotype-level data to allow an examination of the trends and potential replacement of non-PCV13 serotypes in the region.

The pooled analysis conducted in this thesis has several limitations which should be considered when interpreting the results. First, data are representative of high and upper-middle-income countries in the region and with the longest history of PCV use. Yet, the data available for these analyses are representative of early years of highly valent PCV use. Based on evidence of decrease of IPD in other countries and the effectiveness of PCVs, more contemporary data would be required to quantify the longer-term effects of the vaccines in Latin American countries. Countries included in this meta-analysis, except for one (Mexico), are from South America. Data from Central American, Caribbean, and other South American countries were suboptimal as they did not meet the minimum inclusion criteria established. The difference in the number of isolates reported across countries suggests the data reported to SIREVA-II are not representative of the burden of disease in these countries. For instance, in some countries, only four isolates were reported during the year. Second, the use of a common protocol for reporting of isolates could not be verified, but it is important to note that SIREVA-II has been established for several years. Thus, I assumed little variation had taken place in the reporting criteria, and if any, it would have affected countries similarly. Third, key information which would have supported an assessment of data quality is not available from surveillance reports, such as information on serotyping performance (i.e., serotyping/total number of IPD reported). I addressed this limitation by selecting countries with enough isolates reported to conduct a meta-analysis but verification of data from each country should be conducted to strengthen the quality of the data. Examples for this verification is discussed further in section 6.4. Fourth, since the number of years after the introduction of highly valent PCVs varied by country, pooled IRR estimates comparing average annual rate during these years and the year before PCV13 or PCV10 could skew results, overestimating the role of serotypes targeted by the vaccine and underestimating the role of those that are not when presented as a summary estimate. However, annual estimates are also reported to be able to examine these changes separately recognising the dynamic nature of pneumococci epidemiology. As more data become available, analyses per

post-PCV year representative of more countries or based on a similar number of years will be possible. More recent studies have begun to conduct such analyses and focusing on the years when serotype had stabilised after PCV introduction (Garcia Quesada, 2021). To date, the latest annual SIREVA-II report available is from 2016 (made available late 2019). The annual reports from SIREVA-II for 2016 through 2018 became available outside the data collection for this thesis (published in December 2019, December 2020, and July 2021). Due to the COVID-19 pandemic, data for isolates from IPD cases in 2019 and 2020 were requested by PAHO to countries during 2021. The lag in information being released prevents timely and up-to-date analyses, which can inform vaccine policies aiming to decrease pneumococcal disease in Latin American countries.

5.6 Conclusion

Overall IPD incidence in children has decreased in seven Latin American countries implementing highly valent PCVs and with sufficient data to be evaluated. The decrease has been driven by reductions in IPD associated with PCV7 and PCV10non7 serotypes. More research is needed to clarify the role of PCV13non10 and to characterise the role of non-PCV13 serotypes in Latin American countries, especially as the vaccination programmes mature and the majority of the countries are now implementing PCV13. Data from the laboratory surveillance network SIREVA-II is a valuable and essential resource to monitor the characteristics of pneumococcal disease. However, reporting of serotype data and quality checks, which have not changed in the eight years evaluated, could be enhanced to improve assessments of the impact of PCV programmes in the region.

6 Results and general discussion

In this thesis, I aimed to answer questions related to global serotype epidemiology of IPD in young children and their relative importance in settings where PCVs have been introduced. Each chapter presents a detailed discussion of the questions examined. In this section, I aim to summarise the main findings in the thesis and discuss their strengths and limitations to formulate recommendations for future research.

6.1 Summary

In Chapter 1, I presented a general overview of the pneumococcal disease, with emphasis on childhood IPD, PCVs and the characteristics of serotype epidemiology in children. Together, these elements represent the focus of this thesis.

Chapter 2 provides a methodology overview and rationale for the concepts, databases, and analytical processes used throughout the thesis to answer the research questions.

In Chapter 3, through a systematic review of published and grey literature, I examined questions on the magnitude of the impact of vaccination with highly valent PCVs on the incidence of IPD in young children in different settings. I focused on data from research or published population-based studies and conducted a meta-analysis of IRR. A previous study quantifying the impact of PCVs across multiple settings was conducted for after PCV7 introduction. When analysed by serotype categories, there is a consistent overall decrease in the incidence of IPD due to vaccine serotypes and an increase in the incidence of non-PCV13 serotypes, the latter not being enough to offset an overall decrease. Interestingly, while heterogeneity in the meta-estimates for PCV13-IPD was high, it was negligible in the meta-estimate for non-PCV13 IPD. In this chapter, I also described the burden of IPD that is associated with individual serotypes. I showed how the proportional contribution of each of these varies by region. The estimates highlight the leading role of 19A but also show that other serotypes, including some not included in PCV13 such as

15BC, are being commonly detected among IPD cases in young children across settings. Before this research, the distribution of serotypes among IPD cases globally had only been examined in a single previous study. Thus, these estimates add to the body of global health evidence to understand the shifting epidemiology of the pneumococcal disease in the target population for vaccination after PCVs were rolled out.

In Chapter 4, I investigated the invasive disease potential of serotypes circulating in different settings after the introduction of PCVs. By conducting a meta-analysis, I aimed to describe a key feature of individual serotypes that impact the levels of replacement in IPD. Through the analyses conducted, the invasive disease potential of most circulating non-PCV13 serotypes was lower than the highly invasive 19A serotype and other serotypes included in the vaccines. Interestingly, even though serotypes 15BC ranked seventh in terms of invasive disease potential compared to other non-PCV13 serotypes, it ranked first among serotypes causing IPD in young children. The analysis conducted in this thesis with data from study periods after introduction of PCVs confirmed previous findings from the pre-PCV era in that serotypes vary in their ability to cause IPD. The results on the invasive disease potential of individual serotypes circulating in different settings after PCV introduction had not been estimated before. The estimated low disease potential provides evidence as to why there has not been a substantial increase in the incidence of IPD due to non-PCV13 serotypes.

An important gap in the literature, identified in Chapter 1, was further examined in Chapter 5. Considering the lack of population-based incidence data for Latin America, I used data from the regional SIREVA-II system to conduct analyses on the impact of PCV on childhood IPD. The results from this analysis expand on the literature available for this region in which a previous study, using the same database, had focused on serotype 19A. A decrease in the incidence of IPD has been quantified through meta-analysis. However, this change has been variable in the different countries with enough data to analyse. The reductions in the burden of the disease appear to be associated with reductions with PCV7 and PCV10non7 serotypes. Considering the data

scarcity in the region documented and that most of the Latin American countries introduced pneumococcal disease after 2010, this analysis emphasises the need for research to clarify the role of PCV13non10 serotypes and to monitor the role of non-PCV13 serotypes in Latin America.

6.2 Findings in context

Vaccines, and especially childhood vaccines, are considered some of the best cost-benefit interventions in global health. Several reflections on the implications of the results presented in this thesis can be made on the relationship between serotype epidemiology and vaccine programme implementation, development, and research and surveillance of pneumococcal disease. In this section, I contextualise and discuss the results from a global health perspective.

6.2.1 Implications for vaccine development

It is important to remind the reader that available PCVs currently are directed against a limited number of serotypes that have been introduced into national immunisations programmes to prevent IPD.

Four key observations emerge from the analysis of proportional-based contributions of serotypes to IPD, which are related to vaccine development. First, estimates based on data from early years of PCV use show that serotypes included in the available PCV formulations are still circulating and causing IPD in children, with 19A as the main serotype across all regions, except in the Eastern Mediterranean. In this region, where PCVs have not been used widely and for long period yet, PCV7 serotypes still contribute to the largest percentage of childhood IPD. While these findings provide insights into different epidemiological post-highly valent PCV scenarios, they also show that due to the large difference in the introduction year of the vaccines across the globe, early or regional assessments of the role of non-PCV13 and impact of the vaccines can be influenced by heterogeneity and biases, which could underestimate the effect of PCVs on IPD associated with targeted-serotypes. The estimates emphasise the importance of a continued assessment of the

distribution of serotypes causing IPD once the vaccination programmes have matured, and serotype trends have stabilised after PCV introduction. Second, the estimates from the analysis presented in this thesis show that the diversity in non-PCV13 serotypes is dynamic after PCV roll out. A different number of non-PCV13 serotypes featured among the leading types causing IPD in young children, with Europe showing the largest diversity. Among these, serotype 15BC was commonly identified as a leading serotype across the region. Third, based on the data available, 16 serotypes account for 80% of childhood IPD overall, but regionally the number of serotypes accounting for this percentage ranged from 9 to 15. Fourth, no eligible data in published reports describing the proportional contribution of serotypes to IPD in young children were identified for South-East Asian countries.

Together, these observations provide a picture of how PCV programmes are effectively reducing or eliminating IPD caused by the serotypes in the available formulations. The discrepancies across world regions and the quantitative estimation of leading serotypes are informative for the next generation of PCVs in terms of their potential formulation and target populations. The regional estimates agree with previous findings that disease burden associated with specific serotypes declines more rapidly with higher vaccine coverage and longer use over time (Shiri et al., 2017), which applies to North America, Europe and Western Pacific. Naturally, this decline gives room for an increase in the frequency of colonisation, and potentially, IPD associated with serotypes not targeted by the vaccines, which will vary depending on the susceptibility of hosts at risk, the reduction of leading serotypes and the invasive disease potential of the circulating serotypes.

The meta-estimates of the invasive disease potential in this thesis give further insights into the phenomenon of limited serotype replacement in childhood IPD post-higher valent PCVs. Even though the invasive disease potential for serotypes 12F, 8, 33F, 24F, and 22F was high compared to 19A or other non-PCV13 serotypes, none of these serotypes was the top non-PCV13 serotype in IPD isolates from children. Their proportional contribution to IPD was estimated to be less than 4% overall. In fact, in all world regions, 15BC was

found to be the leading non-PCV13 serotype in childhood IPD in the review in Chapter 3, and a serotype commonly carried in the nasopharynx of young children (based on data from databases included in Chapter 4) but its contribution to IPD yet was around 8% and the invasive disease potential on the mid-range of the spectrum of among non-PCV13 serotypes (in Chapter 5). These findings show that while some serotypes can be considered highly invasive, this does not mean that they are causing a substantial amount of disease. Secular trends, antimicrobial resistance profiles, and carriage prevalence can, in addition to other characteristics such as invasive disease potential, can influence the serotype's associated burden of disease. In fact, a 20-valent PCV by Pfizer designed for adults, includes 8, 10A, 11A, 15BC, 22F, and 33F because they are associated with high case-fatality rates and/or associated with antibiotic resistance in this population (Pfizer, 2020).

6.2.2 Implications for vaccination programmes

One key contribution of this thesis to the field of childhood pneumococcal disease is the systematic examination of the magnitude of the impact of highly valent PCVs and the quantification of this impact. As mentioned in the summary before, the impact of vaccination with highly valent PCVs on the incidence of IPD in young children was explored in two chapters. The results in both chapters provide consistent evidence that there has been a reduction of incidence rates of IPD in young children after PCV10 or PCV13 introduction.

Though data are mostly available for the early years after PCV13 introduction, the meta-estimates showed an overall reduction in the incidence of any type-IPD in children under two years. This decline in the incidence of IPD in this age group was of similar magnitude to the reduction estimated for incidence rates among children under five years. In Latin American countries, the pooled estimated change in the incidence of IPD before and after PCV introduction was similar to those estimates from other research studies, especially for countries implementing PCV13 and slightly lower and with wider confidence intervals in countries implementing PCV10 yet still showing a decrease. It is important to note that data are from observational studies and several factors

could play a role in driving this decrease in IPD (e.g., improvements in socio-economic conditions that could prevent severe pneumococcal disease). However, the consistent findings of a similar effect on the incidence of childhood IPD serve as supporting evidence of the magnitude of the impact of PCVs. Awareness of the still high burden of this vaccine-preventable disease and the quantification of the powerful impact of PCVs is important to support the introduction or expansion of immunisation programmes in all countries.

Even though PCVs have existed for two decades, as of 2019, 42 countries had not introduced a pneumococcal vaccine in their childhood immunisation programme (WHO, 2020). Since it was first developed, countries have reported affordability of PCVs as an important concern or barrier for implementation (Alderson et al., 2019). The challenges in accessing a vaccine for one of the biggest killers represents an important global health inequity problem. It has taken decades for PCV to be introduced in countries with the highest burden of pneumococcal disease.

COVID-19

In the context of the COVID-19 pandemic, it is important to note that at the end of 2020, a fourth formulation of PCV became available. The Serum Institute of India's PCV Pneumosil®, with ten serotypes (1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F, and 23F), received marketing authorisation in India (PATH; and India, 2020) and in December gained authorisation by WHO. Although the results of the clinical trial in The Gambia have not yet been published, the available information on safety and immunogenicity (Clarke et al., 2020), and cost were enough to secure a supply agreement with UNICEF for ten million doses annually for ten years (Global News Wire, 2020). The accessibility to this vaccine is an important milestone because it is designed to offer similar or greater protection to the other decavalent formulation (Synflorix®) but at a cost that is affordable for countries with a high burden of pneumococcal disease (US$2 per dose, (Alderson et al., 2019)). It is also regarded as an essential option to address the so-called "middle-income country gap" for pneumococcal

vaccines, enabling these countries to introduce the vaccine since at the current cost and without GAVI support, this public health intervention has been regarded as cost-prohibitive (Usher, 2019).

Based on the estimates from this thesis, the ten serotypes in Pneumosil® would cover 42% of childhood IPD in Africa (based on data from four countries) compared to 32% covered by the other decavalent formulation, Synflorix. For Latin America, Pneumosil® would provide coverage for 60.5% of the serotypes causing IPD, compared to 38.9% by serotypes in PCV10 by Synflorix. Unfortunately, there were no data available from Asian countries to assess this vaccine's potential impact on IPD. Manufacturers in India have pointed that Pneumosil® covers over 71% IPD causing serotype (Pfenex, 2020). It has been estimated that full country introductions in India and Indonesia would increase demand for PCV by ~55 million doses (WHO, 2020). There are limited serotype data from the countries where this vaccine is intended to be used, and in the absence of these data the main factors having a bearing on vaccine choice would be programmatic. This dynamic, highlights the need to support the continuation of vaccinations programmes, establish surveillance systems to monitor coverage, and to invest in the surveillance of immunisation programmes.

Additional challenges related to disruption to availability and demand for immunisation services during the ongoing COVID-19 pandemic are likely to have a negative impact on the progress achieved in reducing IPD burden. As a result, it will be necessary to re-examine the impact of COVID-19 pandemic and the need for mass vaccination among adults to control SARS-CoV-2 infection on childhood IPD –both disease and vaccination. It can be expected that incidence rates of IPD in young children will decrease due to physical distancing measures, stay-at-home orders, mask use, sustained school closures for most of 2020; as opportunities for transmission are reduced. However, due to the same reasons and disrupted health systems, a decline in child vaccination coverage may occur in some places (Bramer et al., 2020).

Intensive efforts will be needed to ensure children are not susceptible to vaccine preventable IPD.

The estimated magnitude of the increase in the incidence of non-PCV-13 IPD across settings is another contribution of this thesis. It is worth noting that there was high heterogeneity in the meta-estimates for the decrease in the incidence of PCV13 serotypes. However, heterogeneity was negligible for the meta-estimate, indicating an increase in incidence due to non-PCV13 serotypes. Even though the heterogeneity in these estimates is similar to that reported in previous studies in this area (Feikin et al., 2013) and are useful to give an idea of the scale of the issues at the global level, it calls for caution when applying the overall meta-analyses results to individual countries. Considering that PCV programmes are adapted to local conditions and that programmes are likely to achieve different coverage, the comparability of populations decreases once heterogenous immunisation programmes are implemented. The high heterogeneity in the estimates thus reemphasises the need to examine local trends.

The overall meta-estimates presented in this thesis are, however, useful to show that, globally, serotype replacement after highly valent PCV use is occurring in childhood IPD. The results also indicate that the magnitude of such replacement at the local level has not been large enough to offset the protective effects, except in two European countries. Evaluating or being able to estimate the magnitude of serotype replacement locally is crucial to understand better the potential burden of disease that is not preventable by immunisation now. The findings from this thesis indicate that evidence of non-PCV13 burden will most likely be realised in high-income settings unless laboratory and epidemiological surveillance of pneumococcal disease are enhanced in resource-limited settings. Despite limitations, the consistency in the results supports the conclusion that serotype replacement in IPD among children is occurring to some extent.

Global health projections by WHO indicates that as manufacturers licence additional PCVs, formulations with seven to 20 serotypes could become

available between 2020 and 2025. This thesis then provides a summary of the serotypes that are currently causing the disease, which is important to know as vaccines able to protect to a wider range of serotypes are likely to be needed. The findings on the impact of highly valent PCVs on IPD by serotype categories and the current proportion of IPD that is associated with a particular serotype presented here can be of use to policymakers to support the introduction, continuation, or expansion of PCV programmes for children depending on the world region.

6.2.3 Implications for surveillance

Firstly, consistently throughout this thesis, a major finding is that the data identified through systematic reviews, including grey literature sources, show there is plenty of need for more research on pneumococcal serotype epidemiology globally. Considering the disparities in implementation, research on the burden of disease associated with serotypes after PCVs have been introduced can only be assessed in countries that have implemented the vaccines. Thus, beyond identifying a need for research or publications in resource-limited settings, there is a need to support the introduction of PCVs to maintain or achieve the positive effects of immunisation. The results for regions such as Africa and Eastern Mediterranean, based on four studies for proportional-based data, for instance, evidence the need for ongoing surveillance of circulating pneumococcal serotypes.

Second, most studies report serotype data from passive surveillance systems, with a focus on laboratory results for which epidemiological or clinical data (e.g., comorbidities) are not always available. These serotype data are affected by surveillance bias, which could result in an underestimate of the true burden of disease and miss cases due to serotypes. However, for the purpose of this thesis, the results show that, despite limitations of surveillance data, these are of great value for countries and for global health efforts to understand the burden of pneumococcal disease. For global health research, it should be noted that IPD serotype data, even in research/peer-reviewed studies, are from notification systems. Despite efforts to obtain re-analysed data from

collaborators to analyse associations between serotypes and clinical syndromes or co-morbidities, only eight countries were able to provide data by the former and none for the latter. Chapter 5 adds to the body of evidence on global pneumococcal disease using a similar approach to research conducted in Europe (Savulescu et al., 2017). Evaluations of the global impact of PCV have benefitted to a large extent from standardised protocols (O'Brien and Nohynek, 2003), the examination of IPD after highly valent PCVs is not exempt from this.

6.3 Strengths

The estimates in this thesis are supported by using standardised methods and strict eligibility criteria to enhance comparability across data to be pooled. A particular strength of IPD and carriage data used to estimate the invasive disease potential is that data were re-analysed to ensure they were classified in comparable age categories and serotypes reported in the same way. Nevertheless, to increase geographical representation and increase the number of studies included in the reviews, different types of data were used, and some data were extracted from figures or images using software. When this was necessary, data were extracted by two researchers according to PRISMA guidelines as part of the publication process of this thesis' results.

In this thesis, I focused only on one age group –children under five years of age. This focus is both a strength and a limitation of the thesis. Young children are common carriers of pneumococci and thus at high risk of IPD. Furthermore, by focusing on the group of children at high risk of severe disease, but whenever possible conducting analyses for narrower age intervals, it was possible to increase comparability of the study population while allowing to examine individual serotypes. In many countries, especially HIC, the highest rates of IPD are reported in persons over age 65 years with a still observable burden in children under five years (Naucler et al., 2017), but the vaccine is not recommended to adults. In this thesis, the relative importance of serotypes in older children, adults or elderly is not examined because the objectives were to inform PCV programmes for which young children are the target population.

An important strength of the results in this thesis is the global and regional scope of the searches and analyses. The analyses contribute to the literature of pneumococcal disease because I adapted methods used to describe serotype epidemiology during the pre-PCV era (Chapter 3) or post-PCV era (Chapter 5) to examine the evidence from other settings after PCV had been implemented. By pooling data and developing estimates from studies with variable quality and availability of studies by geographical region in a systematic way contributes to the body of global health evidence for *S. pneumoniae*. Regional estimates support the interpretation of the results and show the similarities and differences in the serotype landscape.

The fifth chapter estimating the IRR by serotype categories in Latin America is another strength of this thesis. There are no previous studies that had used SIREVA-II data this way and, despite limitations, results show that when data are published/available in a format that enables comparisons, these can be of use to begin answering questions about pneumococcal disease prevention. In a study by Agudelo et al. (2020), which focuses on percentage changes and change in individual countries (rather than pooled annual estimates), researchers reached similar conclusions for the region. However, better quality and more granular data are needed to be able to explore more complex questions and to be able to adjust for confounders, which is not possible using data from passive surveillance system as available for this analysis.

A novel contribution from this thesis is the estimation of the proportional contribution of serotypes and the invasive disease potential at the serotype level and for as many serotypes available as data were available for pooled results. While the estimates for the serotypes at this granular level may suffer from small sample sizes, they allow for a comprehensive assessment of the circulating serotypes globally.

6.4 Limitations

Primarily, the results of this thesis are affected by biases related to the study design of the data sources. Most serotype data included in this review are from

observational, hospital, or laboratory-based notifications, studies which are prone to surveillance and selection biases and limit the conclusions that can be made on the causal inference between vaccination and decrease observed. For the outcomes investigated in this thesis, it is most likely that observational data are underestimating the outcomes of interest, IPD, and carriage because these data emerge from passive surveillance systems (for IPD) or cross-sectional surveys (for carriage). Analyses at the serotype level are limited by small samples sizes and aggregated presentation for multiple years that preclude analyses stratified by years, which increase the risk of chance, heterogeneity and confounding playing a role in the meta-analysis.

The second limitation of the analyses in this thesis is the variable quality of epidemiological and clinical data. The analysis of the quality of data shows that an area where studies were commonly deficient is on the description of the subjects. I aimed to minimise potential problems of misinterpretation of the data, but some issues remain, and exclusion of studies based on quality criteria could have been implemented. I extracted data from images or calculated absolute number of cases based on percentages. This could lead to misclassification of some of the datapoints included in the estimates of this thesis, if not appropriately documented in the original study.

The third limitation of this thesis's research questions was related to morbidity outcomes that fall within the IPD case definition. However, I did not focus on non-invasive pneumococcal pneumonia or mortality. Pneumococcal pneumonia among outpatients and hospitalisations represents the largest burden of disease associated with *S. pneumoniae*. Nevertheless, by focusing on a single case definition, it was possible to conduct subgroup analyses by clinical case definitions of syndromes to analyse invasive disease potential where there can be of particular interest due to the high impact on individuals and healthcare systems.

6.4.1 Reflection on key limitations of the initial approaches taken

In this section, I would like to reflect deeper into the limitations of the approaches taken in this thesis and highlight areas where more appropriate analyses could be conducted.

6.4.1.1 Serotype distribution in the post-highly valent PCV era

The meta-estimates for the proportional contribution to IPD of individual serotypes for the years of PCV10 or PCV13 implementation provide insights into the role of different serotype categories in various epidemiological settings, mainly stratified by world region. However, several limitations to the underlying data and the approaches followed to develop these estimates need to be considered when interpreting these quantitative results.

The summary of results of serotype distribution in childhood IPD cases in this thesis highlights geographical differences post-PCV implementation. However, varying years of PCV7 use prior to a highly valent PCV in different countries and data from the early years of PCV10 or PCV13 are likely to introduce bias in the pooled estimates. PCV7 use prior to highly valent PCVs would have resulted in progressive declines of the PCV7-targeted serotypes in IPD. Additionally, to varying degrees, increases in non-PCV7 IPD – particularly those included in PCV13 would be expected, noticeable as early as the second year of PCV7 use but not enough to offset the overall decline in IPD (Feikin et al., 2013). As the vaccination programme matured and countries switched to higher valency PCV products, further declines in IPD would be expected (for the initially seven targets and the additional three or six, depending on the formulation introduction). It has been estimated that PCV7 shortens the time taken for the vaccination programmes with PCV13 or PCV10 to reach a mature stage, defined as the period when trends in vaccine type and non-vaccine type percentages were no longer evident (Garcia Quesada et al., 2021). Thus, this thesis's estimates are likely to pool serotype data from a biased distribution when the contribution of vaccine targeted serotypes would still be fluctuating and at a varying stage of their decline in individual sites.

In the analysis of serotype distribution after highly valent PCVs, seven settings had not used PCV7 before introducing PCV10 or PCV13. For the settings that had, the number of years of PCV7 use ranged from 1 to 10 (median: 3 years, average: 4 years). The number of studies with prior use of PCV7 for three or fewer years (n=16) was similar to the number of studies with four or more years of PCV7 (n=14). For the settings with no or short PCV7 period, the decreases in IPD due to PCV13-targeted types by the end of the period included in this thesis will be variable, yet not the maximum possible magnitude. Conversely, in the settings with longer use of PCV7, the effect of PCV13 in vaccine targeted IPD to be more noticeable and sooner.

The analyses using data from the post-PCV10/13 period would also be affected by biases due to the methodological approaches regarding the length of PCV use. For settings with prior PCV7 use, the PCV10 or PCV13 introduction calendar year was included as a post-PCV year. For PCV7 naïve settings, whenever possible, I excluded the calendar year the highly valent PCV was introduced. Nevertheless, this exclusion was not always possible. No distinction was made if the vaccine was introduced after a certain point of the year, as it has been done in other analyses of serotype distribution post-PCVs (Garcia Quesada et al., 2021). The high heterogeneity observed in the summary estimates highlights that multi-setting analyses should focus on periods when unbiased serotype distribution and trends have stabilised after vaccine introduction.

A second limitation of the approaches undertaken to estimate serotype distribution in childhood IPD in this thesis is the combination of several post-PCV10 or post-PCV13 years instead of annual data. This limitation is partly associated with the data ascertainment process to develop serotype distribution estimates, mainly relying on published observational studies identified through systematic reviews. Data from multiple years were combined into a single data point to increase the sample size for individual serotypes and to enable meta-analyses. The serotype data were available in an aggregated format rather than case-based and multi-year periods rather than a yearly format. The average length of the post-highly valent ranged from one to seven

years and varied by region (in descending order: Africa: 2 years, North America: 3 years, and Europe, Western Pacific, Eastern Mediterranean and Latin America: 4 years).

The use of aggregated multi-year data limits the ability to address biases due to serotype distribution changes, which will occur as time and the protective effects of PCVs progress. The relative change for declines in PCV10 or PCV13 targeted-serotypes and increases in non-targeted ones will vary compared to an average versus a fixed point in time. Using an average from multiple years, especially one that includes the early years of PCV use, can lead to overestimating the proportional contribution of serotypes targeted by the PCV. Instead, assessing the change in relation to a post-PCV year when the effect of the vaccine is expected to have occurred will provide more accurate estimates of declines in vaccine-type IPD. This bias is also likely to underestimate increases in non-targeted serotypes as these are occurring with a variable magnitude over time, influenced by PCV product, uptake, and individual serotypes' characteristics (e.g., antibiotic resistance).

Several modifications could be made to the methodological approach to improve estimates of serotype distribution in childhood IPD. Firstly, in terms of inclusion criteria in the analysis, serotype data should be available in annual format (whereas from the publication or the corresponding authors) to minimise using biased distributions in the development of estimates. Incidence-based serotype data, which was not available for this thesis, would be valuable in overcoming issues associated with proportion-based data and examining changes. Additionally, the analysis could be restricted to sites for which verification exercises can be conducted prior to pooling of data. For instance, determining the proportion of isolates that were not serotyped in a particular setting and any changes in serotyping methods during the period for which isolates occurred would impact the distribution of serotypes. For key serotypes of interest, efforts to collect case-based data, including vaccination and comorbidity status of IPD cases, would be useful to understand the remaining burden. Future research aiming to estimate the serotype distribution

in IPD cases from multiple settings will continue to be required because cases in individual sites may be small. Quantitative approaches will require considerations to deal with potential variations of the duration of different PCV products to minimise biases and develop comparisons across settings. Estimating a threshold for when serotype data are considered stable (Garcia Quesada et al., 2021) is useful for enabling comparisons across sites.

While geographical estimates of serotype distribution in childhood IPD offer a useful perspective for global health research, stratification of the data by this characteristic alone in the post-PCV era did not address the high heterogeneity in meta-estimates. Further exploration of the sources of the heterogeneity would be needed to obtain regional comparisons. The estimates of PCV13-type IPD at the regional level (Chapter 3, page 91) underscore the importance of recognising that PCV introduction has varied within regions. They also highlight those changes in the proportional contribution of PCV13-specific serotypes will be of variable magnitude depending on previous PCV7 use and the post-highly valent PCV period analysed. Given the variations in pneumococcal vaccination programmes, including within regions, estimates stratified by PCV product provide evidence for vaccine policies in a more suitable format. Analysing and reporting estimates by PCV product, rather than geography, can elucidate differences across settings that are important for vaccine policies. I aimed to conduct the analysis by PCV product, whenever possible, for instance, analyses in HIC with similar lengths of PCV13 use in Chapter 3 or subgroup analyses in Chapter 5. However, heterogeneity remained in many of the estimates. This highlights the important to explore the various potential sources for variability to obtain more reliable summary results.

Considering the large heterogeneity in most of the meta-estimates and the predominance of early years of highly valent PCV use in the available data, the pooled estimates' reliability is limited. It is thus interesting to consider my work in light of two of the studies by Bennett et al. (2021) and Garcia Quesada and colleagues (2021) from the PSERENADE project (Deloria Knoll et al., 2021).

Garcia Quesada et al. (2021) estimated the proportion of meningitis cases due to PCV-targeted serotypes. Using serotype data from meningitis cases from all world regions and regression methods to model compositional data, researchers estimated the contribution of each serotype (components) converted into a fraction that adds up to the total number of IPD cases serotyped (sum total). Researchers found that PCV-targeted serotypes contributed to 5% of meningitis cases in children less than five from settings with mature high-uptake PCV10 programmes (over four and up to seven years with uptake above 70%) and 14% in PCV13 sites of similar characteristics. The study provides evidence that serotypes included in the available PCV formulations remain a cause of IPD but to a much lower level than the estimates in this thesis. The findings from settings with mature PCV programmes show the decreased role vaccine types have on IPD once serotype trends have stabilised.

The majority of sites, though not all, included in this thesis were from sites using PCV13. Though direct comparison cannot be made, it is interesting to note that the ten leading non-PCV13 serotypes in childhood meningitis cases reported by Garcia Quesada and colleagues are similar to the ten top non-PCV13 serotypes in childhood IPD reported in this thesis (Chapter 3); though in different proportion and order of contribution (15BC, 12F, 22F, 15A, 10A, 24F, 33F, 23B, 8). 15BC was the leading non-PCV13 serotype in both studies. It is also interesting that the non-PCV13 serotypes with a point estimate for the invasive disease potential (for IPD) higher or similar to 19A for meningitis (Chapter 4.4.5) feature among the leading serotypes in meningitis cases in children under five in PCV13 sites (Garcia Quesada et al., 2021). However, not all the leading serotypes in the distribution had a relative invasive disease potential estimated to be higher than 19A (e.g. 15BC and 23B). The non-PCV13 serotypes 8, 10A, 12F, 15A, 22F, 24F, 33F, 35B contributed individually to at least 3% of the meningitis cases in PCV13 settings (Garcia Quesada et al., 2021). Limitations withstanding, the estimates in this thesis contribute to the field by starting to point towards potentially serotypes for

prevention of specific outcomes. Further research into the likely mechanism of invasion by non-PCV13 serotypes is required to better understand if some serotypes are more common in the nasopharynx and thus increase their opportunity for invasion or if they are more likely to cause invasive disease with each episode of colonisation (Song et al., 2013).

When considering the limitations of the current approach, it is important to discuss that the results in this thesis are limited in terms of data for PCV10-using sites (six out of 40 settings). In contrast, Garcia Quesada and colleagues identified sufficient data to produce estimates for settings implementing PCV10. They found that the PCV13 serotypes not included in PCV10 play a crucial role in childhood meningitis cases. The proportion of 19A in meningitis cases under five was low in PCV13-implementing sites, but 19A remained an important cause of pneumococcal meningitis in PCV10 sites (~25% of the cases), adding to the body of evidence about the protection of each PCV product and the potential for cross-protection between 19F and 19A. Overall, the choice of model, quality and completeness checks, and the large number of sites with long use of the two PCV available in the market allowed for the development of contemporary estimates of serotype distributions for an important public health concern in children.

Bennett et al. (2021) study demonstrates the importance of incidence data to conduct a multi-site evaluation of the impact of PCVs on IPD, especially when associated with specific serotypes. Using data from 45 sites, they estimated incidence rates for the years after PCV10 or PCV13 was introduced. It is noteworthy that the model combined data from settings using either of the products. This combination of data is required and appropriate for this serotype as case counts are usually low in individual settings. No difference in the impact of either vaccine was expected (or observed). The methodological approach included giving appropriate weight to sites based on the percentage of serotyped cases. Researchers found a sustained reduction of serotype 1 IPD across sites after combining data from 45 surveillance sites. The weighted average incidence rate ratio showed heterogeneity in the early years. In this thesis, the data included were mostly representative of this period (Chapter 3,

Chapter 5). Over time, the pooled estimate was less heterogeneous, and the declines were sustained. For children under five, the estimated reduction compared to pre-PCV years reached and sustained levels over 90% after the 4th year of PCV10 or PCV13 use. Though pooled estimates are of limited reliability because of the high heterogeneity, it is worth mentioning that serotype 1 was commonly reported in studies from Europe, Latin America, Eastern Mediterranean, and Africa, which underscore the importance of this serotype globally (Chapter 3). The finding of near elimination of an important serotype in childhood IPD, though mostly representative of high-income countries, is valuable evidence supporting the long-term benefits of highly valent PCVs.

The studies by Garcia Quesada et al. (2021) and Bennett et al. (2021) provide strong evidence of the large protective effects of available PCVs by assessing the substantial reductions in the burden, including the burden associated with key serotypes (e.g. serotype 1 IPD or serotype 19A meningitis in PCV13 settings). Additionally, the studies provide estimates of the contribution of non-PCV13 serotypes in meningitis cases in settings where PCVs have been implemented for over four years. From a methodological approach perspective, both studies provide a set of essential considerations for quantitative multi-site analyses of the impact of PCVs on the relative importance of serotypes in childhood IPD. Such considerations include: the evaluation of a threshold for serotype distribution stabilisation which allows analyses on unbiased distribution of serotypes; the description of criteria for combining data from settings that have used or are using different PCV products; the demonstration of the importance of a stepped approach to analyse serotypes grouped into categories or individually; and the methods proposed to overcome limitations in serotyping of isolates by adjusting population denominators. These considerations in tandem with the use of models are important contributions to the field of serotype epidemiology in the post-PCV era.

6.4.1.2 Invasive disease potential

The meta-estimates on the invasive disease potential of serotypes in this thesis provide evidence on the spectrum of the invasiveness of circulating serotypes in various settings, including some non-PCV13 types for which no estimates were available. For stratified analyses by narrow age groups or by IPD syndromes, most of the interpretations are based on point estimates due to the high uncertainty in the estimates. Thus, it is important to examine the results and interpretations considering the approaches' limitations.

The distribution influences the evolving serotype epidemiology in each site prior to PCV introduction, the different PCV products used, the duration of their use and the uptake during these periods. As noted in section 4.5.1, the data included in the analyses of invasive disease potential in this thesis combine years in which different PCV products were used. All sites included in the invasive disease potential analysis used PCV7, but differences exist in the post-PCV period for which data are available. Briefly:

- late years of PCV7 use in two sites (USA (Navajo) and Colombia)
- early years of PCV13 use in one site (Italy)
- early through the 4th year of PCV13 in two sites (the UK and Israel)
- late years of PCV7 through early years of PCV13 use in six sites (the Netherlands, Norway, Spain, South Africa, USA (Atlanta) and France)

When estimating the invasive disease potential, it is important to consider that PCVs impacts both carriage and IPD of targeted serotypes. In settings where PCV uptake is high (e.g., >70%), it can be expected that the detection of PCV-targeted serotypes in IPD, especially in children under two years of age, will decrease over time as the vaccine directly impacts them. However, the reductions in carriage and IPD, overall or for targeted serotypes, are not parallel, and vaccine effectiveness against IPD or carriage can vary by serotype or PCV product.

For instance, for serotype 3 it has been hypothesized that while PCV13 provides direct protection against IPD, it does so to a lesser extent to nasopharyngeal carriage (Sings et al., 2019). The efficacy of PCV13 against IPD has ranged between 86-95% for the 3+1 schedule and 67-86% for the 2+1

schedule in reviews of the literature (Davis et al., 2013). For PCV10, the efficacy against PCV10-IPD ranged between 72%-100% for the 3+1 schedule and 92%-97% for the 2+1 schedule. At four months of completing the schedule, efficacy against carriage has been estimated to be 62% (95% CI 52-72%) against all PCV7 types. Even though the protection conferred by PCVs is expected to decline over time, but is estimated to be around 42% after five years of vaccination (Polain De Waroux et al., 2015). At a population level, carriage of vaccine-targeted serotypes will continue to decrease with every cohort vaccinated. This means that if the first cohort had ~50% reduction, the next cohort will see 50% circulation of the vaccine targeted serotypes and thus, carriage of targeted serotypes will drop to ~25%. Thus, the relative rate of decline would have a larger effect on IPD during the initial years relative to carriage, especially among immunised children of 0-23 months. The younger children benefit directly from the vaccine being used and both the acquisition rate and density of carriage is larger among them than in older children.

Considering that the two parameters used for estimating the invasive disease potential in this thesis (carriage and IPD) are dynamic in the context of PCV vaccination, using data from the early years of the immunization programme could lead to an underestimation for non-PCV13 serotypes relative to other non-PCV13 serotypes. The ecological niche and opportunity to invade are still occupied by serotypes targeted by the vaccine and that will decrease as the vaccine continues to be rolled out. As mentioned previously, most of the interpretations of the invasive disease potential estimates are based on the point estimates due to the high uncertainty in the estimates. Meta-analyses of invasive disease potential by age should be interpreted with caution due to a reduced number of datasets, small sample sizes per serotype, because for this analyses the serotype data from PCV7 and PCV13 periods was combined. Using data from mature years of PCV vaccination programmes (i.e. years 6 through 10) would provide more adequate data to analyse the invasive disease potential of non-PCV13 serotypes and minimize the risk of confounding due to fluctuating trends or other factors.

6.4.1.3 Effect of highly valent PCVs on childhood IPD in Latin America

There are also limitations to the initial approach undertaken to analyse the effect of highly valent PCVs on IPD in Latin America. One of these limitations is the post-PCV period analysed. As newer data from the region become available and PCV programmes mature, it is important to recognize the limitation of the data used in the analysis in this thesis to quantify an effect of PCVs and discuss additional considerations to the approach prior to further analyses.

The data collection period for the thesis ended in November 2019. Newer data from the one included in the thesis (up to 2015) are now available from SIREVA-II reports. The reports became available in the dates as shown in the table below.

Report	Publication date	Reference
SIREVA-II report 2016	18 December 2019	PAHO (2019)
SIREVA-II report 2017	11 December 2020	PAHO (2020a)
SIREVA-II report 2018	30 July 2021	PAHO (2021)

The reports with serotype data from IPD isolates collected during 2019 and 2020 will be finalized in 2021 (personal communication, PAHO Regional advisor for bacterial VPD Laboratories).

Early assessments are important to advocate for PCVs' benefits, but the estimates developed with such data could underestimate both the impact on the burden of disease associated with targeted serotypes but also the extent of serotype replacement in IPD if any. Additionally, policy changes in the immunization programme can occur over time (e.g., inclusion or exclusion of adults, changes in the formulation used) that requires explicit considerations to minimize biases that can affect estimates of the effects of PCVs. It is important then to evaluate when and for what periods is suitable to assess the effects of the PCVs on different populations.

As of 2020, most SIREVA-reporting countries are implementing PCV13: 14 (out of 18) countries (IVAC, 2021). Of the four countries currently implementing

PCV10, one entered a mature stage (i.e. more than four years of use) in 2015 (Brazil) and the other three in 2016. The data from these countries represent two to three years of stable serotype trends (based on the threshold estimated by (Garcia Quesada et al., 2021) for the distribution of serotypes in meningitis). The fourth country, El Salvador, switched from PCV13 to PCV10 in 2018, so the data currently available is for the six year-period when PCV13 was used. Importantly, El Salvador reports an annual average of 8 isolates to SIREVA-II. Thus the serotype data from this country are limited and was not eligible for inclusion in the analysis due to the small sample size. Conversely to El Salvador, three PCV10-implementing countries changed to PCV13 after four or five years of PCV10 use: in 2015 Peru (Luna-Muschi et al., 2019b) and Chile (González, 2020) and in 2017 Paraguay (Ministerio de Salud Pública y Bienestar Social, 2017).

For the seven countries that met the inclusion criteria in the analysis in Chapter 5, two have used PCV10 consistently (Brazil, Colombia), three have used PCV13 consistently (Mexico, Uruguay, Argentina), and two switched to PCV13 after four or five years of PCV10 use (Chile and Paraguay). For the latter two, SIREVA-II data are available for the first year of PCV13 use. Of the countries eligible for inclusion in the analysis based on SIREVA-II data for 2016 through 2018, two would represent early and consistent PCV13 implementation (Bolivia, Dominican Republic). The third, Peru, in which PCV13 is also used, would require considerations of prior universal use of PCV10 for four years.

Given the variations in PCV use in the Latin American countries' programmes over time, future analyses on serotype epidemiology of IPD will need to integrate aspects of maturity of the vaccination programme, which includes changes in national immunisation programmes' policies. This thesis focused on the post-PCV year or PCV because most countries had implemented a single PCV product. Additionally, a careful examination of the comparability and quality of the serotype data would be required before conducting any pooling of data, especially in light of the high heterogeneity in the estimates obtained in this thesis with data representative of the early period PCV

programmes. In this regard, the approach could be strengthened by conducting data verification exercises with Ministries to increase the completeness and quality of the data reported to SIREVA-II. This verification could help minimise bias and ensure the most appropriate data are included in the analysis. For instance, the annual number of isolates reported to SIREVA-II for each country does not show large yearly variations, except for Mexico. The number of isolates reported to PAHO decreased substantially from 2015 onwards, as shown in the box below. Given this large difference, data for the year 2015 was excluded from the analysis in the thesis. The number of isolates reported in national reports of bacterial disease surveillance, GIVEBPVac (Gobierno de Mexico), is larger than in SIREVA-II based on a decision by the country's authorities to include data from different reporting units in each report (personal communication, PAHO Regional advisor for bacterial VPD Laboratories).

IPD isolates in children under five years in Mexico

	PCV13 introduction	Early years PCV13 implementation				Mature PCV13 programme years		
Calendar year	2011	2012	2013	2014	2015	2016	2017	2018
National reports GIVEBPVac					*50*	*66*	*56*	*68*
SIREVA-II	122	105	80	77	*4*	*3*	*7*	*6*

The red line indicates the end of the inclusion period for this thesis

The availability of more years of SIREVA-II of serotypes from childhood IPD cases in the region and considerations derived from the analysis in the thesis represents an opportunity to strengthen the approach in this thesis. These data would allow for further exploration of site-specific dynamics of serotypes not targeted by the vaccine and an assessment of the region's extent of consistency and differences. Such analyses can be informative for national and regional decisions, as several Latin American countries purchase vaccines through the PAHO Revolving Fund for Access to Vaccines (PAHO). Because of the continued use of PCVs, the Latin American region represents an important source of information to assess the role of non-PCV13 serotypes in middle-income countries predominantly implementing PCV13.

6.5 Future research

In this section, I discuss potential avenues for future research in the field of serotype epidemiology of *S. pneumoniae,* considering the results on the relative importance of serotypes in three main areas: vaccine development, vaccination programmes, and surveillance and ethics.

6.5.1 Vaccine development

There are at least four technologies available to develop new pneumococcal vaccines, and by 2020 there were at least ten vaccines in clinical trials (as reviewed by Masomian et al. (2020)). Two of these vaccines were conjugated vaccines (15- and 20-valent by Merck Sharp and Pfizer Inc., respectively) and for the moment, the impact of only one, the 15-valent formulation, is being studied in children. The other vaccines in development use the following technologies: killed whole-cell vaccine (WCV), pneumococcal toxins in non-toxic forms (PnuBioVax) and recombinant proteins (PPrV and others, using proteins such as PcpA, PhtD, PlyD1, Ply, PhtD, see Figure 2 for more details). Of these, protein-based vaccines are particularly favourable because they would overcome the limitation of conjugate vaccines: offering partial protection due to formulations with a number of specific serotypes. As there is clear country diversity of pneumococcal serotypes causing IPD in children, more research is needed on the technologies that do not target the capsule, but other features of *S. pneumoniae*. It would be important that clinical trials also considered alternative methods of administration of the vaccine, for instance through oral or nasal routes, to enhance antigen uptake, especially for serotypes for which the effectiveness of PCVs has been limited. For example, serotype 3, which ranks third among leading serotypes post-highly valent PCVs and it was associated with approximately 8% of childhood IPD cases (Chapter 3) and its invasive disease potential is similar to serotype 19A (Chapter 4).

Until new technologies are available, conjugate vaccines remain an effective and important method to prevent pneumococcal diseases. The findings of this thesis support the need for coordinate global research on serotype data.

Studies in the systematic reviews conducted for this thesis reported 79 different individual non-PCV13 serotypes. The ability for genetic exchanges between streptococci and the potential for an increase in diversity of pneumococcal capsules will continue to pose challenges to the prevention of IPD. Thus, it is vital that future research –particularly in resource-limited settings includes elements for strengthening laboratory capacity. Data collection for Chapter 5 was concluded in November 2019, date by which SIREVA-II reports were available for years 2008 to 2015. For seven countries, less than 20 isolates were submitted per year. By early 2020 when this thesis was being finalised, SIREVA-II reports were only available until 2016. By the end of the year, data from 2017 were published and data from 2018 were published in 2021. The multi-year delays in the consolidation and publication of these laboratory data and the small number of isolates from some countries pose important limitations for researchers and hinders the ability to conduct research which could highlight the importance of laboratory-based surveillance. Furthermore, the limitations delay the ability for different global health actors to ensure decision-makers recognise the benefits of vaccination in their own setting and the importance of monitoring serotype replacement.

For pneumococcal vaccine development, one could argue that higher valency vaccines are needed to assist in reducing the incidence of disease. However, as is the case of the newest pneumococcal vaccine, the decavalent Pneumosil®, it is possible future conjugate vaccines will not always include more serotypes. Instead, the formulation's design should seek to find a balance between manufacturing cost and processes and potential coverage that meets the public health needs in the prevention of IPD. For these reasons, Pneumosil® has been labelled as a game changer (PATH; and India, 2020), because it targets the most common serotypes in IPD and pneumonia-high burden countries. Effectiveness studies for Pneumosil®, especially in Asian countries, should be well-funded and closely monitored as these could provide valuable evidence for childhood global health. Immunogenicity studies will also be very important to answer scientific and policy questions.

6.5.2 Vaccination programmes

6.5.2.1 Current vaccines

Research into the factors that could increase uptake of PCVs globally would be useful to support pneumococcal vaccination programmes. The research conducted for this thesis, in agreement with other research, shows there is strong evidence of the benefits of universal vaccination with PCVs. The global decreases in incidence of IPD estimated in the analyses in Chapter 3 and 5 are only one piece of this body of evidence. Other evidence on the benefits of high uptake includes herd protection and indirect effects, such as decreased antibiotic use as it prevents disease (Lewnard et al., 2020). To this end, studies assessing the optimal schedule of PCVs could be useful. Any reduction in the number of doses could release some of the burden associated with cost and logistics of current PCV immunisation programmes. England, a country with a mature PCV programme and well-established herd immunity has already introduced a reduced schedule (Goldblatt et al., 2018).

Research is also needed to understand vaccine failure cases and monitor the characteristics of the serotypes driving serotype replacement at a global level, ideally supported by genomic surveillance. The data gathered in this thesis is from periods and from settings where different PCVs had been implemented. It is concerning that serotype 19A, included in PCV13, remains a leading serotype in IPD, yet, data available were mostly representative of early years of PCV13 use. Nonetheless, the differences in trends of serotype replacement after PCV13 though not able to revert the overall protective effect of PCVs but more noticeable in Europe than in the Americas suggest that once highly valent PCV programmes mature and high coverage is sustained, factors such as antibiotic use may be a key factor in the dynamics of serotype replacement. Based on the information available in studies included in the systematic reviews, usually in aggregate format, it is not possible to determine how many of the IPD cases associated with PCV13 serotypes were vaccine failure. The reported reduction in susceptibility to antimicrobials in serotype 19A and others calls for research in policy and vaccines fronts. PCVs have been demonstrated

to decrease antibiotic use (Lewnard et al., 2020), but questions remain as to which antimicrobials should be closely monitored in relation to serotype replacement. The emergence of vaccine replacement due to antimicrobial resistant serotypes has the potential to compromise the benefits of PCV programmes.

6.5.2.2 New vaccines

As the number of pneumococcal vaccines increases, with different serotype formulations, and national immunisation programmes make changes to immunisation policies, studies in comparable settings on the effect that using different vaccines may have at the population and individual level (vaccine failure cases) level will be needed.

Research to address the high cost of PCVs is ongoing and has already yielded a solution (Pneumosil®). Research is needed to address the second problem that PCV programmes have faced. For this, global health actors need to focus on the issue of access, particularly if one common goal of us all is to “ensure healthy lives and promote wellbeing for all at all ages” (Sustainable Development Goal #3). As access is increased and sustained, so will the vaccine pressure on circulating serotypes and the need for surveillance to monitor serotype replacement.

6.5.3 Surveillance systems and ethics

In addition to the implications of the findings of this thesis for surveillance described in section 6.2 to monitor long term trends, epidemiology, and aetiology after PCV introduction, there are other technical areas where research is needed to understand better the burden of *S. pneumoniae* serotypes in IPD.

Latin America, the focus of Chapter 5, is an example of the important challenges that remain for the prevention of IPD. All countries have introduced PCVs, since around 2010. A regional laboratory-based system has been in place for decades. However, most serotype data are available from high-income settings in the region with very little information from other countries. Considering the available evidence, it is not possible to determine the

incidence of vaccine preventable IPD in children from these latter countries, especially in Central American countries. A multicentre observational study in specific sites, supported by active surveillance and estimation of denominators is needed in Latin America and other regions with resource-limited countries. However, while more research on childhood IPD in African and South-East Asian countries is needed, one key priority in these settings is achieving PCV introduction, hampered by cost and fragile health systems.

In this section, it is also worthwhile to reflect on the ethical aspects of future studies on serotype epidemiology for *S. pneumoniae*, including ethical considerations for global health studies, such as this thesis.

While carriage data were collected through observational studies at the local level requiring approval of protocols by ethics committees, studies on serotypes in IPD are mostly based on secondary data from passive laboratory-based systems. In these studies, consent of those represented in databases is presumed. It is also important to note that all studies included in the reviews and this thesis is focused on paediatric populations. Even though these are vulnerable populations, there is an ethical duty to conduct research on this population since they are at high risk of severe outcomes of pneumococcal disease. Furthermore, the collection and reporting of IPD data are usually mandatory. It is both ethical and necessary to analyse and publish these data, especially by departments of health staff and/or academic researchers. The ethical use of notification data can incorporate the rigour in academic practices to make recommendations for data quality, and aim to advance policy, to implement the changes identified as necessary. The ongoing investment of resources and efforts into surveillance makes it imperative to use the data to generate knowledge that could benefit the population under surveillance. It is also important that this knowledge reaches staff at the local level, where the collection of isolates occurs so that clinicians and staff can make more informed decisions.

For IPD serotype data, all published studies and grey literature sources from notification systems included de-identified data and I requested aggregate

data to reduce risk of disclosure of sensitive information. It should be noted that for several serotypes the number of cases was in the range of single digits which could allow for some re-identification. The problem of small numbers and potential identification can be observed when attempting to examine the association of serotypes to certain populations. For instance, I initially considered answering questions on the invasive disease potential of serotypes in children with comorbidities. However, through an exploratory request of re-analysed data, it was clear the surveillance systems in the countries collaborating with my research did not have the capacity to provide the necessary information. This realisation raises the question of ethics in the design of surveillance systems and when it is necessary to enhance or introduce changes to suit the study of the burden of disease among the most vulnerable.

Finally, there are aspects of the ethics of conducting global health research on a topic with such regional disparity in terms of data. This issue, though, is not unique to the study of *S. pneumoniae* serotypes. In the study of childhood PCV programmes, a geographical bias is introduced through the research question as focusing on post-implementation phase excludes populations that do not have access to the vaccines. It is then ethical that the research process clearly notes the limitations of the data, the results, their interpretation and most importantly highlight the gaps in the evidence base to promote research that can make global health studies more representative. Further research is needed to encompass broader questions of the current state of serotype epidemiology to minimise inequities that could arise from informing vaccine research and design on countries that have data available, which are usually the countries with some capacity for vaccine introduction and monitoring. Multiregional and well-funded studies on serotype epidemiology for IPD would be key to reduce inequities in global child health.

6.6 Conclusion

In conclusion, in this thesis I have addressed questions related to serotype epidemiology in childhood IPD and examined serotypes' relative importance

after PCVs introduction. The estimates of the change in the incidence of childhood IPD before and after highly valent PCVs provide evidence for serotype replacement, which has not yet been sufficient to offset the protective effect of the vaccines. 19A persists as a leading serotype in childhood IPD. Findings of this thesis indicate that as PCV immunisation programmes mature, the relative contribution of serotypes is changing, with non-PCV13 serotypes accounting for over a third of IPD cases in young children and in inconsistent ways across the world. This finding, together with estimates of invasive disease potential for non-PCV13 serotypes show there is a need to closely monitor the burden of serotypes currently not included in the PCV formulations, particularly 15BC, 10A, 12F, 22F, 24F, 33F, and 15A because with the available evidence it is not possible, as of yet, to know which, if any, of these serotype(s) could emerge as the leading serotype in IPD. The estimates in this thesis, and using Latin America as an example, provide evidence that PCV programmes need to be introduced, sustained and expanded to reduce the burden of pneumococcal disease. Finally, the findings of this thesis highlight the need to pay close attention to the diversity of serotypes that are associated with disease in different world regions an at the pace at which these occur to inform the development of future pneumococcal disease vaccines.

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8 Appendices

Appendix 1 List of countries by WHO regional offices

Africa Regional Office (AFRO)
Algeria, Angola, Benin, Botswana, Burkina Faso, Burundi, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Ivory Coast, the Democratic Republic of the Congo, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Mozambique, Namibia, Niger, Nigeria, Republic of the Congo, Rwanda, São Tomé and Príncipe, Senegal, Seychelles, Sierra Leone, Somalia, South Africa, South Sudan, Swaziland, Togo, Uganda, Tanzania, Zambia, Zimbabwe.
Americas Regional Office (AMRO) [or Pan American Health Organization (PAHO)]
Antigua and Barbuda, Argentina, Bahamas, Barbados, Belize, Bolivia, Brazil, Canada, Chile, Colombia, Costa Rica, Cuba, Dominica, Dominican Republic, Ecuador, El Salvador, Grenada, Guatemala, Guyana, Haiti, Honduras, Jamaica, Mexico, Nicaragua, Panama, Paraguay, Peru, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, United States, Uruguay, Venezuela.
Eastern Mediterranean Regional Office (EMRO)
Afghanistan, Bahrain, Djibouti, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Pakistan, Palestine, Qatar, Saudi Arabia, Somalia, Sudan, Syria, Tunisia, United Arab Emirates, Yemen.
European Region (EURO)
Albania, Andorra, Armenia, Austria, Azerbaijan, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Georgia, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Luxembourg, Malta, Monaco, Montenegro, Netherlands, North Macedonia, Norway, Poland, Portugal, Moldova, Romania, Russia, San Marino, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Tajikistan, Turkey, Turkmenistan, Ukraine, United Kingdom, Uzbekistan.
South-East Asia Region (SEARO)
Bangladesh, Bhutan, North Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand, Timor-Leste.
Western Pacific Region (WPRO)
Australia, Brunei, Cambodia, China, Cook Islands, Fiji, Japan, Kiribati, Laos, Malaysia, Marshall Islands, Micronesia, Mongolia, Nauru, New Zealand, Niue, Palau, Papua New Guinea, Philippines, South Korea, Samoa, Singapore, Solomon Islands, Taiwan, Tonga, Tuvalu, Vanuatu, Vietnam.

Appendix 2 Publications associated with the research conducted in this thesis

BALSELLS, E., GUILLOT, L., NAIR, H. & KYAW, M. H. 2017. Serotype distribution of *Streptococcus pneumoniae* causing invasive disease in children in the post-PCV era: A systematic review and meta-analysis. *PLoS ONE,* 12**,** e0177113.

BALSELLS, E., DAGAN, R., YILDIRIM, I., GOUNDER, P. P., STEENS, A., MUNOZ-ALMAGRO, C., MAMELI, C., KANDASAMY, R., GIVON LAVI, N., DAPRAI, L., VAN DER ENDE, A., TRZCINSKI, K., NZENZE, S. A., MEIRING, S., FOSTER, D., BULKOW, L. R., RUDOLPH, K., VALERO-RELLO, A., DUCKER, S., VESTRHEIM, D. F., VON GOTTBERG, A., PELTON, S. I., ZUCCOTTI, G., POLLARD, A. J., SANDERS, E. A. M., CAMPBELL, H., MADHI, S. A., NAIR, H. & KYAW, M. H. 2018. The relative invasive disease potential of *Streptococcus pneumoniae* among children after PCV introduction: A systematic review and meta-analysis. *Journal of Infection,* 77**,** 368-378.

Appendix 3 Self-audit checklist for ethical review

University of Edinburgh,
Centre for Population Health Sciences
RESEARCH ETHICS SUBGROUP

Self-Audit Checklist for Level 1 Ethical Review for Staff/research fellow projects

To be completed by the project PI

See **Intra** website for further information: http://www.cphs.mvm.ed.ac.uk/intra/research/ethicalReview.php

***Proposed Project** (State research question and topic area, and briefly describe method/ data. Specify also countries in which data will be collected.):*

Research Question: What is the distribution of *Streptococcus pneumoniae* (*S. pneumoniae*) causing invasive pneumococcal disease (IPD) in children in the post pneumococcal vaccine (PCV) era?
Methods: Parallel independent systematic review of published studies reporting data of *S. pneumoniae* serotypes causing IPD among children in any world region. The overall objective is to develop percentage summary estimates, including confidence intervals (meta-analysis, random effects) by serotype by age group (infants, young children, any under 21) and/or IPD syndrome (meningitis, sepsis/bacteraemia) to determine the most frequent serotypes causing disease after the introduction of PCVs (any kind). Studies published from 2000 to 2015, retrieved from one of the following databases, will be eligible for consideration: Medline, Embase, Global Health, regional databases from Global Health Library, LILACs, Web of Science. No restrictions on language will be imposed.

1. Bringing the University into disrepute

Is there any aspect of the proposed research which might bring the University into disrepute? YES/(NO)

2. Data protection and consent

Are there any issues of DATA PROTECTION or CONSENT which are NOT adequately dealt with via established procedures? YES/(NO)

These include well-established sets of undertakings. For example, a 'No' answer is justified *only if*:

(a) There is compliance with the University of Edinburgh's Data Protection procedures (see www.recordsmanagement.ed.ac.uk);

(b) Respondents give consent regarding the collection, storage and, if appropriate, archiving and destruction of data;

(c) Identifying information (eg consent forms) is held separately from data;

(d) There is Caldicott Guardian approval for (or approval will be obtained prior to) obtaining/ analysing NHS patient-data.

(e) There are no other special issues arising about confidentiality/consent.

3. Study participants

a) Will a study researcher be in direct contact with participants to collect data, whether face-to-face, or by telephone, electronic means or post, or by observation? (eg interviews, focus groups, questionnaires, assessments) YES/(NO)

b) **Answer this only if qu. 3 above = 'YES':**
In ethical terms, could any participants in the research be considered to be 'vulnerable'?
e.g. children & young people under age of 16, people who are in custody or care (incl. school), a marginalised/stigmatised group
Please tick one: 'vulnerable' ☐ not 'vulnerable' ☐

4. Moral issues and Researcher/Institutional Conflicts of Interest

Are there any SPECIAL MORAL ISSUES/CONFLICTS OF INTEREST? YES/(NO)

(a) An example of conflict of interest for a researcher would be a financial or non-financial benefit for him/herself or for a relative of friend.

(b) Particular moral issues or concerns could arise, for example where the purposes of research are concealed, where respondents are unable to provide informed consent, or where research findings could impinge negatively/ differentially upon the interests of participants.

(c) Where there is a dual relationship between researcher and participant (eg where research is undertaken by practitioners so that the participant might be unclear as to the distinction between 'care' and research)

5. Protection of research subject confidentiality

Are there any issues of CONFIDENTIALITY which are NOT adequately handled by normal tenets of confidentiality for academic research? YES (NO)

These include well-established sets of undertakings that should be agreed with collaborating and participating individuals/organisations. For example, a 'No' answer is justified *only if*:

(a) There will be no attribution of individual responses;

(b) Individuals (and, where appropriate, organisations) are anonymised in stored data, publications and presentation;

(c) There has been specific agreement with respondents regarding feedback to collaborators and publication.

6. Potential physical or psychological harm, discomfort or stress

(a) Is there a FORSEEABLE POTENTIAL for PSYCHOLOGICAL HARM or STRESS for participants? YES (NO)

(b) Is there a FORSEEABLE POTENTIAL for PHYSICAL HARM or DISCOMFORT for participants? YES (NO)

(c) Is there a FORSEEABLE RISK to the researcher? YES (NO)

Examples of issues/ topics that have the potential to cause psychological harm, discomfort or distress and should lead you to answer 'yes' to this question include, but are not limited to:

relationship breakdown; bullying; bereavement; mental health difficulties; trauma / PTSD; violence or sexual violence; physical, sexual or emotional abuse in either children or adults.

7. Duty to disseminate research findings

Are there issues which will prevent all relevant stakeholders having access to a clear, understandable and accurate summary of the research findings if they wish?* YES (NO)

** If, and only if, you answered 'yes' to 3 above, 'stakeholders' includes the participants in the research*

Overall assessment

- If every answer above is a definite NO, the self-audit has been conducted and confirms the ***ABSENCE OF REASONABLY FORESEEABLE ETHICAL RISKS*** – *please tick box* ✓

  *This means that regarding this study, as currently self-audited, no further ethical review actions are required within CPHS. However, if in the coming weeks/months there is any change to the research plan envisaged now (and outlined above), the study should be **re-audited** against a Level 1 form, because it may be that the change made negates the absence of ethical risks signed off here.*

- If one or more answers are YES, then risks have been identified and prior to commencing any data collection **formal ethical review** is required - either:
  - by NHS REC (NB copy of ethics application and decision letter to be sent to CPHS Ethics); or
  - if not to be formally reviewed by NHS REC, then CPHS level 2/3 ethical review required. *[If either 4 is 'yes' or 3b is 'vulnerable' then it is possible level 3 review is required.]*

The completed and signed form should be returned to the CPHS Ethics administrator.

PI name _____ PI Signature * _____

*** NOTE:** *The CPHS Ethics Subgroup cannot check validity of responses made on this form (the light touch Level 1 form means we have insufficient detail to do so). By countersigning this check-list as truly warranting all 'No' answers, you are taking responsibility, on behalf of CPHS and UoE, that the research proposed truly poses no ethical risks. Therefore, if there is any doubt on any issue, it would be a wise precaution to mark it as 'uncertain' and contact the Ethics Subgroup as to whether a level 2 form might be required as well. (See **Intra web-site** at URL given above.)*

25 March 2014

University of Edinburgh,
Centre for Population Health Sciences
RESEARCH ETHICS SUBGROUP

Self-Audit Checklist for Level 1 Ethical Review for Staff/research fellow projects

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Proposed Project (State research question and topic area, and briefly describe method/ data. Specify also countries in which data will be collected.):

RQ: What is the invasiveness capacity of *S. pneumoniae's* serotypes/groups in the post-pneumococcal conjugate vaccine era?
Methods: Systematic review of published studies reporting data for paediatric cases (<5 years) of *S. pneumoniae* carriage and invasive pneumococcal disease (IPD) from similar study populations and similar study periods, after the year 2000. Investigators identified through systematic review (details below) invited to collaborate by providing summary level data of carriage and IPD (any syndrome or for meningitis, pneumonia, or septicaemia) for 4 different age groups (0-11, 12-24, 25-59, and ≥60m). Invasiveness capacity = Meta-analysis OR = $\frac{\text{number of invasive serotype X isolates} \times \text{number of carriage reference isolates}}{\text{number of carriage serotype X isolates} \times \text{number of invasive reference isolates}}$
Investigators invited to collaborate are from: North America - **USA: 3** (Alaska, Atlanta, Boston). Europe – **UK: 2** (England, Oxford), **Norway, Italy (2** in Milan), **Netherlands, Spain, Israel,** Africa – **South Africa**

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In ethical terms, could any participants in the research be considered to be 'vulnerable'?
e.g. children & young people under age of 16, people who are in custody or care (incl. school), a marginalised/stigmatised group
Please tick one: 'vulnerable' ☐ not 'vulnerable' ☐

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7. Duty to disseminate research findings

Are there issues which will prevent all relevant stakeholders having access to a clear, understandable and accurate summary of the research findings if they wish?* YES (NO)

** If, and only if, you answered 'yes' to 3 above, 'stakeholders' includes the participants in the research*

Overall assessment

- If every answer above is a definite NO, the self-audit has been conducted and confirms the ***ABSENCE OF REASONABLY FORESEEABLE ETHICAL RISKS*** – *please tick box* ☑

  *This means that regarding this study, as currently self-audited, no further ethical review actions are required within CPHS. However, if in the coming weeks/months there is any change to the research plan envisaged now (and outlined above), the study should be **re-audited** against a Level 1 form, because it may be that the change made negates the absence of ethical risks signed off here.*

- If one or more answers are YES, then risks have been identified and prior to commencing any data collection **formal ethical review** is required - either:
  - by NHS REC (NB copy of ethics application and decision letter to be sent to CPHS Ethics); or
  - if not to be formally reviewed by NHS REC, then CPHS level 2/3 ethical review required. *[If either 4 is 'yes' or 3b is 'vulnerable' then it is possible level 3 review is required.]*

The completed and signed form should be returned to the CPHS Ethics administrator.

PI name _____ PI Signature* _____

* **NOTE:** *The CPHS Ethics Subgroup cannot check validity of responses made on this form (the light touch Level 1 form means we have insufficient detail to do so). By countersigning this check-list as truly warranting all 'No' answers, you are taking responsibility, on behalf of CPHS and UoE, that the research proposed truly poses no ethical risks. Therefore, if there is any doubt on any issue, it would be a wise precaution to mark it as 'uncertain' and contact the Ethics Subgroup as to whether a level 2 form might be required as well. (See **Intra web-site** at URL given above.)*

25 March 2014

Appendix 4 Search strategies by database for Chapter 3

Medline In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)	
1	exp Streptococcus pneumoniae/
2	Streptococcus pneumonia?.mp.
3	"s? pneumonia?".mp.
4	diplococcus pneumonia?.mp.
5	1 or 2 or 3 or 4
6	exp Pneumonia, Pneumococcal/
7	pneumonia.mp.
8	exp Respiratory Tract Infections/
9	exp Pneumococcal Infections/
10	pneumococc*.mp.
11	exp Meningitis, Pneumococcal/
12	meningitis.mp.
13	exp Bacteremia/
14	bacter?emia.mp.
15	invasive disease.mp.
16	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17	exp Pneumococcal Vaccines/
18	PCV*.mp.
19	exp Vaccines, Conjugate/
20	conjugate vaccine*.mp.
21	polysaccharide vaccine*.mp.
22	7-valent.mp.
23	hepta?valent.mp.
24	seven-valent.mp.
25	10-valent.mp.
26	deca?valent.mp.
27	ten-valent.mp.
28	13-valent.mp.
29	thirteen-valent.mp.
30	23-valent.mp.
31	Prev?nar.mp.
32	Pneumovax*.mp.
33	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
34	exp serogroup/
35	(Serotyp* or Serogroup*).mp.
36	34 or 35
37	5 and 16 and 33 and 36
38	limit 37 to (humans and yr="2000 -Current" and "all child (0 to 18 years)")
Global Health Library	
(streptococcus pneumonia or streptococcus pneumoniae) AND (invasive disease OR meningitis OR bacteremia OR bacteraemia OR pneumonia) AND (serotyp* OR serogroup*) AND (neonate* or neonatal or newborn* or new born* or infant* or infancy or baby or babies or toddler* or preschool or child* or juvenile* or girl* or boy* or young* or youth* or teenager* or adolescen* or pediatric* or paediatric*)	
LILACS	
(streptococcus pneumonia or streptococcus pneumoniae) AND (invasive disease OR meningitis OR bacteremia OR bacteraemia OR pneumonia) AND (serotyp* OR serogroup*) AND (neonate* or neonatal or newborn* or new born* or infant* or infancy or baby or babies or toddler* or preschool or child* or juvenile* or girl* or boy* or young* or youth* or teenager* or adolescen* or pediatric* or paediatric*)	
Web of Science	
TOPIC:(streptococcus pneumonia?) AND (invasive disease OR meningitis OR bacter?emia OR pneumonia) AND TOPIC: (serotyp* OR serogroup*) AND TOPIC: (neonate* or neonatal or newborn* or new born* or infant* or infancy or baby or babies or toddler* or preschool or child* or juvenile* or girl* or boy* or young* or youth* or teenager* or adolescen* or pediatric* or paediatric*) Timespan: 2000-2015. Indexes: SCI-EXPANDED, CPCI-S.	
Embase - 1980	
1	exp Streptococcus pneumoniae/
2	Streptococcus pneumonia?.mp.
3	"s? pneumonia?".mp.
4	diplococcus pneumonia?.mp.

5	1 or 2 or 3 or 4
6	exp Pneumonia, Pneumococcal/
7	pneumonia.mp.
8	exp lower respiratory tract infection/
9	exp Pneumococcal Infections/
10	pneumococc*.mp.
11	exp Meningitis, Pneumococcal/
12	meningitis.mp.
13	exp Bacteremia/
14	bacter?emia.mp.
15	invasive disease.mp.
16	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17	exp Pneumococcal Vaccines/
18	PCV*.mp.
19	exp Vaccines, Conjugate/
20	conjugate vaccine*.mp.
21	polysaccharide vaccine*.mp.
22	7-valent.mp.
23	seven-valent.mp.
24	hepta-valent.mp.
25	10-valent.mp.
26	ten-valent.mp.
27	decavalent.mp.
28	13-valent.mp.
29	23-valent.mp.
30	Prev?nar.mp.
31	Pneumovax*.mp.
32	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
33	exp serotype/
34	(Serotyp* or Serogroup*).mp.
35	33 or 34
36	5 and 16 and 32 and 35
37	limit 36 to (yr="2000 -Current" and (infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>))
Global Health	
1	exp Streptococcus pneumoniae/
2	streptococcus pneumonia?.mp.
3	"s? pneumonia?".mp.
4	diplococcus pneumonia?.mp.
5	1 or 2 or 3 or 4
6	exp lower respiratory tract infections/
7	pneumonia.mp.
8	Pneumococc*.mp.
9	meningitis.mp.
10	bacter?emia.mp.
11	invasive disease.mp.
12	6 or 7 or 8 or 9 or 10 or 11
13	PCV*.mp.
14	conjugate vaccine*.mp.
15	polysaccharide vaccine*.mp.
16	7-valent conjugate vaccine.mp.
17	10-valent conjugate vaccine.mp.
18	13-valent conjugate vaccine.mp.
19	23-valent pneumococcal polysaccharide vaccine.mp.
20	prev?nar.mp.
21	pneumovax*.mp.
22	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23	exp serotype/
24	(serotyp* or serogroup*).mp.
25	23 or 24
26	5 and 12 and 22 and 25
27	limit 26 to yr="2000 -Current"

28	(neonate* or neonatal or newborn* or new born* or infant* or infancy or baby or babies or toddler* or preschool or child* or juvenile* or girl* or boy* or young* or youth* or teenager* or adolescen* or pediatric* or paediatric*).mp.
29	27 and 28

Appendix 5 Characteristics of studies not meeting eligibility criteria for inclusion

Reference: First author, year	Country (PCV intro year) study years	Essential data not provided separately in the eligible format (i.e., ≥3 years of annual incidence rates or data to estimate proportion of individual serotypes and for young children specifically)	Incidence and proportional-based serotype data available for children but pre-PCV only or unable to ascertain PCV coverage	Other reasons (outcome is not IPD, study population is a selected group, total serotyped isolates <20 cases or <50% of IPD cases reported, PCV uptake <25%)
Adebanjo et al., 2018	Mozambique (2013) 2014-16			Specimens were all nasopharyngeal swabs, collected from children with radiologically confirmed pneumonia or without pneumonia
Alari et al., 2016	France (2016) 2001-14	Proportion-based data available in Supplementary Table are for all ages.		
Alexandrova et al., 2015	Bulgaria (2010 2011-16	Proportion-based data not available for invasive isolates from young children, specifically		
Almazrou et al., 2016	Saudi Arabia (2009) 2007-09		Study conducted largely in the pre-PCV era	Upper and lower respiratory tract specimens only, not from sterile sites
Alnimr and Farhat, 2017	Saudi Arabia (2009) 2012-14			
Ampofo et al., 2011	USA, Utah (2000) 1997-10	20% of children were older than 5y		
Antonio et al., 2008	The Gambia (2009) 2000-04 during trial			Only country to trial PCV9, which is not in use in other countries
Arguedas et al., 2012	Costa Rica (2008) 2007-09		Study conducted during introduction of PCV	For year post PCV only 8 cases reported
Artiles et al., 2009	Spain, Canary Islands (2009) 2000-06	Children up to 14 years of age		
Arushothy et al., 2019	Malaysia (2006, 2010) 2014-17		Vaccines only available in the private sector. No percentage of coverage provided. WHO reports vaccine not introduced yet	
Assandri et al., 2015	Uruguay (2008) 2001-10			<20 cases for post-PCV years
Azarian et al., 2018	USA, Navajo and White Mountain Apache Native American communities (2000) 1998-12			Carriage isolates only
Azzari et al., 2015	Italy (2006) 2008-09			<20 IPD cases
Ba et al., 2015	Senegal (2013) 2008-13	Children up to 15 years of age	pre-PCV (except for 2 months overlap)	only 28.89% of IPD cases serotyped
Balaji et al., 2015	India (licensed: 2015) 2007-13		PCV7 optional first, but then removed from marked since 2010. Recommended PCV13	
Baldovin et al., 2016	Italy (2007) 2007-14	Only two incidence rates Proportional-based data only by category		
Bautista-Marquez et al., 2013	Mexico (2008) 2010-11			Duplicated data with SIREVA reports
Benet et al., 2015	Mali (2011) 2011-12		Study period all pre-PCV	
Benito-Fernandez et al., 2007	Spain, Basque country (2001: licensed) 2000-2005			Only 17 cases post-PCV7 introduction

Reference: First author, year	Country (PCV intro year) study years	Essential data not provided separately in the eligible format (i.e., ≥3 years of annual incidence rates or data to estimate proportion of individual serotypes and for young children specifically)	Incidence and proportional-based serotype data available for children but pre-PCV only or unable to ascertain PCV coverage	Other reasons (outcome is not IPD, study population is a selected group, total serotyped isolates <20 cases or <50% of IPD cases reported, PCV uptake <25%)
Ben-Shimol et al., 2018	Israel (2009)		Serotype information provided for penicillin resistant pneumococcal meningitis	
Ben-Shimol et al., 2012	Israel (2009)			Data from this study population has been included
Ben-Shimol et al., 2014	Israel (2009)			Data from this study population has been included
Ben-Shimol et al., 2016	Israel (2009)			Data from this study population has been included
Ben-Shimol et al., 2015	Israel (2009) 2004/05-12/13)			Duplicate data (incidence rates for bacteraemia and non-bacteraemia IPD)
Bibi et al., 2019	Pakistan (2012)*		No study period dates (conference abstract only)	
Boulton et al., 2016	China (ND) 2005-11		PCV only approved and available in the private sector.	
Brandileone et al., 2018	Brazil (2010) 2005-10	Proportion-based data only available for large categories		
Buyukcam et al., 2017	Turkey (2009)			Case report, 2 cases only
Cai et al., 2018	China (licensed: 2008, 2016) 2008-17		Study references other studies, which estimate 10% of children in Shangai vaccinated. Not in national immunisation programme	
Caierao et al., 2014	Brazil (2010) 2007-12	Proportion-based data for <5y only available for large categories		
Casez et al., 2015	France (2006) "2005-10	No serotype-specific data, only clinical syndromes		
Centers for Disease and Prevention, 2011	USA (2000) 2010-11	No serotype data		
Ceyhan et al., 2011	Turkey (			Previously included but more recent publication available from the same setting
Chacon-Cruz et al., 2012	Mexico (2008) 2005-10	Proportion-based data in large categories		
Chapman et al., 2013	UK North East England (2006 2006/07-2009/10)			Data are available for the country after most recent PCV introduced, this is a regional study
Chapoutot et al., 2016	France (2006) "2008-13	Data are for children <18years		
Charfi et al., 2012	Tunisia 2000-09		No date of introduction PCV reported	
Chiang et al., 2014	Taiwan 2008-12	Serotype data reported for all ages	PCV only approved and available in the private sector.	
Chiba et al., 2013	Japan			Repeated data
Chibuk et al., 2010	Canada, Alberta (2002) 1997-07	Data are for children <18years		
Cho et al., 2014	Korea (2003, 2010: PCV10/13) 2006-10	Data are for children <18years	PCV vaccine introduced for optional use in private sector during study period	

Reference: First author, year	Country (PCV intro year) study years	Essential data not provided separately in the eligible format (i.e., ≥3 years of annual incidence rates or data to estimate proportion of individual serotypes and for young children specifically)	Incidence and proportional-based serotype data available for children but pre-PCV only or unable to ascertain PCV coverage	Other reasons (outcome is not IPD, study population is a selected group, total serotyped isolates <20 cases or <50% of IPD cases reported, PCV uptake <25%)
Cho et al., 2016	Korea (2003: PCV7, 2010: PCV10/13 private sector, 2014: PCV10/13 national programme) 2011-13	Data are for children <18years	PCV vaccine introduced for optional use in private sector during study period	
Cohen et al., 2014	South Africa (2009) 2010-12			Data are from vaccine efficacy trial and 99 cases excluded because they were vaccinated with PCV
Croney et al., 2013	USA Alabama (2000) 2002-10			Focus is on non-invasive infections
Davalos et al., 2016	Peru (PCV7 2009, PCV13 2012) 2009-11	Data are for children <16y and serotype data for <2 are only provided specifically for PCV13 types	Low PCV coverage (39.9%)	
De Schutter et al., 2014	Belgium 2008-09	Data are for children <15y		Outcome is CAP
De Wals et al., 2014	Canada, Quebec (PCV 7 2004, PCV10: 2009) 2005-11	Incidence rate data available but not for the necessary categories		
De Waroux et al., 2018	Vietnam		PCV no introduced in the country	
Desai et al., 2015	USA (2000, 2010) 2010-13			Provides data for Atlanta, which overlaps with Moore 2015 which provides information for all cities included in ABC surveillance programme
Diawara et al., 2017	Morocco (PCV13: 2010, PCV10: 2012) 2007-14			Serotype data available for isolates non-susceptible to penicillin
Diawara et al., 2016	Morocco (PCV13: 2010, PCV10: 2012) 2007-14			Serotype data available for isolates non-susceptible to antibiotic resistance genes
dos Santos et al., 2013	Brazil (2010) 2010-12	Incidence rate data only for one data point and for selected PCV10 and non-PCV10 types		
Echaniz-Aviles et al., 2015	Mexico (2008) 1993-12			Duplicated data with SIREVA
Elberse et al., 2012	The Netherlands (2007) 2008-09	Incidence rate (unclear indicator) only for one year after PCV7 introduction, serotype data only available for selected serotypes.		
Eton et al., 2017	Canada, NW Ontario, indigenous population (2010) 2010-15			Only 6 IOD cases
European Centre for Disease Prevention and Control, 2016	Europe	Proportion-based data only available for “most frequent” and are not country specific		
Farrell et al., 2008	UK (2006)	Data not available for <5y specifically	Study period all pre-PCV	
Farrell et al., 2007	USA (2000) 2002-04	Data are for children <14years		
Flasche et al., 2011	UK	Incidence rate data not available for <5y specifically and for a single data point		Repeated data
Foster et al., 2011	UK Oxford			Overlap with Moore 2014
Gaensbauer et al., 2016	Guatemala (ND) 1996-07		Study period all pre-PCV	
Gendrel et al., 2011	France (2006) 2006-09			Only 4 IPD cases

Reference: First author, year	Country (PCV intro year) study years	Essential data not provided separately in the eligible format (i.e., ≥3 years of annual incidence rates or data to estimate proportion of individual serotypes and for young children specifically)	Incidence and proportional-based serotype data available for children but pre-PCV only or unable to ascertain PCV coverage	Other reasons (outcome is not IPD, study population is a selected group, total serotyped isolates <20 cases or <50% of IPD cases reported, PCV uptake <25%)
Georgalis et al., 2017	Spain (PCV7: 2006, PCV13 2010)	No serotype data		
Giele et al., 2007	Australia (PCV7 2002) 1996-05	Incidence rate available for a single data point post-vaccine (2002-05)		
Glikman et al., 2018	Israel (2009) 2009/10-14/15	Serotype data are only provided for proportion-based data for large categories, not specific types		
Godot et al., 2015	France (2003) 2003-13			Serotype data provided for vaccine breakthrough and vaccine failure cases only
Golden et al., 2018	Canada			Provides information on the predominant serotypes that were analysed for antimicrobial susceptibility. No information on all cases
Gonzalez-Escartin et al., 2017	Spain, Cantabria (2010) 2001-15	Data are for children ≤14 years old		Only 18 patients
Greenberg et al., 2015	Israel (2009) 2002/03-2012/13			Duplicate data
Greenhill et al., 2015	Papua New Guinea (ND) 1996-05		Study period all pre-PCV	
Guevara et al., 2009	Spain, Navarre (2001 2001-07		PCV only approved and available in the private sector.	
Guevara et al., 2016	Spain, Navarre (2001) 2001-14	No serotype data		
Hamaluba et al., 2015	Nepal (2010 trial)			Carriage only
Hanke et al., 2016	Peru			Carriage only
Hanna et al., 2008	Australia, north Queensland			Duplicate data: more recent data available
Hanna et al., 2010	Australia, north Queensland			Duplicate data: more recent data available
Hanquet et al., 2011	Belgium (2006) 2006-08	Only 2 data points for incidence rates by serotype		
Harboe et al., 2010	Denmark (2007)	Incidence data only available for one year		
He et al., 2017	China Dongguan (ND) 2011-16	No serotype data		
Hicks et al., 2007	USA (2000) 2004			Even though it reports various, not just leading non-vaccine serotypes, it does not provide case counts for all serotypes and "other" cannot be assumed to be non-vaccine serotypes
Hirose et al., 2015	Brazil (2010) 1998-11	Data only provided for serotypes reported as “vaccine coverage” for <2y (46.7%) and 12-23 (20.0%)		
Ho et al., 2011	Hong Kong	Serotype specific proportion-based data not disaggregated by age groups		

Reference: First author, year	Country (PCV intro year) study years	Essential data not provided separately in the eligible format (i.e., ≥3 years of annual incidence rates or data to estimate proportion of individual serotypes and for young children specifically)	Incidence and proportional-based serotype data available for children but pre-PCV only or unable to ascertain PCV coverage	Other reasons (outcome is not IPD, study population is a selected group, total serotyped isolates <20 cases or <50% of IPD cases reported, PCV uptake <25%)
Houri et al., 2017	Iran (NA) 2013-16		Study reports no routine or public vaccination in Iran. Available commercially as voluntary. No introduction date in IVAC	
Howie et al., 2014	The Gambia (ND) 2007-09		No routine use of PCV	
Hsieh et al., 2009	Taiwan (2005) 2007		PCV7 use at the time: 15.9% had received at least one dose	
Hsu et al., 2005	USA, national (2000) 2001-03			Partial overlap with more recent publication Hsu 2010
Hsu et al., 2009	USA, national (2000) 2004-05			The country has now introduced PCV13 and data can only be extracted for PCV7 and nonPCV7 categories
Huang et al., 2015	China (ND) 2011-13		No information about PCV use in the study location	
Ingels et al., 2012	Denmark (2007) 2000-10			The country has now introduced PCV13 and data can only be extracted for PCV7 and nonPCV7 categories
Inghammar et al., 2018	Cambodia (2015) 2008-14		Study period before PCV introduction	
Iraurgui et al., 2010	Spain, Seville			Comparison of laboratory testing results
Jacobs et al., 2008	USA Cleveland			The country has now introduced PCV13 and data can only be extracted for PCV7 and nonPCV7 categories
Jauneikaite et al., 2014	Singapore (2009) 2009-10		Low uptake 21.6% and 41%	Only 12 cases
Jayaraman et al., 2018	India (ND) 2012-13		No information about PCV use in the study location	
Jiang et al., 2018	China (Jingzhou City, Hubei) 2010-12		No information about PCV use in the study location	
Jin et al., 2016	China			Modelling
John et al., 2018	India (NA) 2007-16 [		PCV use described as "India is in the process of universalising the coverage of PCV. No description of PCV use	
Kambire et al., 2016	Burkina Faso (2013) 2011-13		PCV introduced two months before the end of the study period	
Kang et al., 2016	China (ND) 201-13	Children less than 11 years	Pneumococcal recently been introduced, unknown coverage rate	
Keck et al., 2014	USA, Alaska (2000) 2006-09	Single incidence rate for the entire study period post-PCV		Repeated data
Ktari et al., 2017	Tunisia			PCV uptake <10%
Kovacs et al., 2019	Hungary (PCV13 introduced: 2010, mandatory: 2014)			The main outcome is not IPD

Reference: First author, year	Country (PCV intro year) study years	Essential data not provided separately in the eligible format (i.e., ≥3 years of annual incidence rates or data to estimate proportion of individual serotypes and for young children specifically)	Incidence and proportional-based serotype data available for children but pre-PCV only or unable to ascertain PCV coverage	Other reasons (outcome is not IPD, study population is a selected group, total serotyped isolates <20 cases or <50% of IPD cases reported, PCV uptake <25%)
Lacapa et al., 2008	USA (2000) White Mountain Apache 2001-06			Only 13 cases under five years in the PCV7 period
Ladhani et al., 2013a	UK (2006: PCV7, PCV13: 2010) Infants <90days			Repeated data as infants included in other datasets from the surveillance system
Ladhani et al., 2013b	UK (2006: PCV7, PCV13: 2010) 2006-10			Repeated data included in the publication by the same author in 2016
Lai et al., 2014	Taiwan (2005: PCV7, 2010: PCV10, 2011:PCV13) 2000-12	Proportion-based data only provided for the most frequently identified	PCV7 coverage rates reported: ≤25	
Lamb et al., 2014	Scotland (2006: PCV7) 1999-10	Incidence data provided for post-PCV7 only in a country where PCV13 has been introduced already		
Lehmann et al., 2010	Australia Non-Aboriginal (2001) 1997-07	Incidence data provided for two data points only (two periods)		The data source is the national enhanced surveillance, the population considered to be included in surveillance reports
Leal et al., 2012	Canada (Alberta, 2001, 2002: PCV7; 2010: PCV13)	Incidence data provided for post-PCV7 only in a country where PCV13 has been introduced already		
Leite et al., 2016	Brazil (2010) 2010-13	Proportion-based data for two serotypes categories only		
Li et al., 2016	Canada, Ottawa (2002) 2006-13			
Liao et al., 2010	Taiwan (2005)		PCV coverage estimated around 25%	
Liesenborghs et al., 2013	Belgium (2004) 2007-10	No serotype data, only serogroup		
Lim et al., 2013				
Mackenzie et al., 2017	The Gambia (2009) 2008-15			The outcome is radiologically confirmed pneumonia, no serotype data
Madhi et al., 2017	South Africa (trial PCV10) 2009-12			No IPD outcome, no serotype data
Mahon et al., 2016	New Zealand (2008) 1998-12			Only 4 S pneumoniae cases
Manoharan et al., 2017	India () 2011-15		PCV not introduced in the study setting	
Maraki et al., 2010	Greece (2006) 2001-08	Adults only		
Marzouk et al., 2015	Tunisia (2008: PCV7) 2007-13	Children up to 14 years	PCV used largely in the private sector, no estimate of coverage provided. No official number of children receiving pneumococcal vaccines.	
Medeiros et al., 2016	Brazil (2010) 1998-13			Only 19 cases reported the post-PCV introduction period
Medeiros et al., 2017	Brazil (2010) 1998-13			Only 19 cases reported the post-PCV introduction period

Reference: First author, year	Country (PCV intro year) study years	Essential data not provided separately in the eligible format (i.e., ≥3 years of annual incidence rates or data to estimate proportion of individual serotypes and for young children specifically)	Incidence and proportional-based serotype data available for children but pre-PCV only or unable to ascertain PCV coverage	Other reasons (outcome is not IPD, study population is a selected group, total serotyped isolates <20 cases or <50% of IPD cases reported, PCV uptake <25%)
Mihret et al., 2016	Ethiopia (2011) 2012-13	No serotype data		Only 9 cases during the study period
Miyahara et al., 2015	Japan (2007) 2008-13	Data are for children up to 18 years old		Only 15 cases, including one recurrence during the study period
Mohale et al., 2016	South Africa (2009) 2003-13	Focus is only on the genomics of non-typeable isolates		
Moisi et al., 2017	Togo (ND) 2010-13		PCV not introduced in the study setting during the study period	
Mokaddas and Albert, 2012	Kuwait (2006) 2006-11			Serotype data are for invasive and non-invasive isolates combined
Moore et al., 2014	Oxfordshire Region of England (2006)			Duplicate study population
Moore et al., 2016	Cambodia (2015) 2007-12		PCV not introduced in the study setting during the study period	
Moraga-Llop et al., 2016	Spain, Catalonia (2010: PCV13, PCV7:2011, 2009: PCV10) 2012-13		The vaccine only in the private market	Focus is on vaccine failure cases
Mott et al., 2014	Brazil (2010) 2010-12			Only 17 cases
Mount et al., 2017	New Zealand (2008) 2009-13			Only 19 cases reported as serotype data are on IPD cases among infants <7 days
Munoz-Almagro et al., 2008	Spain (2001: licenced PCV7) 1997-2001		PCV not introduced in the study setting during the study period	
Nair et al., 2016	Scotland (2006) 2006-10	No serotype data		The outcome is pneumonia hospitalisation
Naito et al., 2016	Japan (2010) 2012-13	Only four isolates from blood		The outcome is pneumonia hospitalisations,
Navarro Torne et al., 2014	Europe 26 countries (2010)	Data are provided for all of Europe but are only provided for the most frequent serotypes.		
Nhantumbo et al., 2016	Mozambique (2013) 2013-14		"recently introduced". Study period pre-PCV	
Nhantumbo et al., 2017	Mozambique (2013) 2013-15			If the year of introduction is not included (2013) only 12 cases reported for the other two years included
Nicolosi et al., 2019	Italy, Rome (2010) 2008-12	The study population includes children up to 16 years		
Nisarga et al., 2015	India (NA) 2009-11 [n=45 total, 36 typed]		Pneumococcal conjugate vaccines are not currently included in the national immunization program in India	
Nurse-Lucas et al., 2016	Trinidad and Tobago (< 2010 –	Serotype data not provided for IPD only, mixed with non-invasive	PCV7 only available in the private market for children at high risk, PCV10 (2011) PCV13 (2015) – PCV coverage: 95% Dec 2014	
Ribitzky-Eisner et al., 2016	Israel (2010) 2010-12 [10 isolates, <36mo, Occult			Only 10 cases in the post-PCV period

Reference: First author, year	Country (PCV intro year) study years	Essential data not provided separately in the eligible format (i.e., ≥3 years of annual incidence rates or data to estimate proportion of individual serotypes and for young children specifically)	Incidence and proportional-based serotype data available for children but pre-PCV only or unable to ascertain PCV coverage	Other reasons (outcome is not IPD, study population is a selected group, total serotyped isolates <20 cases or <50% of IPD cases reported, PCV uptake <25%)
	bacteraemia with fever only]			
Oftadeh et al., 2013	Australia New South Wales (2001) 2002-09			More recent data available from Australia's surveillance system
Ojal et al., 2017	Kenya (2011: PCV10) 2009-12			Modelling study, carriage data only
Okade et al., 2014	Japan (2010) 2008-12			Non-invasive isolates only
Olanrewaju et al., 2016	Nigeria (2010)		PCV is available by private pharmaceutical companies, not in EPI. No estimate coverage	Only 9 *S. pneumoniae* cases
Olarte et al., 2013	USA (2000) 2001-10	Focus is on children <90 days		Repeated data with publications by the same group
Olarte et al., 2017a	USA (2000) 2006-14	Includes children up to 18 years		The outcome is hospitalised pneumococcal pneumonia
Olarte et al., 2017b	USA (2000) 2000-15	Includes children up to 18 years (data in Sup Fig 2)		The outcome is osteoarticular infections
Oligbu et al., 2017	UK England and Wales (2006) 2006-14			Focus is on vaccine failure
Oliver et al., 2015	Spain, Valencia (2010: PCV13) 2007-12	Proportion-based data only for large categories	PCV use only in high-risk groups	
Ozdemir et al., 2017	Turkey (2005, 2008 PCV7, NOP; 2011: PCV13)			39 cases in total, which by PCV period were <20: cases for children <59 months 19 cases PCV13 and 10 after PCV7
Pan et al., 2015	China (2008: PCV7) 2013		PCV was available through private pharmaceutical companies, not in Expanded Programme on Immunisation. No estimate coverage	
Park et al., 2010	USA (2000) 2001-04			Focus is on breakthrough cases
Paulke-Korinek et al., 2014	Austria (2001: PCV7, 2009: PCV13, PCV10) 2002-12	Serotype data only provided for cases that had not fully recovered at the time of hospital discharge		
Perniciaro et al., 2019	Germany (2006: PCV7) 2007-15	No detailed proportion-based data on non-vaccine types for young children, IR data not available by serotype categories	PCV available by private pharmaceutical companies, the study estimates 18% of children are fully vaccinated with PCV13	
Petras and Adamkova, 2016	Czech Republic (2007) 2012-13	Proportion-based serotype data only by categories		
Petrovic et al., 2016	Serbia, Vojvodina (ND) 2009-16	Proportion-based serotype data only by categories	Study period before routine use of the pneumococcal conjugate vaccine	
Picazo et al., 2017	Spain, Madrid (2010/2012) 2007-15	Incidence-rate data by large categories		Duplicate study population
Poehling et al., 2006	The USA, eight states, (2000) 1997-04			Duplicate study population

Reference: First author, year	Country (PCV intro year) study years	Essential data not provided separately in the eligible format (i.e., ≥3 years of annual incidence rates or data to estimate proportion of individual serotypes and for young children specifically)	Incidence and proportional-based serotype data available for children but pre-PCV only or unable to ascertain PCV coverage	Other reasons (outcome is not IPD, study population is a selected group, total serotyped isolates <20 cases or <50% of IPD cases reported, PCV uptake <25%)
Polkowska et al., 2019	Poland (2017) 2005-15		Study period before routine use of PCV	
Polkowska et al., 2017	Finland (2010) 1995-14	No serotype data		
Ramdani-Bouguessa et al., 2015	Algeria (ND) 2005-12		PCV not included in use in the country during the study period	
Riaz et al., 2019	Pakistan (2013: PCV10)	Focus is on the effectiveness of the vaccine. Serotype info only for vaccine serotype cases		
Ribitzky-Eisner et al., 2016	Israel, South (2009) 2005-12			Only 10 cases of the post-PCV period. Focus is on occult bacteraemia
Richter et al., 2019	Austria (2012) 2013-17	No proportion-based serotype data, incidence rate data only provided for pre and post (single data point)		
Richter et al., 2014	USA (2000: PCV7, 2010: PCV13) 2012-12	Serotype data by age groups available only for predominant serotypes		Focus is on antimicrobial-resistant strains
Richter et al., 2013	USA (2000: PCV7, 2010: PCV13) 1999-11			Surveillance period less than 12 months
Ricketson et al., 2018	Canada, Calgary (2002, 2010) 200-15	Serotype data by age groups available only for large categories		
Rodenburg et al., 2010	Netherlands (2006) 2004-08	No proportion-based serotype data, incidence rate data only provided for pre and post (single data point)		
Rojas et al., 2016	Colombia, Bogota (2010) 2008-14			Focus is only on deaths due to IPD
Ruiz-Contreras et al., 2017	Spain, Madrid () 2007-15	No detailed serotype data (proportion-based or incidence rates)		
Saha et al., 2016	Bangladesh (2015) 2007-13		PCV not included in use in the country during the study period	
Sakata, 2016	Japan (2010: PCV7, 2013 PCV13) 2000-10		PCV not included in use in the country during the study period	
Sakata et al., 2018	Japan (PCV7: 2010) 2010: 6 months and six months in 2012	Serotype data provided for children up to 14 years	Surveillance period less than 12 months	
Santana Hernandez et al., 2018	Spain, Gran Canarias 2001-16	Serotype data provided for all children up to 14 years		
Scott et al., 2012	USA American Indian (2001), 2006-08			Duplicate data
Setchanova et al., 2018	Bulgaria (2010) 2011-17	Serotype data include data for children and adults		
Setchanova et al., 2017	Bulgaria (2010) 2011-16	Serotype data include data for children and adults		
Shen et al., 2013	Taiwan (2005) 1998-10	Data are provided for children up to 18 years	Pneumococcal vaccine coverage rate is low, PCV7 not added into the routine immunization program	
Shinjoh et al., 2017	Japan () 2013-15	Unclear age distribution for *S. pneumoniae* cases, no detailed serotype data		

Reference: First author, year	Country (PCV intro year) study years	Essential data not provided separately in the eligible format (i.e., ≥3 years of annual incidence rates or data to estimate proportion of individual serotypes and for young children specifically)	Incidence and proportional-based serotype data available for children but pre-PCV only or unable to ascertain PCV coverage	Other reasons (outcome is not IPD, study population is a selected group, total serotyped isolates <20 cases or <50% of IPD cases reported, PCV uptake <25%)
Sigauque et al., 2018b	Mozambique (2013) 2001-12		Study period before the introduction of PCV	
Sigauque et al., 2018a	Mozambique (2013) 2001-12		Study period before the introduction of PCV	
Singh and Manoharan, 2016	India (ND)		Unclear coverage/use of vaccine during the study period	Conference abstract, no detailed information available
Skoczynska et al., 2015	Poland () 2001-13		No mass vaccination implemented during the study period. Study report that based on recent data vaccine coverage would be approximately 15%	
Solorzano-Santos et al., 2017	Mexico			Study population restricted to those with congenital heart disease
Soto-Nogueron et al., 2018	Mexico			Study population restricted to those with cancer
Srifeungfung et al., 2010	Thailand (2006) 2006-09	No detailed information about non-PCV13 types	PCV not included in the national immunisation program	
Stanek et al., 2016	The USA, West Virginia, Ohio, Kentucky (2000) 1983-2014	Serotype data are for large categories, and individual information is not specific for children under five years		
Subramaniam et al., 2018	Malaysia (ND) 2013-15	Data are for up to 12 years		Nasopharyngeal and bronchoalveolar lavage isolates
Suphanklang et al., 2017	Thailand (2006) 2006-15	Serotype data are not provided for children specifically		Only two children < 2 years
Syrogiannopoulos et al., 2016	Greece (2010: PCV13) 2006-16			Only 19 cases, the outcome is community acquired pneumonia with empyema
Tagarro et al., 2016	Spain, Madrid (2010/12) 2009-14	Data are for children up to 14 years (bacteraemia)		
Talbot et al., 2004	USA Tennessee (2000) 2000-02	Incidence rate available as a single data point		Study population part of ABC surveillance
Tanir Basaranoglu et al., 2017	Turkey (2008: PCV7, 2010: PCV13) 2015-16			The study population is breakthrough cases
Tempia et al., 2015	South Africa (2009) 2009-12			The study population included in other publications from the same setting
Turner et al., 2015	Cambodia (2015) 2013-14		PCV not in use in the country during the study period	
Valenzuela et al., 2014	Chile (2011) 2007-12			The study population included in other publications from the same setting
van den Biggelaar et al., 2019	Papua New Guinea			None of the outcomes investigated included IPD
Verhagen et al., 2016	Venezuela Amerindian		No description of the PCV coverage in the study setting	Carriage only

Reference: First author, year	Country (PCV intro year) study years	Essential data not provided separately in the eligible format (i.e., ≥3 years of annual incidence rates or data to estimate proportion of individual serotypes and for young children specifically)	Incidence and proportional-based serotype data available for children but pre-PCV only or unable to ascertain PCV coverage	Other reasons (outcome is not IPD, study population is a selected group, total serotyped isolates <20 cases or <50% of IPD cases reported, PCV uptake <25%)
Vestrheim et al., 2010	Norway (2006) 1989-08			The study population included in other publications from the same setting
Vestrheim et al., 2008	Norway (2006) 2002-07			The study population included in other publications from the same setting
Vila Corcoles et al., 2018	Spain, Tarragona (2009/10) 2012-15	Data are for children up to 14 years	48% coverage among high-risk children	Only 13 cases
von Mollendorf et al., 2016	South Africa (2009: PCV7, 2011: PCV13) 2003-13			Focuses only on serotype 1
Wagenvoort et al., 2016	Netherlands (2008)			Study overlaps with Knol et al. which provides data from the same surveillance system in the country. More cases are reported in Knol et al
Wang et al., 2017	China (ND) 2011-14		No description of the PCV use or coverage in the study setting	
Webber et al., 2016	USA Wisconsin (2000) 2013-14			Focuses on a period during a cluster, of 7 patients
Whitney et al., 2006	USA ABC (2000) 2001-03			Study population part of ABC surveillance
Wysocki et al., 2016	Poland (2009: PCV7, 2011: PCV13) 2008-09		Introduction PCV at the end of the study period	Only 7 IPD cases
Yan et al., 2019	China (ND) 2016-18	Data are for children up to 12 years	Eligibility for study inclusion was no vaccination against S pneumoniae	
Yasin et al., 2011	Malaysia (2009: PCV10, 2010:PCV13) 2008-09	No details on non-PCV types		
Yildirim et al., 2010	USA Massachusetts (2000) 2003-09, 3 years)			Surveillance period for IPD less than 12 months
Yildirim et al., 2017	USA Massachusetts (2000) 2010/11-2013/14)			Surveillance period for IPD less than 12 months
Yu et al., 2011	USA Ohio (2000) 2007-09			Microbiology tests comparison study
Zabihullah et al., 2017	Afghanistan (ND) 2012-13		PCV not in use in the country during the study period	Carriage only
Zampoli et al., 2015	South Africa (2009) 2006-11, 12-14	Data are for children up to 12 years	Serotype data provided for pre- and post-PCV period combined	
Zhang et al., 2017	China (ND) 2010-15	Data are for children up to 15 years		
Zhao et al., 2017	China (ND) 2011-16	No serotype-specific data for children only, only “PCV coverage” categories	PCV7: commercially available in China in 2008 and replaced by 13 in 2017. PCV7 is not included in the national immunisation program, and PCV immunisation is given only on an individual basis	
Ziane et al., 2016	Algeria (ND) 2010-14		Pre-PCV period.	

Appendix 6 Search Strategies by database for Chapter 4

Medline: In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present	
1	exp Streptococcus pneumoniae/
2	Streptococcus pneumonia?.mp.
3	"s? pneumonia?".mp.
4	diplococcus pneumonia?.mp.
5	1 or 2 or 3 or 4
6	carr*.mp.
7	exp Pneumonia, Pneumococcal/
8	pneumonia.mp.
9	exp Respiratory Tract Infections/
10	exp Pneumococcal Infections/
11	pneumococc*.mp.
12	exp Meningitis, Pneumococcal/
13	meningitis.mp.
14	exp Bacteremia/
15	bacter?emia.mp.
16	invasive disease.mp.
17	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18	exp Pneumococcal Vaccines/
19	PCV*.mp.
20	exp Vaccines, Conjugate/
21	conjugate vaccine*.mp.
22	polysaccharide vaccine*.mp.
23	7-valent.mp.
24	hepta?valent.mp.
25	seven-valent.mp.
26	10-valent.mp.
27	deca?valent.mp.
28	ten-valent.mp.
29	13-valent.mp.
30	thirteen-valent.mp.
31	23-valent.mp.
32	Prev?nar.mp.
33	Pneumovax*.mp.
34	18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35	exp serogroup/
36	(Serotyp* or Serogroup*).mp.
37	35 or 36
38	5 and (17 or 34) and 37
39	limit 38 to (humans and yr="2000 -Current" and "all child (0 to 18 years)")
Embase	
1	exp Streptococcus pneumoniae/

2	Streptococcus pneumonia?.mp.
3	"s? pneumonia?".mp.
4	diplococcus pneumonia?.mp.
5	1 or 2 or 3 or 4
6	carr*.mp.
7	exp Pneumonia, Pneumococcal/
8	pneumonia.mp.
9	exp lower respiratory tract infection/
10	exp Pneumococcal Infections/
11	pneumococc*.mp.
12	exp Meningitis, Pneumococcal/
13	meningitis.mp.
14	exp Bacteremia/
15	bacter?emia.mp.
16	invasive disease.mp.
17	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18	exp Pneumococcal Vaccines/
19	PCV*.mp.
20	exp Vaccines, Conjugate/
21	conjugate vaccine*.mp.
22	polysaccharide vaccine*.mp.
23	7-valent.mp.
24	seven-valent.mp.
25	hepta-valent.mp.
26	10-valent.mp.
27	ten-valent.mp.
28	decavalent.mp.
29	13-valent.mp.
30	23-valent.mp.
31	Prev?nar.mp.
32	Pneumovax*.mp.
33	18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
34	exp serotype/
35	(Serotyp* or Serogroup*).mp.
36	34 or 35
37	5 and (17 or 33) and 36
38	limit 37 to (yr="2000 -Current" and (infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>))
LILACS	
(Streptococcus pneumonia or Streptococcus pneumoniae) AND (carri* OR invasive disease OR meningitis OR bacteremia OR bacteraemia OR pneumonia) AND (serotyp* OR serogroup*) AND (neonate* or neonatal or newborn* or new born* or infant* or infancy or baby or babies or toddler* or preschool or child* or juvenile* or girl* or boy* or young* or youth* or teenager* or adolescen* or pediatric* or paediatric*)	

Global Health Library	
(Streptococcus pneumonia or Streptococcus pneumoniae) AND (carri* OR invasive disease OR meningitis OR bacteremia OR bacteraemia OR pneumonia) AND (serotyp* OR serogroup*) AND (neonate* or neonatal or newborn* or new born* or infant* or infancy or baby or babies or toddler* or preschool or child* or juvenile* or girl* or boy* or young* or youth* or teenager* or adolescen* or pediatric* or paediatric*)	
Global Health	
1	exp Streptococcus pneumoniae/
2	streptococcus pneumonia?.mp.
3	"s? pneumonia?".mp.
4	diplococcus pneumonia?.mp.
5	1 or 2 or 3 or 4
7	carr*.mp.
8	exp lower respiratory tract infections/
9	pneumonia.mp.
10	meningitis.mp.
11	bacter?emia.mp.
12	invasive disease.mp.
13	7 or 8 or 9 or 10 or 11 or 12
14	pcv*.mp.
15	conjugate vaccine*.mp.
16	polysaccharide vaccine*.mp.
17	7-valent conjugate vaccine.mp.
18	10-valent conjugate vaccine.mp.
19	13-valent conjugate vaccine.mp.
20	23-valent pneumococcal polysaccharide vaccine.mp.
21	prev?nar.mp.
22	pneumovax*.mp.
23	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24	exp serotype/
25	(serotyp* or serogroup*).mp.
26	24 or 25
27	5 and (13 or 23) and 26
28	limit 27 to yr="2000 -Current"
29	(neonate* or neonatal or newborn* or newborn* or infant* or infancy or baby or babies or toddler* or preschool or child* or juvenile* or girl* or boy* or young* or youth* or teenager* or adolescen* or pediatric* or paediatric*).mp.
30	28 and 29
Web of Science	
TOPIC:(streptococcus pneumonia?) AND (carr* OR invasive disease OR meningitis OR bacter?emia OR pneumonia) AND TOPIC: (serotyp* OR serogroup*) AND TOPIC: (neonate* or neonatal or newborn* or new born* or infant* or infancy or baby or babies or toddler* or preschool or child* or juvenile* or girl* or boy* or young* or youth* or teenager* or adolescen* or pediatric* or paediatric*) Timespan: 2000-2015. Indexes: SCI-EXPANDED, CPCI-S.	

Appendix 7 Distribution of serotypes (%) not included in meta-analyses among IPD cases and carriers

Total isolates with a serotype identified (n)	0-59 month		0-23 months	
	2677	15931	2648	10930
Serotype	**IPD (%)**	**Carriage (%)**	**IPD (%)**	**Carriage (%)**
Others	3.9	0.32	1.3	0.18
21	0.8	3.36	0.8	3.17
9N	0.6	1.47	0.6	1.58
9V	0.6	0.54	0.4	0.50
11A	0.6	5.44	0.8	5.41
7FA	0.6	0.04	0.2	0.05
23A	0.5	3.83	0.8	3.76
27	0.5	0.08	0.7	0.08
7B	0.5	0.48	0.4	0.59
2	0.3	0.04	0.3	0.04
4	0.3	0.18	0.4	0.14
17F	0.3	2.59	0.6	3.01
34	0.3	1.93	0.3	1.70
35F	0.3	2.31	0.7	2.15
13	0.2	1.06	0.1	1.13
18A	0.2	0.12	0.1	0.15
22A	0.2	0.17	0.1	0.13
24	0.2	0.02	0.1	0.00
29	0.2	0.26	0.2	0.32
33A	0.2	0.16	0.2	0.22
7C	0.2	0.65	0.4	0.60
9L	0.1	0.04	0.1	0.05
11	0.1	0.03	0.0	0.02
12B	0.1	0.01	0.1	0.01
20	0.1	0.40	0.2	0.37
23	0.1	0.00	0.0	0.00
31	0.1	1.35	0.2	1.12
33	0.1	0.03	0.1	0.04
24B	0.1	0.01	0.3	0.01
24A	0.1	0.08	0.1	0.09
6D	0.0	0.06	0.0	0.06
7	0.0	0.01	0.0	0.01
7A	0.0	0.03	0.0	0.02
9A	0.0	0.04	0.0	0.05
15F	0.0	0.06	0.1	0.10
18	0.0	0.03	0.1	0.02
19	0.0	0.00	0.0	0.00
22	0.0	0.00	0.0	0.00
36	0.0	0.02	0.0	0.05
19FBC	0.0	0.05	0.0	0.03
35A	0.0	0.18	0.0	0.15
25F	0.0	0.01	0.0	0.01
11AD	0.0	0.06	0.0	0.02
9VANL	0.0	0.00	0.0	0.00
6AC	0.0	0.19	0.0	0.08
11B	0.0	0.01	0.1	0.01

Appendix 8 Sensitivity analyses invasive disease potential of *S. pneumoniae* serotypes in children 0–59 months

	All datasets				PCV ≥70 coverage in the study setting				HIV low prevalence settings				Industrialised settings				Data from years post-higher valent PCV (10/13)			
	N	OR (95% CI)	p OR=1	I^2 (%)	N	OR (95% CI)	p OR=1	I^2 (%)	N	OR (95% CI)	p OR=1	I^2 (%)	N	OR (95% CI)	p OR=1	I^2 (%)	N	OR (95% CI)	p OR=1	I^2 (%)
1*	8	15.1 (10.2-22.3)	*<0.001*	0.0	7	14.8 (9.8-22.5)	*<0.001*	0.0	7	15.7 (10.4-23.7)	*<0.001*	0.0	5	15.7 (10.3-23.9)	*<0.001*	0.0	5	9.7 (4.1-23)	*<0.001*	30.1
3†	9	1 (0.5-1.9)	0.997	75.9	8	0.8 (0.4-1.6)	0.602	73.3	8	0.9 (0.5-1.9)	0.836	78.6	6	1.1 (0.5-2.4)	0.868	78.1	6	0.7 (0.3-1.8)	0.503	74.6
5*	5	9 (1.1-74.8)	0.042	91.0	4	26.5 (10.1-69.8)	*<0.001*	27.9	4	8.2 (0.5-127.2)	0.131	93.2	3	8.2 (0.2-274.6)	0.240	95.5	3	47.8 (26.3-86.8)	*<0.001*	0.0
6A†	6	0.4 (0.3-0.6)	*<0.001*	35.6	5	0.5 (0.3-0.8)	0.002	23.4	5	0.3 (0.2-0.5)	*<0.001*	0.0	4	0.3 (0.2-0.5)	*<0.001*	0.0	5	0.6 (0.3-1.3)	0.177	16.2
6B*	8	0.4 (0.2-0.6)	*<0.001*	28.8	7	0.4 (0.2-0.8)	0.006	25.1	7	0.3 (0.2-0.5)	*<0.001*	17.8	5	0.3 (0.1-0.6)	*0.001*	36.7	6	0.5 (0.3-0.9)	0.022	0.0
6C	9	0.1 (0.1-0.2)	*<0.001*	0.0	8	0.1 (0.1-0.2)	*<0.001*	0.0	8	0.1 (0.1-0.2)	*<0.001*	0.0	6	0.1 (0.1-0.2)	*<0.001*	0.0	6	0.1 (0.1-0.3)	*<0.001*	0.0
7F*	9	4.5 (3.2-6.3)	*<0.001*	0.0	8	4.4 (3.1-6.2)	*<0.001*	0.0	8	4.6 (3.2-6.4)	*<0.001*	0.0	6	4.3 (2.7-6.8)	*<0.001*	0.0	6	3.8 (2.4-6.1)	*<0.001*	0.0
8	8	2 (0.7-5.4)	0.172	59.9	7	2.1 (0.7-6.4)	0.172	64.9	7	1.4 (0.6-3.7)	0.467	39.1	5	2.4 (1.2-4.6)	0.013	0.0	6	3.1 (1.5-6.2)	0.002	8.7
10A	9	0.4 (0.2-0.7)	0.005	65.7	8	0.4 (0.2-0.9)	0.020	62.7	8	0.3 (0.1-0.6)	0.002	66.2	6	0.3 (0.1-0.7)	0.010	74.1	6	0.4 (0.2-0.8)	0.018	65.5
10B	3	0.3 (0.0-3.0)	0.293	67.3	3	0.3 (0-3)	0.293	67.3	2	0.3 (0-3.7)	0.331	83.4	2	0.3 (0-3.7)	0.331	83.4	3	0.3 (0-3.1)	0.290	66.8
12F	7	5.8 (2.5-13.1)	*<0.001*	74.5	7	5.8 (2.5-13.1)	*<0.001*	74.5	6	5 (1.8-13.8)	0.002	78.7	4	4.9 (0.9-25.7)	0.064	82.3	5	6.7 (2.4-18.3)	*<0.001*	76.6
14*	7	1.1 (0.7-1.6)	0.646	0.0	6	1 (0.6-1.5)	0.847	0.0	6	1 (0.7-1.6)	0.849	0.0	5	1 (0.7-1.6)	0.957	0.0	5	1.1 (0.6-2.3)	0.706	21.2
15A	9	0.3 (0.1-0.5)	*<0.001*	55.2	8	0.3 (0.1-0.5)	*<0.001*	59.6	8	0.2 (0.1-0.4)	*<0.001*	30.0	6	0.2 (0.1-0.4)	*<0.001*	48.2	6	0.2 (0.1-0.5)	*<0.001*	54.6
15BC	9	0.3 (0.2-0.4)	*<0.001*	67.7	8	0.3 (0.1-0.5)	*<0.001*	71.2	8	0.2 (0.1-0.4)	*<0.001*	71.3	6	0.2 (0.1-0.5)	*<0.001*	78.3	6	0.3 (0.1-0.5)	*<0.001*	66.9
16F	9	0.2 (0.1-0.3)	*<0.001*	0.0	8	0.2 (0.1-0.3)	*<0.001*	5.2	8	0.2 (0.1-0.2)	*<0.001*	0.0	6	0.2 (0.1-0.3)	*<0.001*	0.0	6	0.2 (0.1-0.3)	*<0.001*	0.0
18C*	6	1.1 (0.6-1.9)	0.820	0.0	5	1.1 (0.6-1.9)	0.826	0.0	5	1.1 (0.6-2)	0.824	0.0	4	0.9 (0.3-2.5)	0.783	19.4	5	1.4 (0.7-2.8)	0.297	0.0
19A*	9	Reference			8	Reference			8	Reference			6	Reference			6	Reference		
19F*	9	0.2 (0.2-0.4)	*<0.001*	31.0	8	0.2 (0.1-0.5)	*<0.001*	38.8	8	0.2 (0.1-0.4)	*<0.001*	29.5	6	0.2 (0.1-0.4)	*<0.001*	42.6	6	0.4 (0.2-0.6)	*<0.001*	0.0
22F	9	0.6 (0.4-0.8)	*0.001*	0.0	8	0.6 (0.4-0.8)	*0.001*	0.0	8	0.6 (0.4-0.8)	*0.001*	0.0	6	0.7 (0.5-1)	0.044	0.0	6	0.8 (0.5-1.1)	0.149	0.0
23B	9	0.1 (0.1-0.2)	*<0.001*	0.0	8	0.1 (0.1-0.2)	*<0.001*	0.0	8	0.1 (0.1-0.2)	*<0.001*	0.0	6	0.1 (0.1-0.2)	*<0.001*	0.0	6	0.1 (0.1-0.2)	*<0.001*	0.0
23F*	7	0.4 (0.2-0.7)	*0.001*	40.7	6	0.4 (0.2-0.8)	0.015	42.3	6	0.3 (0.2-0.6)	*<0.001*	28.4	5	0.3 (0.1-0.7)	0.003	42.7	5	0.4 (0.2-1)	0.045	41.4
24F	5	0.7 (0.3-1.6)	0.334	74.8	4	0.6 (0.2-1.7)	0.363	81.1	5	0.7 (0.3-1.6)	0.334	74.8	5	0.7 (0.3-1.6)	0.334	74.8	4	0.7 (0.3-1.7)	0.425	66.8
33F	9	1 (0.5-2)	0.915	71.7	8	1 (0.4-2.1)	0.910	75.2	8	0.9 (0.4-2)	0.824	75.2	6	1.2 (0.5-2.8)	0.631	61.5	6	1 (0.4-2.5)	0.946	69.8
35B	8	0.3 (0.1-0.7)	0.007	74.9	7	0.3 (0.1-0.9)	0.024	78.3	7	0.2 (0.1-0.3)	*<0.001*	11.0	5	0.2 (0.1-0.4)	*<0.001*	0.0	5	0.3 (0.2-0.6)	*0.001*	37.0
38	9	0.6 (0.3-1.1)	0.073	44.5	8	0.6 (0.3-1.1)	0.115	48.8	8	0.6 (0.3-1.1)	0.098	51.0	6	0.4 (0.2-1.1)	0.089	62.4	6	0.5 (0.3-1.1)	0.075	35.0
NT	9	0.2 (0-5.4)	0.348	90.1	8	0.1 (0-11.7)	0.366	91.4	8	0.1 (0-1.4)	0.084	67.2	6	0.1 (0-1.3)	0.079	70.0	6	0.2 (0-7.7)	0.358	89.8

Notes: *PCV10/13 and †PCV13 serotype. N: Number of settings included in the meta-analysis. IPD: Invasive pneumococcal disease, OR: odds ratio (invasive disease potential in relation to 19A) 95% CI confidence intervals, pOR1: p-value OR equals 1, where a value of <0.002 denotes significant difference with the reference serotype (in *italics*). I^2: percentage of heterogeneity, where values of less than 25% indicate low heterogeneity, of 25% to 50% as moderate and above 50% as considerable heterogeneity (Higgins et al., 2003)... PCV ≥70% coverage: excludes data from Barcelona, Spain. HIV low prevalence settings: Excludes data from South Africa, Industrialised settings: Excludes data from Alaska which reported data from rural settings, Navajo communities, and South Africa. Meta-analyses for settings with years of higher valent PCVs include data from Alaska, Israel, Italy, Norway, the UK, and South Africa.

Appendix 9 Sensitivity analyses invasive disease potential of *S. pneumoniae* serotypes in children 0–23 months

	All datasets				PCV ≥70 coverage in the study setting				HIV low prevalence settings				Industrialised settings			
	N	OR (95% CI)	pOR1	I2 (%)	N	OR (95% CI)	pOR1	I2(%)	N	OR (95% CI)	pOR1	I2 (%)	N	OR (95% CI)	pOR1	I2 (%)
1*	11	4.8 (2-11.5)	0.001	26.3	10	4.6 (1.8-11.6)	0.001	32.0	10	4.7 (1.7-13.3)	0.003	30.5	8	4.4 (1.4-14)	0.012	44.6
3†	11	1.5 (1-2.4)	0.057	30.2	10	1.5 (1-2.4)	0.070	35.7	10	1.5 (0.9-2.5)	0.107	37.2	8	1.7 (1.1-2.8)	0.020	20.5
5*	7	7.2 (0.6-84.9)	0.118	84.1	6	31.7 (15.1-66.4)	<0.001	0.0	6	6.5 (0.3-136.3)	0.229	86.7	5	6.3 (0.3-140.3)	0.246	89.4
6A†	10	0.4 (0.2-0.7)	0.001	55.5	9	0.4 (0.2-0.7)	0.005	60.3	9	0.3 (0.2-0.6)	0.001	56.7	7	0.3 (0.1-0.8)	0.013	65.8
6B*	10	0.3 (0.2-0.5)	<0.001	0.0	9	0.4 (0.2-0.6)	<0.001	0.0	9	0.3 (0.2-0.5)	<0.001	0.0	7	0.3 (0.2-0.5)	<0.001	0.0
6C	11	0.1 (0-0.1)	<0.001	0.0	10	0.1 (0-0.1)	<0.001	0.0	10	0.1 (0-0.1)	<0.001	0.0	8	0.1 (0-0.1)	<0.001	0.0
7F*	9	7.2 (4.6-11.5)	<0.001	19.3	8	7.2 (4.4-11.7)	<0.001	28.2	9	7.2 (4.6-11.5)	<0.001	19.3	8	7.8 (4.4-13.8)	<0.001	23.0
8	9	2.2 (0.9-5.3)	0.069	41.9	8	2.2 (0.9-5.4)	0.095	49.1	8	1.7 (0.6-4.5)	0.333	40.2	6	3.1 (1.7-5.6)	<0.001	0.0
10A	11	0.7 (0.4-1.2)	0.219	64.9	10	0.8 (0.4-1.4)	0.348	65.5	10	0.6 (0.3-1.2)	0.152	67.7	8	0.7 (0.3-1.3)	0.246	71.5
10B	4	0.3 (0.1-1.6)	0.152	48.9	4	0.3 (0.1-1.6)	0.152	48.9	3	0.3 (0-1.8)	0.177	65.5	3	0.3 (0-1.8)	0.177	65.5
12F	7	5.7 (2-16.2)	0.001	73.5	7	5.7 (2-16.2)	0.001	73.5	6	5 (1.3-18.8)	0.017	77.6	5	4.7 (0.8-29.2)	0.092	80.0
14*	10	0.8 (0.5-1.3)	0.461	0.0	9	0.8 (0.5-1.3)	0.309	0.0	9	0.9 (0.5-1.4)	0.590	0.0	7	0.7 (0.4-1.3)	0.254	0.0
15A	11	0.3 (0.2-0.4)	<0.001	34.5	10	0.3 (0.2-0.4)	<0.001	40.5	10	0.2 (0.1-0.4)	<0.001	26.2	8	0.2 (0.1-0.4)	<0.001	39.9
15BC	11	0.2 (0.1-0.4)	<0.001	71.3	10	0.2 (0.1-0.4)	<0.001	72.3	10	0.2 (0.1-0.3)	<0.001	73.3	8	0.2 (0.1-0.4)	<0.001	78.3
16F	11	0.2 (0.1-0.4)	<0.001	26.3	10	0.2 (0.1-0.4)	<0.001	29.6	10	0.2 (0.1-0.4)	<0.001	32.8	8	0.2 (0.1-0.4)	<0.001	22.6
18C*	10	1.6 (0.7-3.2)	0.237	0.0	9	1.5 (0.7-3.2)	0.241	0.0	9	1.8 (0.8-3.9)	0.140	0.0	7	1.7 (0.7-4.1)	0.214	0.0
19A*	11	Reference			10	Reference			10	Reference			8	Reference		
19F*	11	0.3 (0.2-0.5)	<0.001	0.0	10	0.3 (0.2-0.5)	<0.001	0.0	10	0.3 (0.2-0.4)	<0.001	0.0	8	0.3 (0.2-0.5)	<0.001	0.0
22F	11	0.7 (0.5-1)	0.059	16.8	10	0.7 (0.5-1)	0.067	24.3	10	0.7 (0.5-1)	0.084	24.1	8	0.8 (0.6-1.2)	0.353	5.7
23B	11	0.1 (0.1-0.2)	<0.001	0.0	10	0.1 (0.1-0.2)	<0.001	0.0	10	0.1 (0.1-0.2)	<0.001	0.0	8	0.1 (0.1-0.2)	<0.001	0.0
23F*	10	0.4 (0.2-0.6)	<0.001	0.0	9	0.3 (0.2-0.6)	<0.001	0.0	9	0.3 (0.2-0.5)	<0.001	0.0	7	0.3 (0.2-0.5)	<0.001	0.9
24F	8	1 (0.5-2)	0.929	57.1	7	1 (0.5-2)	0.895	63.1	8	1 (0.5-2)	0.929	57.1	7	1 (0.5-2.1)	0.950	62.6
33F	10	1.1 (0.5-2.1)	0.837	69.2	9	1.1 (0.5-2.1)	0.855	72.6	9	1.1 (0.5-2.2)	0.840	72.4	8	1.3 (0.6-2.5)	0.522	65.9
35B	10	0.2 (0.1-0.5)	<0.001	71.6	9	0.2 (0.1-0.5)	0.001	74.7	9	0.2 (0.1-0.3)	<0.001	5.7	7	0.2 (0.1-0.3)	<0.001	26.2
38	10	0.9 (0.6-1.4)	0.656	0.0	9	1 (0.6-1.5)	0.856	0.0	9	0.9 (0.6-1.5)	0.761	0.0	8	0.8 (0.5-1.3)	0.344	0.0
NT	11	0.2 (0-1.6)	0.127	83.7	10	0.2 (0-2.2)	0.181	85.3	10	0.1 (0-0.3)	<0.001	25.1	8	0.1 (0-0.3)	<0.001	22.4

Notes: *PCV10/13 and †PCV13 serotype. N: Number of settings included in the meta-analysis, i.e., there was at least 1 IPD case or carrier to enable calculation of OR for the serotype. IPD: Invasive pneumococcal disease, OR: odds ratio (invasive disease potential in relation to 19A) 95% CI confidence intervals, pOR1: p-value OR equals 1, where a value of <0.002 denotes significant difference with the reference serotype (in *italics*). I^2: percentage of heterogeneity, where values of less than 25% indicate low heterogeneity, of 25% to 50% as moderate and above 50% as considerable heterogeneity (Higgins et al., 2003) PCV ≥70% coverage: excludes data from Barcelona, Spain. HIV low prevalence settings: Excludes data from South Africa, Industrialised settings: Excludes data from Alaska, which reported data from rural settings, South Africa, and Colombia. Meta-analyses for settings with years of higher valent PCVs include data from 6 European settings, Alaska, Boston, and South Africa.

Appendix 10 Sensitivity analyses invasive disease potential of *S. pneumoniae* serotypes in children 0–23 months

	All datasets				Data from years post-higher valent PCV (10/13)				Data from settings implementing PCV13 (PCV10 excluded)				Setting implementing PCV10			
	N	OR (95% CI)	pOR1	I2 (%)	N	OR (95% CI)	pOR1	I2 (%)	N	OR (95% CI)	pOR1	I2 (%)	N	OR (95% CI)	pOR1	
1*	11	4.8 (2-11.5)	0.001	26.3%	5	3.3 (0.4-26.7)	0.267	59.9%	9	7.2 (3.3-16.1)	<0.001	10.8%	1	1.9 (0.5-7.7)	0.392	
3†	11	1.5 (1-2.4)	0.057	30.2%	9	1.4 (0.7-2.7)	0.288	29.8%	9	1.4 (0.8-2.4)	0.235	38.6%	1	1.8 (0.8-4.1)	0.192	
5*	7	7.2 (0.6-84.9)	0.118	84.1%	4	40.8 (17.9-92.9)	<0.001	0.0%	5	6.3 (0.3-149.1)	0.257	89.4%	1	11.2 (1.1-109.4)	0.038	
6A†	10	0.4 (0.2-0.7)	0.001	55.5%	8	0.4 (0.2-0.7)	0.002	0.0%	8	0.4 (0.2-0.8)	0.012	58.1%	1	0.1 (0-0.6)	0.009	
6B*	10	0.3 (0.2-0.5)	<0.001	0.0%	5	0.4 (0.2-0.8)	0.010	0.0%	8	0.3 (0.2-0.5)	<0.001	0.0%	1	0.1 (0-1)	0.054	
6C	11	0.1 (0-0.1)	<0.001	0.0%	9	0.1 (0.1-0.2)	<0.001	0.0%	9	0.1 (0-0.1)	<0.001	0.0%	1	0.1 (0-0.5)	0.003	
7F*	9	7.2 (4.6-11.5)	<0.001	19.3%	8	8.4 (4.4-16)	<0.001	0.0%	8	5.6 (3.7-8.5)	<0.001	0.0%	1	22.3 (9.5-52.5)	<0.001	
8	9	2.2 (0.9-5.3)	0.069	41.9%	6	2.5 (1.2-5)	0.013	0.0%	7	1.6 (0.5-4.9)	0.456	48.8%	1	5 (2-12.4)	0.001	
10A	11	0.7 (0.4-1.2)	0.219	64.9%	9	1 (0.6-1.8)	0.920	40.5%	9	0.6 (0.4-1)	0.038	41.1%	1	2.3 (1.3-3.9)	0.002	
10B	4	0.3 (0.1-1.6)	0.152	48.9%	5	0.6 (0.3-1.5)	0.276	3.3%	4	0.3 (0.1-1.6)	0.152	48.9%	0	NA	.	
12F	7	5.7 (2-16.2)	0.001	73.5%	7	5.7 (1.4-22.5)	0.013	71.2%	6	4.9 (1.5-15.9)	0.008	77.9%	1	14.9 (1.6-135.8)	0.017	
14*	10	0.8 (0.5-1.3)	0.461	0.0%	5	0.6 (0.3-1.1)	0.090	0.0%	8	0.8 (0.5-1.2)	0.274	0.0%	1	1.2 (0.1-12.2)	0.854	
15A	11	0.3 (0.2-0.4)	<0.001	34.5%	9	0.3 (0.2-0.6)	<0.001	29.9%	9	0.2 (0.1-0.4)	<0.001	27.7%	1	1.2 (0.2-6.3)	0.797	
15BC	11	0.2 (0.1-0.4)	<0.001	71.3%	9	0.3 (0.2-0.6)	<0.001	61.7%	9	0.2 (0.1-0.3)	<0.001	72.6%	1	0.6 (0.3-1.2)	0.145	
16F	11	0.2 (0.1-0.4)	<0.001	26.3%	9	0.2 (0.1-0.3)	<0.001	0.0%	9	0.2 (0.1-0.3)	<0.001	0.0%	1	0.6 (0.2-1.4)	0.208	
18C*	10	1.6 (0.7-3.2)	0.237	0.0%	5	1 (0.4-2.6)	0.938	0.0%	8	0.9 (0.4-2.3)	0.853	0.0%	1	4.6 (1.2-17.9)	0.026	
19A*	11	Reference			9	Reference			9	Reference			1	Reference		
19F*	11	0.3 (0.2-0.5)	<0.001	0.0%	9	0.6 (0.3-1.2)	0.178	33.1%	9	0.3 (0.2-0.5)	<0.001	0.0%	1	0.2 (0-1.3)	0.086	
22F	11	0.7 (0.5-1)	0.059	16.8%	9	0.8 (0.5-1.2)	0.297	0.0%	9	0.6 (0.4-0.9)	0.012	7.7%	1	1.4 (0.6-3)	0.426	
23B	11	0.1 (0.1-0.2)	<0.001	0.0%	9	0.1 (0.1-0.2)	<0.001	0.0%	9	0.1 (0.1-0.2)	<0.001	0.0%	1	0.1 (0-0.5)	0.002	
23F*	10	0.4 (0.2-0.6)	<0.001	0.0%	5	0.3 (0.1-0.6)	<0.001	0.0%	8	0.4 (0.2-0.6)	<0.001	7.8%	1	0.002 (0-2.0e)	0.657	
24F	8	1 (0.5-2)	0.929	57.1%	7	1.1 (0.5-2.1)	0.836	38.2%	6	0.8 (0.3-1.9)	0.572	66.1%	1	2.5 (0.8-7.3)	0.099	

	All datasets				Data from years post-higher valent PCV (10/13)				Data from settings implementing PCV13 (PCV10 excluded)				Setting implementing PCV10			
33F	10	1.1 (0.5-2.1)	0.837	69.2%	9	1.6 (0.9-2.8)	0.107	28.8%	9	0.8 (0.4-1.7)	0.635	63.8%	1	3.9 (1.9-8.2)	<0.001	
35B	10	0.2 (0.1-0.5)	<0.001	71.6%	8	0.3 (0.2-0.5)	<0.001	0.0%	8	0.2 (0.1-0.6)	0.004	77.5%	1	0.1 (0-0.8)	0.031	
38	10	0.9 (0.6-1.4)	0.656	0.0%	9	0.9 (0.4-1.9)	0.788	16.5%	9	0.9 (0.6-1.5)	0.766	0.0%	1	0.5 (0.1-3.8)	0.475	
NT	11	0.2 (0-1.6)	0.127	83.7%	9	0.5 (0-4.2)	0.485	79.7%	9	0.2 (0-1.7)	0.143	86.4%	1	0.001 (0-8.5e)	0.613	

Notes: *PCV10/13 and †PCV13 serotype. N: Number of settings included in the meta-analysis, i.e., there was at least 1 IPD case or carrier to enable calculation of OR for the serotype. IPD: Invasive pneumococcal disease, OR: odds ratio (invasive disease potential in relation to 19A) 95% CI confidence intervals, pOR1: p-value OR equals 1, where a value of <0.002 denotes significant difference with the reference serotype (in *italics*). I^2: percentage of heterogeneity, where a value of I^2 below 50% denotes low to moderate and above 50% considerable heterogeneity where values of less than 25% indicate low heterogeneity, of 25% to 50% as moderate and above 50% as considerable heterogeneity (Higgins et al., 2003). PCV ≥70% coverage excludes data from Barcelona, Spain. HIV low prevalence settings: Excludes data from South Africa, Industrialised settings: Excludes data from Alaska, which reported data from rural settings, South Africa, and Colombia. Meta-analyses for settings with years of higher valent PCVs include data from 6 European settings, Alaska, Boston, and South Africa. Data from settings implementing PCV13 (PCV10 excluded): Excludes data from Colombia (study period is for PCV7 implementation period only) and the Netherlands (PCV10 implemented in this setting).

Appendix 11 Meta-estimates of the invasive disease potential of *S. pneumoniae* serotypes by age group

				0–23 months					24–59 months			
	N	IPD/ Carriage (n)	%	OR (95% CI)	p-value OR=1	I^2	N	IPD/ Carriage (n)	%	OR (95% CI)	p-value OR=1	I^2
1*	6	65/15	4.2/0.2	6.3 (1.7-23)	0.005	29.0%	5	165/25	19.1/0.4	25 (14-44.8)	*<0.001*	0.0%
3†	6	79/90	5.1/1.1	1.3 (0.6-2.7)	0.552	52.7%	6	56/195	6.5/2.8	1.3 (0.7-2.7)	0.428	39.7%
5*	3	68/14	4.4/0.2	5.7 (0.2-155.2)	0.300	94.7%	3	86/11	10/0.2	20.2 (3.2-127.4)	*0.001*	75.8%
6A†	5	31/267	2/3.3	0.4 (0.3-0.6)	*<0.001*	0.0%	5	21/159	2.4/2.3	0.9 (0.3-3.1)	0.873	65.8%
6B*	5	18/162	1.2/2	0.3 (0.2-0.6)	*<0.001*	0.0%	6	14/129	1.6/1.9	1 (0.5-2.1)	0.960	0.0%
6C	6	10/224	0.6/2.7	0.1 (0-0.1)	*<0.001*	0.0%	6	7/272	0.8/3.9	0.3 (0.1-0.9)	0.024	10.2%
7F*	5	70/25	4.5/0.3	6.1 (3.6-10.4)	*<0.001*	0.0%	6	40/57	4.6/0.8	5.2 (3-9)	*<0.001*	0.0%
8	5	23/41	1.5/0.5	1.9 (0.5-8)	0.368	57.1%	6	6/30	0.7/0.4	2 (0.7-5.4)	0.191	0.0%
10A	6	45/170	2.9/2.1	0.6 (0.3-1.2)	0.124	58.4%	6	5/177	0.6/2.5	0.4 (0.1-1.1)	0.078	0.0%
10B	3	19/114	10.9/1.4	0.2 (0-3.2)	0.283	62.8%	2	6/52	6.3/0.7	1 (0.3-2.6)	0.932	0.0%
12F	4	169/52	2.1/0.6	5.7 (1.6-20.9)	0.008	84.4%	4	54/37	3/0.5	10.3 (5.6-18.8)	*<0.001*	0.0%
14*	5	33/115	1.8/1.4	0.8 (0.5-1.4)	0.406	0.0%	5	26/59	1.2/0.8	2.4 (1.2-4.8)	0.013	0.0%
15A	6	28/374	1.3/4.6	0.3 (0.2-0.5)	*<0.001*	3.5%	6	10/245	1.3/3.5	0.5 (0.2-1.7)	0.281	33.2%
15BC	6	93/844	0.5/10.3	0.2 (0.1-0.4)	*<0.001*	80.0%	6	31/613	1.3/8.8	0.5 (0.3-0.7)	0.002	0.0%
16F	6	20/446	14.3/5.4	0.2 (0.1-0.3)	*<0.001*	0.0%	6	11/353	8.8/5.1	0.3 (0.1-0.5)	*<0.001*	0.0%
18C*	5	7/34	2.4/0.4	0.8 (0.3-2.2)	0.655	0.0%	5	11/32	0.5/0.5	2.9 (1.2-6.8)	0.018	0.0%
19A†	6	222/607	3/7.4	Reference			6	76/429	2/6.2	Reference		
19F*	6	38/340	1.4/4.1	0.3 (0.2-0.5)	*<0.001*	17.8%	6	4/248	1.7/3.6	0.1 (0-0.3)	*<0.001*	0.0%
22F	6	46/174	1.3/2.1	0.6 (0.4-0.9)	0.009	0.0%	6	17/207	1.4/3	0.8 (0.4-1.4)	0.399	0.0%
23B	6	21/411	2.2/5	0.1 (0.1-0.2)	*<0.001*	0.0%	6	15/421	1.6/6.1	0.2 (0.1-0.4)	*<0.001*	0.0%
23F*	5	20/205	4.6/2.5	0.3 (0.2-0.7)	0.004	31.1%	6	12/141	1.3/2	0.7 (0.2-2.2)	0.575	43.7%
24F	4	34/73	1.9/0.9	0.4 (0.1-2.7)	0.382	77.2%	4	14/93	0.2/1.3	0.9 (0.5-1.9)	0.861	0.0%
33F	6	72/157	1.8/1.9	0.8 (0.3-2.3)	0.662	71.9%	5	11/137	0.8/2	1.7 (0.4-7.5)	0.499	61.6%
35B	6	30/383	2.7/4.7	0.4 (0.1-1.2)	0.094	76.8%	6	2/304	1.6/4.4	0.2 (0-0.8)	0.023	0.0%
38	6	28/86	1.2/1	0.8 (0.4-1.5)	0.461	31.0%	5	7/109	0.7/1.6	0.9 (0.3-2.2)	0.759	0.0%
NT	6	42/356	6/4.3	0.2 (0-6.3)	0.374	90.5%	6	14/328	3.6/4.7	1.5 (0.1-28.1)	0.806	67.7%

Notes: *PCV10/13 and †PCV13 serotype. N: Number of settings included in the meta-analysis. IPD: Invasive pneumococcal disease, OR: odds ratio (invasive disease potential in relation to 19A) 95% CI confidence intervals, pOR1: p-value OR equals 1, where a value of <0.002 denotes significant difference with the reference serotype (*in italics*). A value of I^2: percentage of heterogeneity, where values of less than 25% indicate low heterogeneity, of 25% to 50% as moderate and above 50% as considerable heterogeneity (Higgins et al., 2003).

Appendix 12 Meta-analyses results for serotypes invasive disease potential by clinical syndrome

	Meningitis						Bacteraemia/Sepsis						Pneumonia					
	N	(n)	(%)	OR (95% CI)	p-value OR1	I^2 (%)	N	(n)	(%)	OR (95% CI)	p-value OR1	I^2 (%)	N	(n)	(%)	OR (95% CI)	p-value OR1	I^2 (%)
1*	4	7/39	2.2/0.3	5.6 (2.2-14.4)	<0.001	0.0	3	27/39	3.8/0.3	6.3 (2.6-15.4)	<0.001	17.2	5	186/39	3.8/0.3	25.3 (15.9-40.1)	<0.001	0.0
3†	5	9/258	2.8/1.8	1.5 (0.5-4.6)	0.511	31.9	4	25/258	3.5/1.8	1.1 (526-2.4)	0.765	38.3	5	89/258	3.5/1.8	1.3 (0.5-3.5)	0.583	82.5
5*	3	19/25	5.9/0.2	14 (1-196)	0.05	87.5	3	30/25	4.2/0.2	7 (0.8-59.6)	0.073	84.2	3	103/25	4.2/0.2	8.4 (0.3-213.9)	0.197	96.2
6A†	5	9/426	2.8/3	0.7 (0.3-1.6)	0.389	0.0	5	18/426	2.5/3	0.5 (0.3-0.8)	0.01	0.0	5	26/426	2.5/3	0.4 (0.2-0.8)	0.01	54.7
6B*	5	6/289	1.9/2	0.7 (0.3-1.7)	0.408	0.0	4	12/289	1.7/2	0.6 (0.3-1.1)	0.121	0.0	5	14/289	1.7/2	0.4 (0.2-1.1)	0.07	30.1
6C	5	4/468	1.2/3.2	0.4 (0.1-1.3)	0.125	0.0	5	5/468	0.7/3.2	0.2 (0.1-0.5)	<0.001	0.0	5	7/468	0.7/3.2	0.1 (0-0.2)	<0.001	0.0
7F*	5	12/74	3.7/0.5	7.6 (3.4-16.9)	<0.001	0.0	5	32/74	4.5/0.5	5 (3-8.5)	<0.001	0.0	5	53/74	4.5/0.5	4.6 (3-7.2)	<0.001	0.0
8	5	13/70	4/0.5	13.5 (5.2-35)	<0.001	43.6	5	5/70	0.7/0.5	1.3 (0.5-3.4)	0.585	0.0	5	6/70	0.7/0.5	1.5 (0.4-6.5)	0.564	24.4
10A	5	10/310	3.1/2.2	1.9 (0.8-4.6)	0.134	0.0	5	22/310	3.1/2.2	0.9 (0.5-1.5)	0.636	7.5	5	5/310	3.1/2.2	0.2 (0.1-0.4)	<0.001	0.0
10B	3	2/166	0.6/1.2	0.7 (0.2-3.4)	0.685	0.0	3	10/166	1.4/1.2	0.7 (0.4-1.5)	0.406	0.0	3	7/166	1.4/1.2	0.7 (0.3-1.5)	0.339	0.0
12F	3	32/80	9.9/0.6	23 (11.6-45.9)	<0.001	0.0	3	101/80	14/0.6	9.8 (2.4-41.2)	0.002	62.7	3	65/80	14/0.6	9.3 (5.3-16.4)	<0.001	30.2
14*	5	5/174	1.2/1.2	0.9 (0.3-2.9)	0.877	0.0	5	19/174	2.6/1.2	1.4 (0.8-2.4)	0.277	0.0	5	35/174	2.6/1.2	1.4 (0.7-2.6)	0.309	19.0
15A	5	9/587	2.8/4.1	1.2 (0.5-3)	0.682	0.0	5	7/587	1/4.1	0.2 (0.1-0.4)	<0.001	0.0	5	16/587	1/4.1	0.3 (0.2-0.6)	<0.001	0.0
15BC	5	22/1372	6.8/9.5	0.7 (0.3-1.4)	0.312	21.2	5	55/1372	7.6/9.5	0.5 (0.4-0.7)	<0.001	0.0	5	25/1372	7.6/9.5	0.1 (0.1-0.3)	<0.001	67.5
16F	5	5/779	1.5/5.4	0.4 (0.1-1.1)	0.086	0.0	5	12/779	1.7/5.4	0.2 (0.1-0.4)	<0.001	0.0	5	12/779	1.7/5.4	0.1 (0-0.4)	0.001	63.1
18C*	4	4/66	1.2/0.5	2.4 (0.7-7.5)	0.149	0.0	5	11/66	1.5/0.5	1.7 (0.8-3.9)	0.203	0.0	4	3/66	1.5/0.5	0.7 (0.2-2.6)	0.641	0.0
19A†	5	25/1000	7.7/6.9	Reference			5	83/1000	11.5/6.9	Reference			5	156/1000	11.5/6.9	Reference		

	Meningitis						Bacteraemia/Sepsis						Pneumonia					
	N	(n)	(%)	OR (95% CI)	p-value OR1	I^2 (%)	N	(n)	(%)	OR (95% CI)	p-value OR1	I^2 (%)	N	(n)	(%)	OR (95% CI)	p-value OR1	I^2 (%)
19F*	5	13/586	4/4.1	1 (0.5-2)	0.951	0.0	5	19/586	2.6/4.1	0.4 (0.2-0.7)	0.002	0.0	5	9/586	2.6/4.1	0.2 (0.1-0.3)	<0.001	0.0
22F	5	8/350	2.5/2.4	1 (0.3-2.9)	0.934	0.0	5	19/350	2.6/2.4	0.7 (0.4-1.2)	0.216	0.0	4	17/350	2.6/2.4	0.4 (0.2-0.8)	0.005	20.4
23B	5	9/756	2.8/5.2	0.5 (0.2-1.1)	0.076	0.0	5	13/756	1.8/5.2	0.2 (0.1-0.4)	<0.001	0.0	5	5/756	1.8/5.2	0 (0-0.1)	<0.001	0.0
23F*	5	12/345	3.7/2.4	1.1 (0.5-2.6)	0.783	0.0	5	12/345	1.7/2.4	0.5 (0.3-0.9)	0.026	0.0	5	10/345	1.7/2.4	0.2 (0.1-0.7)	0.015	37.0
24F	3	9/148	2.8/1	1.7 (0.6-5)	0.36	14.9	3	14/148	1.9/1.0	0.8 (0.2-2.4)	0.624	45.4	3	12/148	1.9/1	0.5 (0.1-2.5)	0.38	79.3
33F	4	13/278	4/1.9	1.9 (0.9-4.4)	0.111	0.0	4	31/278	4.3/1.9	1.1 (0.3-3.4)	0.896	61.9	5	34/278	4.3/1.9	0.9 (0.2-4)	0.859	83.4
35B	5	5/660	1.5/4.6	1.1 (0.1-8.9)	0.957	35.8	5	13/660	1.8/4.6	0.3 (0.2-0.6)	<0.001	0.0	5	9/660	1.8/4.6	0.2 (0-3.2)	0.244	83.9
38	5	1/181	0.3/1.3	0.6 (0.1-4.5)	0.592	0.0	5	18/181	2.5/1.3	1.7 (1-2.9)	0.064	0.0	5	8/181	2.5/1.3	0.4 (0.2-0.9)	0.017	0.0
NT	5	9/663	2.8/4.6	0.04 (0-3.8)	0.657	54.5	5	6/663	0.8/4.6	0 (0-0)	0.624	78.3	5	37/663	0.8/4.6	0.5 (0-14.5)	0.67	90.0

Notes: *PCV10/13 and †PCV13 serotype. N: Number of settings included in the meta-analysis. IPD: Invasive pneumococcal disease, OR: odds ratio (invasive disease potential in relation to 19A) 95% CI confidence intervals, pOR1: p-value OR equals 1, where a value of <0.002 denotes significant difference with the reference serotype (*in italics*). I^2: percentage of heterogeneity, where values of less than 25% indicate low heterogeneity, of 25% to 50% as moderate and above 50% as considerable heterogeneity. (Higgins et al., 2003)