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Pneumococcal serotypes missing prespecified efficacy threshold in immunogenicity trials: real-world evidence from national immunization programs

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ABSTRACT

Objectives: The 13-valent (PCV13) and 10-valent (PCV10) pneumococcal conjugate vaccines missed non-inferiority for certain 7-valent (PCV7) serotypes in immunogenicity trials. This study examines the population-level IPD case trends for these serotypes.

Methods: We identified six countries with national IPD surveillance data that introduced PCV13 (Canada, Germany, Israel, Italy, South Africa, and the United States) and three with PCV10 (Finland, Brazil, and the Netherlands). We extracted country-specific annual IPD case counts for PCV7 serotypes that missed non-inferiority and met non-inferiority (6B + 23F and PCV7 minus [6B + 23F] serotypes for PCV10 countries; 6B +9V + 23F, and PCV7 minus [6B +9V + 23F] serotypes for PCV13 countries) in clinical trials. Case count data for each country were plotted for observed serotype trends in different age groups (<5 and ≥5 years) for 8 years following PCV13/PCV10 introduction.

Results: For all ages and countries, IPD cases due to PCV7 serotypes that missed non-inferiority either decreased or remained suppressed following PCV13/PCV10 introduction. Similar trends were found for PCV7 serotypes that met non-inferiority in those <5 years. Paradoxically, cases increased in those ≥5 years in Canada, Italy, and the US, primarily driven by increases in serotypes 4 and 19F disease.

Conclusions: Despite missing non-inferiority of serotypes in immunogenicity trials, higher-valent PCVs effectively suppressed these serotypes across all ages. Non-inferiority criteria from immunogenicity trials may not fully predict real-world disease impact after PCV implementation.

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Pneumococcal disease; pneumococcal vaccination; public health impact; immunogenicity; invasive pneumococcal disease; pneumococcal conjugate vaccine

1. Introduction

Since the early 2000s, pneumococcal conjugate vaccines (PCVs) have been available as part of pediatric national immunization programs (NIPs) for the prevention of pneumococcal disease. [1] A 7-valent PCV (PCV7) was the first PCV introduced globally, which covered serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. Approval of PCV7 was based on both safety and immunogenicity data as well as large, randomized, controlled studies which demonstrated the efficacy of PCV7. [2] Subsequently, two higher valent PCVs were developed to address the evolving disease etiology, a 10-valent vaccine (PCV10), and a 13-valent vaccine (PCV13). Each of these vaccines covered the seven serotypes in PCV7 as well as additional serotypes (1, 5, and 7F in PCV10; 1, 3, 5, 6A, 7F, and 19A in PCV13).

The phase 3 clinical trials for PCV13 and PCV10 were immunogenicity studies designed to determine if the new intervention (PCV13 or PCV10) performs the same (i.e. non-inferiority) compared with an established intervention (PCV7). [3–7] For these PCV pediatric clinical trials, serotype-specific responses in the new PCV were compared to the corresponding serotype in the PCV7 group for the seven shared serotypes. [3–7] Assessment of PCV10 and PCV13 has been based on their ability to induce serotype-specific antibody production, which can be evaluated by serotype-specific Immunoglobulin G (IgG) concentrations, including IgG geometric mean concentrations (GMCs) (post-primary series and post-toddler dose) and the percentage of participants above prespecified IgG concentrations. [3–7] Clinical evaluations of PCVs have used an immunological correlate of protection post-primary series, which is based on pooled and meta-analyzed data from PCV7 clinical trials resulting in a value of ≥0.35 µg/mL with the Pfizer Inc assay, [8] and when IgG is measured using the GlaxoSmithKline (GSK) assay, the equivalent correlate of protection is 0.20 µg/mL. [9] For each serotype, the percentage of participants above a prespecified IgG concentration non-inferiority margin is typically set at −10% (i.e. if the lower bound of the 95% confidence interval (CI) for the difference in the proportion of individuals reaching prespecified IgG levels is above −10%, non-inferiority can be declared). Therefore, non-inferiority is met when the lower bound of the confidence interval (CI) is above a certain, a priori determined threshold. In the clinical studies of PCV13 and PCV10, non-inferiority was not reached for a percentage of participants above a prespecified IgG concentrations. Non-inferiority was not shown for serotypes 6B and 9V when comparing PCV13 to PCV7 and may have failed on serotype 23F, but this study was not sufficiently statistically powered. [3,4,7]

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Moreover, non-inferiority was not shown for serotypes 6B and 23F when comparing PCV10 to PCV7.[6]

Both PCV10 and PCV13 have been implemented as part of pediatric NIPs in numerous countries, providing the opportunity to examine the real-world impact of these two PCVs on serotypes that missed non-inferiority endpoints in immunogenicity bridging studies. Therefore, the objectives of this descriptive multi-country longitudinal study were as follows: (1) to retrospectively report the number of IPD cases due to serotypes for which PCVs missed non-inferiority in immunogenicity studies: serotypes 6B, 9V, and 23F for PCV13 versus PCV7; serotypes 6B and 23F for PCV10 versus PCV7; and (2) to compare these case trends to the case trends for other PCV7 serotypes that met the non-inferiority endpoints for PCV13 (serotypes 4, 14, 18C, or 19F) and PCV10 (serotypes 4, 9V, 14, 18C, or 19F).

2. Patients and methods

2.1. Invasive pneumococcal disease data

To address the study objectives, we identified countries that met the following criteria: (1) had implemented a PCV program with either PCV10 or PCV13 in the pediatric NIP; and (2) for which national IPD surveillance data were available for age group-specific case counts for each PCV7 serotype before and after implementation of PCV10/13. Among countries which implemented PCV13, Canada, Germany, Israel, Italy, South Africa, and the US met these criteria. Among countries that introduced PCV10, Brazil, Finland, and the Netherlands met the criteria.

Details on the vaccination program history for each country can be seen in Table 1. The countries identified differ in several relevant aspects. In addition to differences in population and geography, the countries had differing use of PCV7 prior to implementation of PCV13/PCV10. Brazil and Finland did not implement PCV7 prior to introducing PCV10. Germany, Israel, Italy, and South Africa had introduced PCV7 for a few years (2–4 years) prior to PCV13 introduction. The Netherlands introduced PCV7 5 years prior to introducing PCV10. Canada and the US each had nearly 10 years of PCV7 use prior to the PCV13 introduction. The vaccination schedule also differed between countries, with some using two primary doses and a booster dose (a '2 + 1' schedule) and some using a 3 + 1 schedule, and some switched from a 3 + 1 to a 2 + 1 schedule. Differences in vaccination uptake over time were also noted between countries (Supplementary Table S1), especially with respect to PCV7 uptake. The US had a substantial uptake of PCV7 for several years, while Canada had a fairly low uptake of PCV7 and relatively low overall uptake (~80%) of PCV13. Israel and the Netherlands had very high uptake of PCV13/PCV10, but relatively little use of PCV7. Italy and South Africa had very little reported uptake of PCV7.

We extracted data by serotype and age group from available surveillance systems for each of the nine countries meeting the inclusion criteria for the study as outlined above (Table 1). [10–19,23,24,26–28,30–35,37] The data underlying the results figures, along with details on the data collection

Table 1. Countries included and data sources.

Countries	Original data source	PCV7 used in NIP for healthy children <2 years	PCV7 year of introduction and schedules used	Higher-valent PCV used in NIP for healthy children <2 years	Higher-valent PCV year of introduction and schedules used
Brazil	SIREVA [10–19]	-	-	PCV10	2010 (3 + 1) 2016 (2 + 1)
Canada† [20–22]	PHAC [23]	PCV7	2001 (3 + 1) 2007 (2 + 1)	PCV13	2010 (2 + 1)
Finland	THL [24]	-	-	PCV10	2010 (2 + 1)
Germany‡ [25]	GNRCS* [26,27]	PCV7	2006 (3 + 1)	PCV13	2010 (3 + 1) 2015 (2 + 1)
Israel [28]	IPBMG [28]	PCV7	2009 (2 + 1)	PCV13	2011 (2 + 1)
Italy‖ [29]	MIB [30–33]	PCV7	2007 (2 + 1)	PCV13	2010-2012 (2 + 1)
Netherlands	RIVM* [34]	PCV7	2006 (3 + 1)	PCV10	2011(3 + 1) 2013 (2 + 1)
South Africa	GERMS-SA [35]	PCV7	2009§ (2 + 1)	PCV13	2011 (2 + 1)
United States▲ [36]	ABCs [37]	PCV7	2000 (3 + 1)	PCV13	2010 (3 + 1)

ABC = Active Bacterial Core; CDC = Centers for Disease Control and Prevention; GERMS-SA = Group for Enteric, Respiratory and Meningeal disease – Surveillance in South Africa; GNRCS = German National Reference Center for Streptococci; IPBMG = Israeli Pediatric Bacteremia and Meningitis Group; MIB = National Surveillance System of Invasive Bacterial Diseases; PHAC = Public Health Agency of Canada; RIVM = National Institute for Public Health and the Environment; SIREVA = Regional System for Vaccines; THL = Finnish Institute for Health and Welfare; NNDSS = National Notifiable Disease Surveillance System.

† The National Advisory Committee on Immunization (NACI) recommended PCV7 for routine administration in a 3 + 1 to all children ≤2 years, with subsequent implementation in provinces through 2002–2006 with variation in uptake. From 2007 on, the recommended schedule was 2 + 1 for healthy infants. PCV10 replaced PCV7 as the vaccine of choice in 2009 in four provinces briefly until 2011. After this, PCV13 was implemented in all provinces from 2010–2011 in a 2 + 1 schedule, a catch-up program for previously vaccinated children was provided in two provinces (Ontario and Manitoba); one additional dose for all children ages aged 12–35 months.

*.The German Standing Committee on Vaccination (STIKO) recommended PCV7 for routine administration in a 3 + 1 to all children ≤2 years in 2006. Both PCV10 and PCV13 were recommended by STIKO in 2009 under a 3 + 1 schedule and switch to a 2 + 1 schedule in 2015; PCV13 was historically preferred, with > 90% uptake in NIP.

In Italy, PCV7 was not mandatorily recommended for all children ≤2 years in each 21 regions, and major regional variation existed (i.e. no vaccination policy versus all infants actively called). By 2012, all regions switched to PCV13 in a 2 + 1 schedule.

§.▲In the United States, a large PCV13 catch-up program was implemented for previously vaccinated children that included one additional dose for all children ages 14–59 months.

*Data were provided through direct communication reports (Pfizer data on file).

approach, can be seen in Supplementary Tables S1-S9. Briefly, we obtained annual case counts by serotype and age groups for each country from various data sources as outlined. For most of the countries, the data were obtained from publicly available national or nationally representative surveillance data sets. In two cases, data were obtained from analyses of nationally representative data. In the case of Israel, case counts were derived from incidence rates reported from a published national surveillance study. The data reported for each country were not stratified into identical age groups. To best align the data across the different countries, we thus pooled age group case data into two age groups as follows: ages <5 years and ages 5+ years. We obtained data for each serotype of interest (6B, 9V, and 23F individually; and PCV7 pooled) for each age group for each country for the year preceding the introduction of PCV10/PCV13 and all available subsequent years up through 2019. We excluded data for 2020 onward due to the COVID pandemic, which reduced disease incidence worldwide and as such including these data would artificially inflate the impact of the PCV pediatric programs. Analyses were then capped at 8 years after PCV10/PCV13 introduction because all countries contributed data over this period.

Throughout the analyses, the observed changes in cases among the vaccinated age group aged <5 years (including routine and catch-up vaccination) were considered as direct vaccine effects, as these ages represent the age group vaccinated with each vaccine. Observed changes in cases among the older age groups not targeted for pediatric vaccination were considered as indirect vaccine effects, as these ages did not receive the pediatric vaccine.

2.2. Descriptive analyses

Our analysis approach was similar to that outlined in a previous publication on the indirect effects of higher-valent vaccines. [38] In this study, we examined the effects of vaccination at the individual country level. For each country, we calculated the case counts for the year prior to the introduction of a PCV10/PCV13 program (referred to as 'Yr0' in the tables and figures) and for up to 8 years ('Yr1' to 'Yr8') following implementation of the vaccine program. Specifically, we computed the case counts for two age groups (<5 years; 5 + years) and 2 serotype groups (6B + 23F and PCV7 minus [6B + 23F] for PCV10 countries; 6B +9V + 23F, and PCV7 minus [6B +9V + 23F] for PCV13 countries). We pooled the individual serotypes due to small numbers of cases in certain age groups and years. Thus, we included the following data for each country as follows: 2009–2010 to 2017–18 epidemiologic years for the Netherlands and South Africa; 2010–11 to 2018–19 epidemiologic years for the remaining countries. For consistency, we included only the first 8 years following PCV13/10 introduction so as not to exclude any countries for any years.

We did not estimate relative changes in cases due to differences in the previous vaccine history and population sizes of the countries. Specifically, not all countries had implemented PCV7 prior to PCV10 or PCV13, and the duration of PCV7 implementation prior to PCV10/PCV13 varied substantially among the countries which did implement PCV7. Therefore, in some PCV10 and PCV13 countries, the PCV7 serotypes were already suppressed, whereas in other countries the PCV7 serotypes were not. As such, any comparisons across countries or vaccine programs would potentially be biased. We also did not conduct statistical analyses of the country-level data for similar reasons. Instead, we examined the within-country qualitative trends in cases over time following PCV13/PCV10 compared with the year prior to PCV13/PCV10 introduction.

3. Results

3.1. Results for ages <5 years

In the countries which implemented PCV13, cases of IPD due to serotypes 6B, 9V, and 23F decreased over time or remained at already low levels following introduction of PCV13 (Figure 1a). Trends in disease were generally consistent across countries but varied by age groups. Among children <5 years, IPD cases due to these serotypes were virtually eliminated by Yr5 of introduction of PCV13 in Canada, Germany, Israel, Italy, and the US (only eight cases reported for these five countries combined across Yr5-Yr8). Cases in South Africa continued to decline steadily, reaching a plateau around Yr6. In the countries which implemented PCV10, cases of IPD due to serotypes 6B and 23F decreased over time following the introduction of PCV10 (Figure 1c). Trends in disease were generally consistent across countries but varied by age group. IPD cases due to these serotypes declined in Finland (from 26 cases in Yr0 to 4 total cases in Yr5-Yr8) and Brazil (from 50 cases in Yr0 to 8 total cases in Yr5-Yr8), while disease suppression was maintained following the transition from PCV7 to PCV10 in the Netherlands (1 total case in Yr5-Yr8).

Decreases in cases of IPD due to the remaining serotypes in PCV7 (serotypes 4, 14, 18C, and 19F) exhibited more variability over the 8 years of implementation of PCV13. In PCV13 countries (Figure 1b), disease suppression was maintained from Yr0 to similar levels by Yr8 in Canada (a decrease from 14 to 6 cases) and Italy (from 7 to 4 cases); case counts decreased from Yr0 to Yr8 in Germany (from 24 to 4 cases), Israel (from 34 to 3 cases), and South Africa (from 66 to 21 cases). Cases in the US increased slightly from two cases in Yr0 to 10–11 cases in Yr5-Yr8. In Canada, the US, and Italy, case counts remained at or below 10 in Yr8 for each country. In PCV10 countries (Figure 1d), case counts due to the remaining PCV7 serotypes (4, 9V, 14, 18C, and 19F) decreased from Yr0 to Yr8 in Finland (from 58 cases to 0 cases) and Brazil (from 90 cases to 4 cases), while disease suppression was maintained in the Netherlands (3 total cases in Yr5-Yr8).

3.2. Results for ages 5+ years

Among individuals ages 5+, disease reduction was more gradual (Figure 2). In the PCV13 countries, disease trends remained relatively stable from Yr5 onwards, and in no countries did total cases of 6B, 9V, and 23F return to or exceed pre-PCV13 levels (Figure 2a). In the PCV10 countries, disease case reduction was also observed for serotypes 6B and 23F (Figure 2c). In Finland, the disease decreased from 92 cases

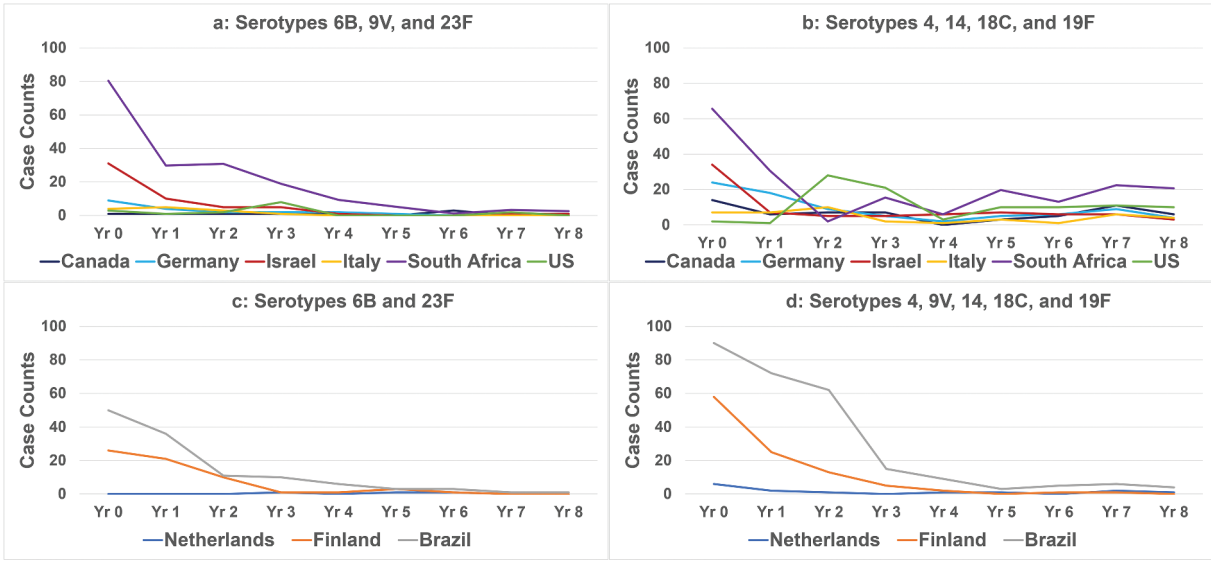

Figure 1. Trends in invasive pneumococcal disease cases for populations ages <5 years.

US = United States. The figures present the change in cases for serotypes 6B, 9V, and 23F (1a) and serotypes 4, 14, 18C, and 19F (1b) for countries which implemented PCV13; and cases for serotypes 6B and 23F (1c) and serotypes 4, 9V, 14, 18C, and 19F (1d).

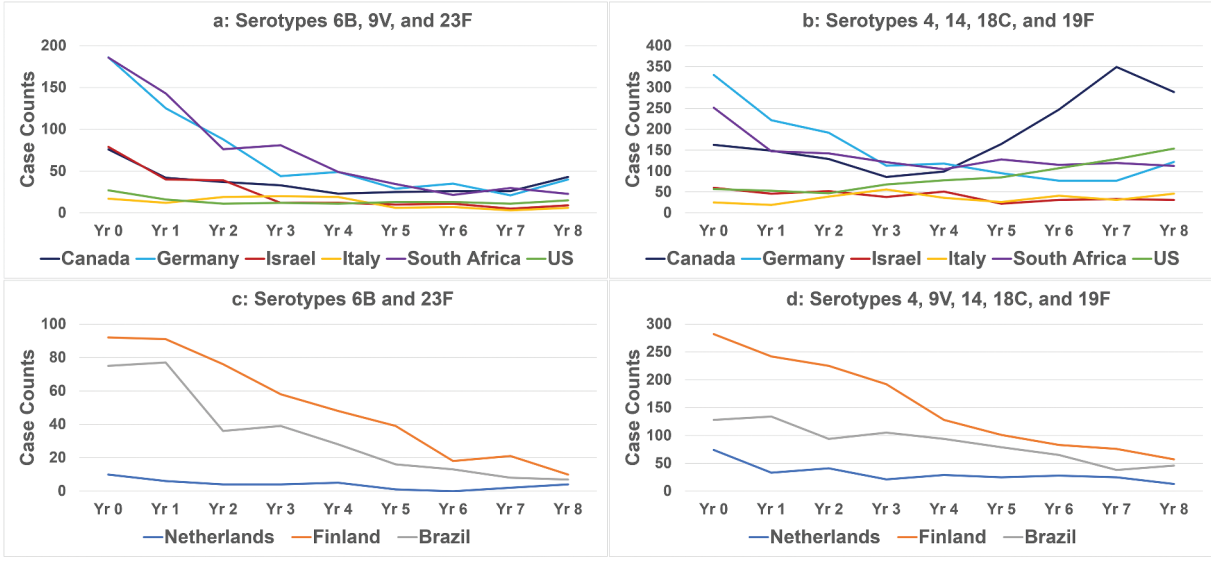

Figure 2. Trends in invasive pneumococcal disease cases for populations ages 5+ years.

US = United States. The figures present the change in cases for serotypes 6B, 9V, and 23F (2a) and serotypes 4, 14, 18C, and 19F (2b) for countries which implemented PCV13; and cases for serotypes 6B and 23F (2c) and serotypes 4, 9V, 14, 18C, and 19F (2d).

in Yr0 to 10 cases in Yr8, while in Brazil, the case count decreased from 75 cases in Yr0 to 7 cases in Yr8. In the Netherlands, disease suppression was maintained following the transition from PCV7 to PCV10, with cases decreasing from 10 cases in Yr0 to 4 cases in Yr8.

Decreases in cases due to the remaining PCV7 serotypes (4, 14, 18C, and 19F) For individuals ages 5+ years (Figure 2b), cases decreased from Yr0 to Yr8 in Germany (from 330 cases to 122 cases), Israel (from 29 cases to 13 cases), and South Africa (from 252 cases to 112 cases). Increases in cases from Yr0 to Yr8 were observed in Canada (163 to 289 cases), Italy (25 to 46 cases), and the US (from 57 to 154 cases). These increases in case counts were primarily due to increases in serotypes 4 (Supplementary Figure S1) and 19F. In PCV10 countries (Figure 2d), cases due to the remaining PCV7 serotypes (4, 9V, 14, 18C, and 19F) decreased from Yr0 to Yr8 in the Netherlands (from 74 cases to 13 cases), Finland (from 282 cases to 57 cases), and Brazil (from 128 cases to 46 cases).

4. Discussion

We estimated the annual population-level impact of PCV10 and PCV13 NIPs on PCV7-type IPD across all ages using national surveillance data of countries with PCV10 or PCV13 in their pediatric NIP. The number of IPD cases of serotypes 6B/9V/23F for PCV13 (serotypes 6B and 23F for PCV10) and PCV7 minus these serotypes for each year following introduction of the higher-valent vaccine were estimated for children and adults in countries with

established NIPs. IPD cases attributed to serotypes 6B, 9V, and 23F decreased or were already low across all countries and age groups following higher valent PCV introduction. The degree of reduction varied across countries, which may have been attributed to the duration and uptake of a prior vaccine (from implementation of PCV7), given certain countries had no prior PCV7 use (Brazil and Finland), PCV7 use but low uptake (Canada, Germany, Italy, Israel, and South Africa), to PCV7 use with high uptake (United States). For the PCV7 minus 6B/9V/23F serotypes, IPD case counts decreased or remained suppressed among children targeted for vaccination. Generally, disease was also reduced in older ages, although variability exists across countries and among those 5+ years of age.

These findings illustrate that missing non-inferiority in the clinical trials of these higher-valent PCVs did not translate to a loss of real-world impact on pneumococcal disease. Across all the countries that implemented PCV13, a decrease in or maintenance of already low case counts was observed for serotypes 6B, 9V, and 23F. Similarly, each country that implemented PCV10 also achieved a substantial reduction or maintained suppression in case counts of 6B and 23F. Direct and indirect effects from PCV13 and PCV10 vaccination were observed with decreases in case counts both in children under 5 years of age and those in older age groups. Decreases in case counts or maintenance of suppression were observed regardless of prior vaccination programs with PCV7. For those countries in which PCV7 was implemented prior to the introduction of the higher-valent vaccine (all six PCV13 countries plus the Netherlands), we observed that the higher valent vaccine maintained suppression of disease due to serotypes 6B/9V/23F. Similarly, in the two countries that did not implement PCV7 (Finland and Brazil), we observed that PCV10 suppressed disease due to 6B and 23F. The impact on cases was also observed regardless of whether the country implemented a 2 + 1 schedule or a 3 + 1 schedule, for PCV7 or PCV13.

Unexplainably, evidence of rebound in disease was observed for serotypes in which PCV10 and PCV13 did meet immunogenicity non-inferiority endpoints. In several countries, serotypes 4 and 19F case counts increased over time in adults following the implementation of the higher valent vaccine. [39] The reasons for this could potentially vary by country. In Canada, surveillance systems and reporting may have improved over time in adults, which may have inflated case counts. Additionally, countries which have difficulties with program implementation will face a reduction in the opportunity for herd effects. This phenomenon was observed in Canada, which has not seen as high an uptake nationwide of PCV as other countries. [40] Furthermore, it is important to see an uptake in the booster dose to maximize herd protection. Finally, an outbreak of serotype 4 was observed within adults experiencing homelessness in Canada, which may be a case of an isolated population not able to receive indirect protection coupled with compromised immune systems. [41] Similarly, serotypes 4 and 19F are reemerging in the US adult population. Among those experiencing homelessness, serotype 4 IPD incidence was 100–300 times higher than those not homeless in the Western US. [42] Further, Native Alaskan adults have seen an 88-fold increase in serotype 4 IPD incidence from 2011 to 2018 vs 2019 to 2020. [43] Serotype 4 outbreaks have also been observed in the Netherlands. [44]

The reemergence of disease due to serotypes 4 and 19F within adult populations is an important consideration with respect to implementing new adult vaccination programs, as those vaccines which do not cover these two serotypes may result in even greater reemergence of disease. While we do observe evidence of indirect protection, disease burden in adults remains for PCV7-type disease even after 7 years of PCV10 or PCV13 pediatric NIP implementation. This illustrates the importance of direct vaccination programs within the adult population. Pediatric PCV programs do provide the benefit of indirect protection, as can be seen within the data presented. However, these data illustrate that pediatric programs alone may be insufficient to eradicate disease in older populations.

One important question is whether the aggregate correlate of protection (0.2 or 0.35 µg/mL for PCV10 and PCV13, respectively) used for licensing of higher valent PCVs adequately predicts a vaccine's impact on serotype-specific IPD, and our study adds to this body of literature. Based on the real-world experiences with PCV13 and PCV10, multiple measures of the immune response from clinical trials should be evaluated for serotypes that miss statistical non-inferiority for one endpoint in the future, using both primary and secondary prespecified immunogenicity criteria for PCV licensure. While this descriptive study does not definitively answer the question of the predictive value of the correlates of protection, it illustrates the possibility that immunogenicity studies do not provide a sufficient prediction of the real-world effectiveness of a vaccine program.

Due to the differences in the populations considered in this study, no comparative inferences should be made regarding the magnitude of the effect of the vaccination program. Instead, this qualitative study focuses on the within-country case count trends rather than any statistical comparison of the disease trends between countries. A statistical analysis to assess the degree of vaccine efficacy would require controlling for many variables, including population size and density, vaccine history and uptake, and demography. Other factors may also affect the case counts within a country. For example, South Africa has a substantial burden of HIV infection [45], and as such their population has an elevated risk of pneumococcal disease. As a result, South Africa frequently had a higher case count than the other studied countries during the time period considered. Because of these country-level differences, we did not attempt to estimate the magnitude of effect or conduct a statistical analysis. Instead, we focus on within-country trends, for which any variation in these uncaptured parameters is less of a concern.

The results of this study may have implications for recently licensed higher valent vaccines and other PCVs in development. A 20-valent PCV (PCV20) completed its immunogenicity trials for 2 + 1 and 3 + 1, and some serotypes missed non-inferiority post-primary series compared to PCV13 in Phase 3 clinical trials. [46,47] Historic data presented in this study demonstrate that missing non-inferiority for the percent of participants with prespecified IgG levels after the primary series might not be cause for concern. Data from our study demonstrate that the original correlate of protection did not necessarily predict real-

world outcomes for PCV10 and PCV13 and similarly may not be predictive of direct and indirect protection for PCV20. However, recently, the European Medical Association (EMA) has made the decision to only license PCV20 in a 3 + 1 schedule, [48] whereas other regulatory bodies, such as in Australia and Argentina, have approved by the 2 + 1 schedule. [49–51] For all current vaccines (PCV7, PCV10, and PCV13), infant responses after 2 doses are significantly lower than after 3 doses, and PCV20's data are encouraging, as both schedules provide boosting of IgG and OPA following the toddler dose for all vaccine serotypes. This is an important finding, given the most important contributor to the overall population impact of an infant vaccine program is the potential to reduce carriage rates of pneumococcal vaccine serotypes in toddlers who are the main responsible for the transmission of pneumococci in the community (i.e. indirect protection). Based on the totality of clinical trial data for PCV20, this vaccine is expected to provide direct and indirect protection against pneumococcal disease caused by all 20 vaccine serotypes when administered in either a 2 + 1 or 3 + 1 dosing schedule. For any new licensed PCV, data on effectiveness/impact are required to confirm the potential benefits in a real-world setting.

This study is subject to a few limitations. First, this study is a descriptive observational study and therefore changes in disease trends (decreases and increases) may not be attributed to PCVs. It can also be difficult to compare case counts across countries as the populations are not equivalent. Population sizes within countries also fluctuate annually, a factor not accounted for in this study. Additionally, our analysis defines the baseline disease burden using a single year of data (the year prior to the introduction of PCV10 or PCV13). As IPD is rare and case counts can fluctuate from year to year, annual impact estimates can be unstable. As such, the exact serotype-specific case count data may not be as relevant as the overall trajectory of the PCV7-type disease. Also, we did not have complete age stratifications for the adult populations in all countries. Case counts for ages 5+ was used for both ages 5–64 and ages 65+ when these age-stratified data were unavailable (e.g. Italy, South Africa), which may not allow us to capture any age-specific changes for the elderly and those in the lower risk age range of 5–64 years for those countries. Additionally, in some countries, the data were not exactly aligned with the data available for other countries. For the US and the Netherlands, we used data from a representative subsample of the national population. For the Netherlands, this resulted in very low case counts, even after pooling the 6B and 23F serotype counts. It is unclear what impact these data limitations have on the findings. Finally, there are several country-specific variables not considered in this analysis. Duration of prior history of PCV7 use before PCV13 implementation; differing methods of IPD surveillance across countries (with case count estimates potentially affected by the surveillance methodology); and variable regional and NIP characteristics may lead to differences in impact of the program. For example, the uptake of the vaccine program, the vaccine dosing schedule (2 + 1 vs 3 + 1), and the availability and uptake of an adult PCV program differ across countries considered in this study. Each of these may affect the impact of the vaccination program over time.

5. Conclusion

Our analysis illustrates that despite failing to meet a prespecified clinical endpoint post-primary series for certain serotypes in immunogenicity trials, both PCV10 and PCV13 protected against cases of IPD for these serotypes in directly vaccinated populations, as well as provided indirect protection across the entire population. This suggests that immunogenicity trial results may not fully predict the real-world impact of PCVs on disease when implemented in a NIP setting. Understanding changes in disease burden due to pediatric vaccination may help predict the potential impact of the implementation of next-generation higher valent PCVs and highlights the need to directly vaccinate against the original PCV7 serotypes.

Declaration of interest

J Perdrizet, K Apodaca, and L Grant are employees of Pfizer Inc. and may own stock or stock options at the time of this study. W Wannaadisai provided paid contract services to Pfizer Inc. at the time of this study. RTI Health Solutions received consulting fees from Pfizer Inc. for the study and manuscript development, which is the employer of M Wilson. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

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Author contribution statement

J Perdrizet and W Wannaadisai contributed to the concept and design of the study, interpretation of the data, and revision of the manuscript. M Wilson contributed to the design of the study, analysis and interpretation of data, and drafting the manuscript. K Apodaca and L Grant contributed to the interpretation of the data and revision of the manuscript. All authors approved the final version to be published and agreed to be accountable for all aspects of the work.

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Data availability statement

All data generated or analyzed during this study are included in this published article/as supplementary information files.

Ethics statement

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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