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ORIGINAL RESEARCH

Clinical and Economic Burden of Pneumococcal Disease Due to Serotypes Contained in Current and Investigational Pneumococcal Conjugate Vaccines in Children Under Five Years of Age

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ABSTRACT

Introduction: The widespread implementation of pneumococcal conjugate vaccines (PCVs) has significantly reduced the burden of pneumococcal disease around the world. Although licensed 10-valent (PCV10) and 13-valent (PCV13) vaccines have considerably reduced mortality and morbidity, a sizeable disease burden attributable to serotypes not contained in these PCVs remains. This study aimed to estimate the annual clinical and economic burden of pneumococcal disease attributable to licensed (PCV10 and PCV13) and investigational PCVs, notably 15-valent (PCV15) and 20-valent (PCV20) vaccines, in 13 countries in children under 5 years of age.

Methods: A decision-analytic model was created to aggregate total cases [inclusive of invasive pneumococcal disease (IPD), pneumonia, and otitis media (OM)], deaths, and direct costs in each country of interest [stratified by PCV10/PCV13 countries, depending on national immunization programs (NIPs)] over 1 year, using up to the three most recent years of available serotype coverage data. Data inputs were sourced from local databases, surveillance reports, and published literature.

Results: In 5 PCV10 NIPs (Austria, Finland, Netherlands, New Zealand, Sweden), most remaining PCV20-type disease was due to PCV13-unique serotypes (30–85%), followed by PCV20-unique (9–50%), PCV15-unique (4–15%), and PCV10-unique (2–14%) serotypes. In 8 PCV13 NIPs (Australia, Canada, France, Germany, Italy, South Korea, Spain, United Kingdom), most remaining PCV20-type disease was caused by PCV20-unique serotypes (16–69%), followed by PCV13-unique (11–54%), PCV15-unique (2–33%), and PCV10-unique serotypes (3–19%). Across all countries, PCV20 serotypes caused 3000 to 345,000 cases of disease and cost between $1.3 and $44.9 million USD annually with variability driven by population size, NIP status, and epidemiologic inputs. In aggregate, PCV20 serotypes caused 1,234,000 cases and $213.5 million in annual

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direct medical costs in children under 5 years of age.
Conclusion: Despite the success of PCV10 and PCV13 in reducing pneumococcal disease, a substantial clinical and economic burden remains due to serotypes contained in investigational vaccines.

Keywords: Invasive pneumococcal disease; Pneumococcal conjugate vaccine; Burden of disease; Vaccine serotypes

Key Summary Points

Why carry out this study?

Currently licensed pneumococcal conjugate vaccines (PCVs) i.e., PCV10 and PCV13 have reduced the burden of pneumococcal disease; however, due to a rise in the prevalence of serotypes not covered by these PCVs, a significant proportion of disease burden remains to be addressed.

This study sought to estimate and compare the clinical and economic burden attributable to the serotypes covered by licensed PCVs, as well as investigational PCVs (PCV15 and PCV20) that are currently in development, in 13 countries with established national immunization programs (NIPs) and robust surveillance data.

What was learned from the study?

Serotypes not targeted by licensed PCVs are a substantial cause of the residual disease burden in all 13 countries; notably the largest proportion of the residual clinical and economic burden is due to PCV20 serotypes.

Investigational PCVs have the potential to reduce the disease burden in these countries by targeting additional serotypes that are not covered by lower-valent PCVs.

INTRODUCTION

Streptococcus pneumoniae (S. pneumoniae), the causative pathogen for pneumococcal disease, is one of the leading contributors of vaccine-preventable morbidity and mortality worldwide [1, 2]. Pneumococcal disease can range from life-threatening invasive pneumococcal disease (IPD), such as meningitis, septicemia, bacteremia, and bacteremic pneumonia (PNE), to mucosal infections, such as otitis media (OM), non-bacteremic PNE, and sinusitis. Notably, children younger than 5 years of age, older adults, and adults with comorbid conditions are most affected by pneumococcal disease [3]. Pneumonia due to *S. pneumoniae* is a significant contributor to childhood morbidity and mortality, and estimates from 2016 indicate that around 45 million episodes of lower respiratory infections and 350,000 deaths are due to pneumococcal PNE in children younger than 5 years of age annually [4].

Pneumococcal disease is caused by 100 different pneumococcal serotypes, but most cases are caused by a subset of pathogenic serotypes [5]. To address the burden of pneumococcal disease in children, pneumococcal conjugate vaccines (PCVs) were developed and originally targeted serotypes most prevalent among IPD (Fig. 1). The 7-valent PCV (PCV7) containing 7 pneumococcal serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) was the first PCV to be approved in 2000 in the United States, and later in Europe in 2001 [6, 7]. In 2009, a 10-valent PCV (PCV10) containing additional serotypes 1, 5, and 7F and a 13-valent PCV (PCV13) containing PCV10 serotypes and additional serotypes 3, 6A, and 19A were introduced, replacing PCV7 in national immunization programs (NIPs) [6, 8]. As of 2020, PCV10 and PCV13 have been introduced in 160 NIPs around the world [9]. Considering the incremental serotype coverage provided by PCV13, over 80% of NIPs currently include PCV13 to provide the broadest protection against pneumococcal disease [9].

Over the last 20 years, use of PCV in pediatric NIPs around the world has demonstrated a significant impact in reducing morbidity and mortality associated with pneumococcal disease

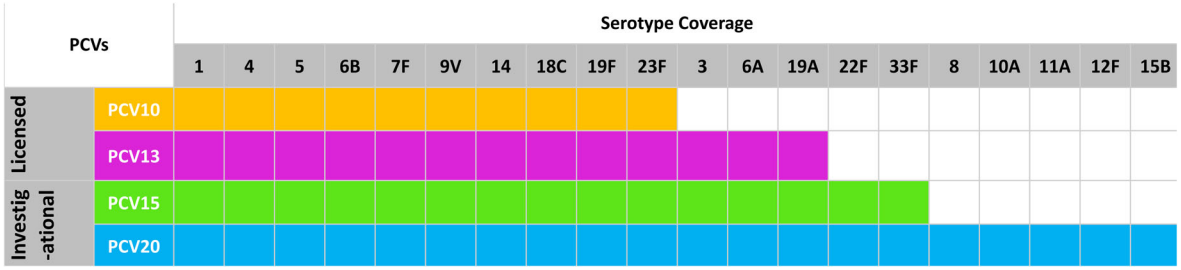

Fig. 1 Serotypes included in current and investigational PCVs. *PCV* pneumococcal conjugate vaccine

caused by vaccine serotypes in children. In the years following the introduction of PCV7, and again after its subsequent replacement by PCV10/PCV13, there have been marked declines in cases of IPD [10–13], OM [14–17], and PNE [18–21] attributable to vaccine serotypes. Global modeling studies provide further evidence of the impact of PCV programs, estimating that 175 million cases of pneumococcal disease and 625,000 deaths have been prevented by PCV13 in children under 5 years of age worldwide between 2010 and 2019 [1]. Apart from protecting young children against pneumococcal disease, routine pediatric immunization has also provided indirect protection to non-vaccinated populations through a reduction in nasopharyngeal carriage of vaccine serotypes, thereby reducing transmission of disease [19, 22, 23]. As more countries increase PCV uptake, PCV vaccination offers the potential to prevent 54.6 million episodes and 399,000 deaths annually in children under 5 years of age due to pneumococcal disease globally [24].

While PCVs have considerably reduced disease burden of vaccine serotypes, there has been a rise in cases caused by non-vaccine serotypes, a phenomenon termed serotype replacement [25]. This replacement occurs because *S. pneumoniae* is a commensal bacterium that resides in the nasopharynx of healthy children and currently available PCVs offer protection against nasopharyngeal carriage of covered pneumococcal serotypes. While overall nasopharyngeal carriage has remained constant, the non-vaccine serotypes that have replaced the vaccine serotypes in circulation are generally less pathogenic, therefore overall rates of IPD remain substantially lower than pre-vaccine levels. However, wide variations in the incidence of these emerging serotypes by geography and age have been observed [26–29]. Countries with sustained use of PCV13 in NIPs, where the incidence of serotypes 3, 6A, and 19A have already been reduced as compared to countries with PCV10 NIPs, have observed an increase in the incidence of multiple non-PCV13 serotypes, including but not limited to serotypes 6C, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 22F, 23B, 24F, 33F, 35B, and 38 [27]. Other global studies have reported on the high disease potential of serotypes not contained in currently licensed PCVs [30–32].

To address the rise in non-vaccine serotypes and increase protection against pneumococcal disease, higher-valent PCVs are in clinical development, with two vaccines currently under regulatory review[1]: a 15-valent PCV (PCV15) that includes the PCV13 serotypes plus 22F and 33F and a 20-valent PCV (PCV20) that includes the PCV15 serotypes and 5 additional serotypes (8, 10A, 11A, 12F, and 15B) (Fig. 1). These new PCV formulations have the potential to address an increasing unmet need by providing additional protection against emerging serotypes not covered by currently licensed PCVs. Notably, the serotypes included in investigational PCVs have a propensity for antimicrobial resistance (11A, 15B, 22F, and 33F), are associated with outbreaks (8 and 12F), are a common cause of meningitis (12F, 22F, and 33F), have a higher case fatality rate (CFR)

[1] The pneumococcal 20-valent conjugate vaccine PREVNAR 20® (Pfizer) and the pneumococcal 15-valent conjugate vaccine VAXNEUVANCE® (Merck) received marketing approval for adults aged 18 years or older in June 2021 and July 2021, respectively [42, 43].

(10A and 11A), and tend to cause more severe disease (8, 10A, 11A, 15B, 22F, and 33F) compared with other serotypes [33–41]. The aim of this study is to estimate and compare the annual clinical and economic burden of pneumococcal disease outcomes including IPD, inpatient PNE, outpatient PNE, and OM due to serotypes attributable to the licensed (PCV10 and PCV13) and investigational PCVs (PCV15 and PCV20) in 13 countries with established NIPs and robust surveillance data. Specifically, this analysis considers Australia, Austria, Canada, Finland, France, Germany, Italy, Netherlands, New Zealand, South Korea, Spain, Sweden, and United Kingdom (UK), in children under 5 years of age.

METHODS

Model Description

A Microsoft Excel-based decision-analytic model was developed to estimate the annual clinical and economic pneumococcal disease burden due to serotypes contained in licensed and investigational PCVs (PCV10, PCV13, PCV15, and PCV20) in children under 5 years of age (Fig. 2). The cohort-based model is based on a cohort of children under 5 years of age and includes age- and country-specific incidence rates of pneumococcal disease outcomes (i.e., IPD, inpatient/outpatient PNE, and OM) which are used to calculate the estimated number of pneumococcal disease cases per year. Disease outcomes are subsequently stratified based on local serotype coverage for each PCV. Thereafter, age- and country-specific associated costs and CFRs are applied to pneumococcal disease outcomes to estimate the direct costs and total deaths associated with each disease outcome by PCV product. Finally, total cases, deaths, and direct costs are aggregated to estimate the annual clinical and economic burden of disease in each country over 1 year. This decision analytic model is informed by previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Inclusion criteria for countries in this study were the presence of well-established national population-based pneumococcal surveillance systems and public data available after the introduction of PCV10/PCV13, including published evidence of non-invasive pneumococcal disease (non-IPD) incidence and disease-related costs. Following a targeted literature review, Australia, Austria, Canada, Finland, France, Germany, Italy, Netherlands, New Zealand, South Korea, Spain, Sweden, and UK were chosen for this analysis (Table 1).

Austria, Finland, and Netherlands exclusively used PCV10 in their NIP at the time serotype coverage was reported, while Australia, France, Spain, and UK exclusively use PCV13 for routine pediatric vaccination. Austria switched its NIP to PCV13 at the beginning of 2020; however, for the purposes of this analysis, it is assumed to use PCV10, given serotype coverage is available from 2017 to 2019 [44]. Spain, Italy, and Canada have regional immunization programs; however, while all of Spain uses PCV13, one region in Italy and Canada uses PCV10 (Piedmont in Italy and Quebec in Canada), with the remaining regions using PCV13. Quebec switched to PCV10 in 2018, so only 6 months of epidemiologic data for Canada represent any PCV10 use. In Germany and South Korea, both PCV13 and PCV10 are reimbursed; acknowledging this, most infants (> 85%) are vaccinated with PCV13 [45, 46]. Therefore, Italy, Canada, Germany, and South Korea are categorized as PCV13 NIPs in our study, given that most infants receive PCV13 in these countries. In Sweden, individual counties could choose either PCV10 or PCV13 until 2019, after which PCV10 was selected at the national level as the only PCV [47]. However, the majority of children in Sweden received PCV10 before 2019; therefore, we have categorized it as a PCV10 NIP [48]. Finally, New Zealand has switched its PCV program several times, switching from PCV7 to PCV10 in 2011, then to PCV13 in 2014, and back to PCV10 in 2017. We categorized New Zealand as a PCV10 country and included only 2018 surveillance data post-PCV10 transition.

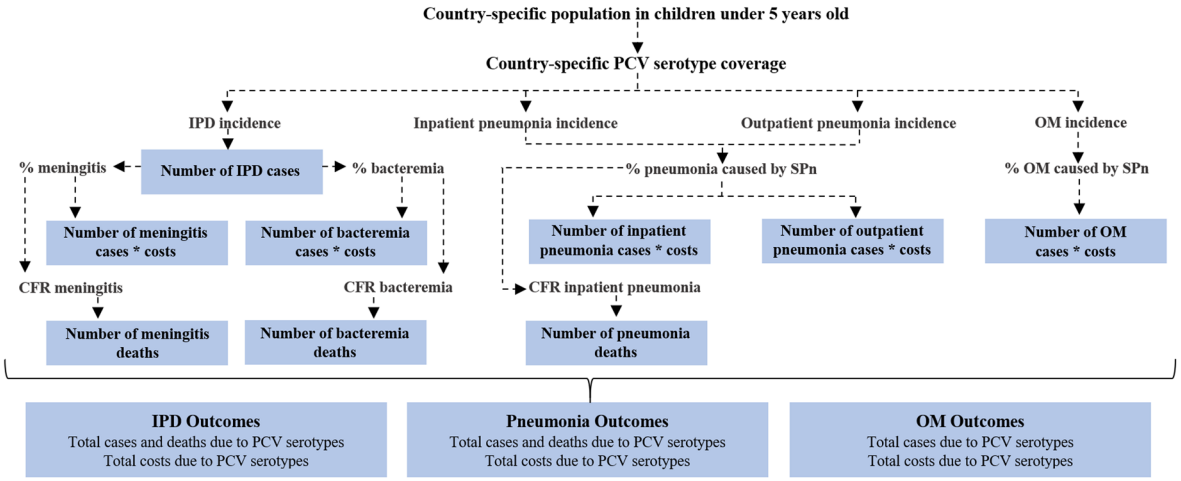

Fig. 2 Derivation of clinical and cost outcomes. *CFR* case fatality rate, *IPD* invasive pneumococcal disease, *OM* otitis media, *PCV* pneumococcal conjugate vaccine, *SPn Streptococcus pneumoniae*

Model Inputs

Input parameters (i.e., population, clinical, and cost data) were derived from published sources available in the public domain or from locally available databases/registries (see Table S1 in the supplementary material for details). The model inputs derived per country for children under 5 years of age included: (1) *Serotype coverage*: the proportion of serotypes in each PCV formulation (PCV10, PCV13, PCV15, and PCV20) responsible for cases of IPD; (2) *IPD incidence*: the total incidence of IPD, and the relative proportion caused by meningitis or bacteremia; (3) *non-IPD (OM/PNE) incidence*: the incidence of all-cause OM, the incidence of all-cause PNE (inpatient and outpatient), and the proportion of all-cause OM/PNE caused by *S. pneumoniae;* (4) *Mortality*: the CFR for meningitis, bacteremia, and inpatient PNE; and (5) *Direct healthcare costs*: the direct healthcare cost per event of meningitis, bacteremia, inpatient PNE, outpatient PNE, and OM.

Serotype Coverage

Serotype coverage for children under 5 years of age was derived from nationally or regionally representative IPD surveillance systems for each country. Using up to the three most recent years of available data, coverage was calculated for PCV10-, PCV13-, PCV15-, and PCV20-unique serotypes. Only 1 year of data was used in New Zealand and Netherlands to account for the only year of data since switching to a PCV10 NIP and the availability of data by individual serotypes, respectively. In South Korea, 4 years of data were used, given that the passive surveillance system reported aggregated data over the entire period. In the base case analysis, we did not include any potentially cross-reactive serotypes (i.e., 6C or 15C); however, this was explored in the sensitivity analysis. These serotype coverage estimates were then applied to IPD incidence to ascertain the nationally representative serotype-specific IPD incidence for each PCV considered in the analysis.

Country-specific serotype coverage for licensed and investigational PCVs is presented in Fig. 3. In Austria, Finland, Netherlands, New Zealand, and Sweden, countries that all used PCV10 in the NIP at the time of data collection, 1–9% of all cases were caused by PCV10-unique serotypes. Among these countries, disease caused by PCV13-unique serotypes (3, 6A, and 19A) accounted for most of the remaining disease, ranging from 15–66%, with an additional 3–8% caused by the PCV15-unique serotypes (22F and 33F), and a further 7–33% caused by the five additional PCV20-unique serotypes (8, 10A, 11A, 12F, and 15B). In countries predominantly using PCV13, i.e., Australia, Canada, France, Germany, Italy, South Korea, Spain, and

Table 1 Overview of pediatric NIPs in selected countries

Country	PCV used during reported surveillance (dosing schedule)	Year of PCV10/13 introduction	Years serotype coverage data reported
PCV10 NIPs			
Austria[a]	PCV10 (2 + 1)	2012	2017–2019
Finland	PCV10 (2 + 1)	2010	2017–2019
Netherlands	PCV10 (2 + 1)	2011	2019
New Zealand[b]	PCV10 (3 + 1)	2011	2018
Sweden[c]	PCV10 (2 + 1) / PCV13 (2 + 1)	2010	2016–2018
PCV13 NIPs			
Australia[d]	PCV13 (3 + 0/2 + 1)	2010	2016–2018
Canada[e]	PCV13 (2 + 1) / PCV10 (2 + 1)	2010	2016–2018
France	PCV13 (2 + 1)	2010	2013, 2015, 2017
Germany[f]	PCV13 (2 + 1) / PCV10 (2 + 1)	2009	July 2015–June 2018
Italy[e]	PCV13 (2 + 1) / PCV10 (2 + 1)	2012	2017–2019
South Korea[g]	PCV13 (3 + 1) / PCV10 (3 + 1)	2014	2014–2018
Spain	PCV13 (2 + 1)	2010	2016–2018
United Kingdom[h]	PCV13 (2 + 1)	2010	July 2016–June 2017

NIP national immunization program, *PCV* pneumococcal conjugate vaccine

[a] At the time of available serotype coverage data, Austria used PCV10 but has since changed to PCV13 as of 2020

[b] New Zealand switched from PCV7 to PCV10 in 2011, then to PCV13 in 2014, and back to PCV10 in 2017, which is why only 2018 data was included

[c] At the time of serotype coverage data availability, Sweden used both PCV10 and PCV13 in different counties, but has exclusively used PCV10 since 2020

[d] Australia used a 3 + 0 schedule and transitioned to a 2 + 1 schedule in 2018

[e] Italy and Canada both have regional PCV10 use in Piedmont and Quebec, respectively

[f] Both PCV10 and PCV13 are used in Germany, with over 90% of infants vaccinated with PCV13. Published data for Germany were available for children < 2 years; this was assumed uniform for all children < 5 years

[g] Both PCV10 and PCV13 are used in South Korea, with over 85% of infants vaccinated with PCV13

[h] Surveillance is specifically from England and Wales, but this analysis extrapolates to the totality of the population under 5 years of age in the UK. The UK has also switched from 2 + 1 to 1 + 1 schedule as of 2020

UK, 2–11% of disease was caused by PCV10-unique serotypes, with an incremental 6–33% of disease caused by PCV13-unique serotypes. Additional PCV15-unique serotypes were responsible for 1–18% of disease in these countries, while the additional PCV20-unique serotypes were responsible for 10–41% more disease over PCV15. Across both PCV10 and PCV13 NIP countries, the cumulative coverage of PCV20 ranged from 46–77% of all remaining pneumococcal disease burden.

Invasive Pneumococcal Disease

The proportion of IPD caused by either pneumococcal meningitis or bacteremia was

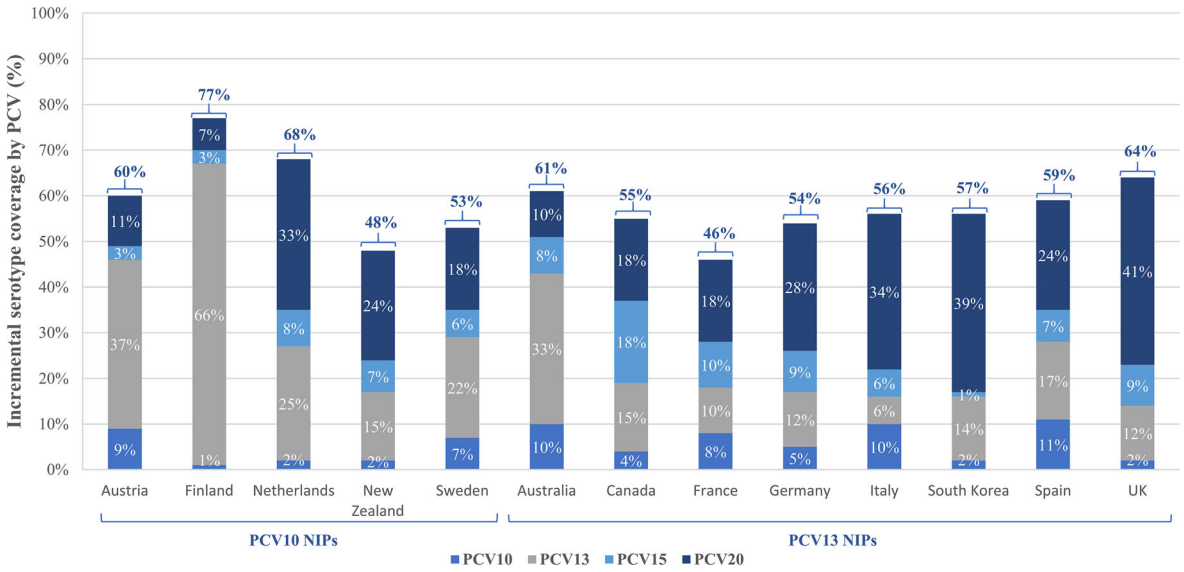

Fig. 3 Incremental serotype coverage by PCV, in children < 5 years in 13 selected countries. *PCV10*-serotypes: 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F; *PCV13*-serotypes: PCV10 serotypes + 3, 6A, and 19A; *PCV15*-serotypes: PCV13 serotypes + 22F and 33F; *PCV20*-serotypes: PCV15 serotypes + 8, 10A, 11A, 12F, 15B. *NIP* national immunization program, *PCV* pneumococcal conjugate vaccine, *UK* United Kingdom

calculated to capture differences in CFRs and associated costs per disease event. Due to the lack of available data on the proportion of IPD cases resulting in meningitis or bacteremia in four countries (UK, Finland, Austria, and Netherlands), it was assumed that 76–90% of IPD cases were pneumococcal bacteremia, and the remaining 10–24% were pneumococcal meningitis, as per previously published work [49, 50]. Sequelae resulting from meningitis and bacteremia were not included in our analysis.

Non-Invasive Pneumococcal Disease

Non-IPD in the model included inpatient PNE, outpatient PNE, and OM. Data on the pneumococcal etiology of non-IPD in children are sparse and inconsistent to fully ascertain vaccine-preventable disease burden. Consequently, we leveraged available data on all-cause PNE and OM for each country, identified through a targeted literature review, and assumed that a proportion of all-cause disease was caused by *S. pneumoniae*. This proportion ranged from 20–53% for inpatient and outpatient PNE and 20–38% for OM among included countries. For countries where no data were available, we conservatively assumed that 20% of both all-cause PNE and OM disease were attributable to *S. pneumoniae* [46, 51, 52]. Furthermore, given that the etiology is not known, the serotypes causing non-IPD are also uncertain. Therefore, we assumed that the serotype distribution causing non-IPD disease was equivalent to IPD, consistent with previous economic burden and cost-effectiveness evaluations [46, 52, 53].

Case Fatality Rates

Bacteremia, meningitis, and inpatient PNE carried a risk of death and their respective country-specific CFRs were taken from published literature for children under 5 years of age. Outpatient PNE and OM were assumed to have no risk of death.

Economic Inputs

The study took a healthcare payer perspective and only considered the direct medical acute healthcare costs associated with each respective health state as reported in each country (see Table S1 in the supplementary material for details). We therefore did not include any costs

of productivity loss due to caregiver time or missed work due to illness. We also did not include long-term costs associated with any potential sequelae of disease following acute conditions such as meningitis, as these were considered rare, and data were inconsistently reported across countries. All local costs were inflated to 2020 values in United States dollars (USD) based on local consumer price index (CPI) values.

Analysis

Leveraging country-level population data of children under 5 years of age, IPD serotype coverage proportions were extrapolated to calculate the annual number of cases of IPD (bacteremia and meningitis), inpatient and outpatient PNE, and OM, as well as the annual number of deaths and associated costs attributable to each disease outcome. From this extrapolation, the cumulative number of cases, deaths, and direct costs associated with serotypes in each PCV formulation were estimated. The resulting annual vaccine-preventable clinical and economic burden in children under 5 years of age were reported for each PCV by country. Absolute serotype coverage and burden by PCV serotype group are presented in tables, while incremental differences are discussed in the text.

Sensitivity analyses were also undertaken to evaluate the impact of cross-reactive serotypes 6C for PCV13, PCV15, and PCV20 and 15C for PCV20 on the potential preventable disease burden and associated costs (see Tables S2 and S3 in the supplementary material for details). This analysis was conducted because studies have shown that PCV13 may elicit a cross-functional opsonophagocytic killing response between serotype 6A, contained in PCV13, and serotype 6C [54]. This has been substantiated with observed reductions in IPD caused by serotype 6C in countries using PCV13. Similarly, it is hypothesized that serotype 15B antigen may be cross-reactive with serotype 15C due to a high degree of genetic homology [55]. Furthermore, in some countries, serotypes 15B and 15C are not differentiated in the laboratory and are reported together as 15B/C. For countries reporting serotype data in this manner (i.e., France, Italy, and UK), the percentage of IPD due to 15B/C was consequently excluded in PCV20 base case coverage estimates but was included in sensitivity analyses. We did not include a sensitivity analysis where PCV10 provides cross-protection for serotype 19A, despite PCV10 showing some early cross-reactivity between serotypes 19F and 19A [56]. This hypothesized cross-protection was excluded because countries using PCV10 as part of their NIP have observed a steady rise in cases due to serotype 19A [56, 57].

RESULTS

Clinical Burden

Annual pneumococcal disease morbidity and mortality attributable to PCV10, PCV13, PCV15, and PCV20 serotypes were evaluated across the included countries in children under 5 years of age (Table 2). In addition, the estimated incremental proportion of disease caused by PCV serotypes, excluding non-PCV20 serotypes, is captured in Fig. 4.

PCV10 NIP Countries (Austria, Finland, Netherlands, New Zealand, and Sweden)

In PCV10 NIP countries, the disease burden due to serotypes covered by PCV10 was 2–14% (398–4170 cases annually) of the remaining PCV20-type disease. In Austria and Finland, an additional 62–85% of remaining PCV20-type disease (17,957–21,976 cases annually) was due to PCV13-unique serotypes; in Netherlands, New Zealand, and Sweden, PCV13-unique serotypes accounted for a comparatively lower proportion of residual disease, i.e., 30–41% (1303–5509 cases annually). An additional 4–5% (1162–1374 cases annually) and 9–19% (2324–5544 cases annually) vaccine-preventable cases in Austria and Finland were attributable to PCV15-unique serotypes and PCV20-unique serotypes, respectively. In contrast, the proportion of remaining PCV20-type disease due to PCV15-unique and PCV20-unique serotypes was higher in Netherlands,

Table 2 Annual clinical burden attributable to PCV serotypes, in children < 5 years in 13 selected countries

	PCV10 NIPs					PCV13 NIPs							
	Austria	**Finland**	**Netherlands**	**New Zealand**	**Sweden**	**Australia**	**Canada**	**France**	**Germany**	**Italy**	**South Korea**	**Spain**	**UK**
Population < 5 years old	435,133	255,924	861,472	305,930	595,076	1,572,293	1,921,944	3,739,757	3,926,397	2,572,948	1,909,183	1,967,261	3,957,956
IPD cases													
PCV10-serotypes	2	0	1	1	3	31	10	29	15	8	0	73	7
PCV13-serotypes	9	16	19	8	11	135	46	67	48	13	3	185	48
PCV15-serotypes	10	17	25	11	14	159	89	103	73	17	3	229	80
PCV20-serotypes	12	19	48	22	21	191	131	172	154	43	11	387	226
PNE cases													
PCV10-serotypes	228	5	72	27	178	478	393	511	3348	1716	41	1601	121
PCV13-serotypes	1212	261	975	186	731	2084	1858	1157	10,818	2776	305	4046	870
PCV15-serotypes	1287	275	1264	266	887	2467	3610	1787	16,420	3820	325	5019	1434
PCV20-serotypes	1591	302	2456	532	1343	2953	5317	2979	34,451	9474	1058	8479	4049
OM cases													
PCV10-serotypes	3940	393	367	412	240	7643	8188	27,488	30,191	10,130	8133	28,908	984
PCV13-serotypes	20,906	22,097	4956	2887	982	33,350	38,736	62,307	97,540	16,387	60,996	73,044	7093
PCV15-serotypes	22,204	23,244	6424	4125	1193	39,464	75,268	96,209	148,052	22,545	65,063	90,595	11,700
PCV20-serotypes	27,442	25,539	12,481	8250	1805	47,246	110,854	160,349	310,619	55,915	211,454	153,056	33,030
Total cases													
PCV10-serotypes	4170	398	441	440	421	8151	8591	28,028	33,554	11,854	8174	30,582	1111
PCV13-serotypes	22,127	22,374	5950	3082	1724	35,569	40,640	63,531	108,407	19,176	61,305	77,275	8011
PCV15-serotypes	23,501	23,536	7713	4402	2094	42,091	78,967	98,100	164,546	26,382	65,392	95,842	13,215
PCV20-serotypes	29,045	25,860	14,985	8805	3169	50,390	116,303	163,499	345,223	65,432	212,523	161,921	37,305
Total deaths													
PCV10-serotypes	1	0	0	0	0	2	1	1	5	1	0	5	1

Table 2 continued

	PCV10 NIPs					PCV13 NIPs						
	Austria	Finland	Netherlands	New Zealand	Sweden	Australia	Canada	France	Germany	Italy	South Korea	Spain	UK
PCV13-serotypes	3	2	3	1	1	8	4	2	16	2	1	13	6
PCV15-serotypes	4	2	4	1	1	10	8	3	24	3	1	16	11
PCV20-serotypes	4	2	7	2	2	12	12	5	51	6	2	28	30

PCV10-serotypes: 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F; PCV13-serotypes: PCV10 serotypes + 3, 6A, and 19A; PCV15-serotypes: PCV13 serotypes + 22F and 33F; PCV20-serotypes: PCV15 serotypes + 8, 10A, 11A, 12F, 15B

IPD invasive pneumococcal disease, *NIP* national immunization program, *OM* otitis media, *PCV* pneumococcal conjugate vaccine, *PNE* pneumonia, *UK* United Kingdom

New Zealand, and Sweden, estimated to be 12–15% (370–1763 cases annually) and 34–50% (1075–7272 cases annually), respectively. Similar trends were modeled in the 5 countries for all outcomes (IPD cases, PNE cases, OM cases, and total deaths).

PCV13 NIP Countries (Australia, Canada, France, Germany, Italy, South Korea, Spain, and UK)

In the eight countries that predominantly use PCV13 as part of their NIP, the remaining PCV20-type disease burden due to PCV10-unique serotypes ranged from 3–19% (1111–33,554 cases annually). An additional 11–29% of vaccine-preventable cases (6900–74,853 cases annually) were due to the PCV13-unique serotypes; Australia had a relatively higher distribution at 54% (27,418 cases annually). An additional 2–33% of vaccine-preventable cases (4087–56,139 cases annually) were attributable to the PCV15-unique serotypes, whereas the most remaining cases i.e., 16–69% (8299–180,677 cases annually) were due to the additional PCV20-unique serotypes. Similar trends were modeled in the 8 countries for all outcomes (IPD cases, PNE cases, OM cases, and total deaths).

Economic Burden

Across all countries, similar trends were observed in the proportion of annual economic burden attributable to the incremental PCV serotypes as compared to the presented clinical burden. The remaining direct economic burden due to PCV10-unique serotypes ranged from \$0.06–6.74 million, with an additional economic burden of \$0.40–10.29 million due to PCV13-unique serotypes, and \$0.18–7.30 million due to PCV15-unique serotypes. The PCV20-unique serotypes contributed to a considerably higher proportion of annual economic burden ranging from \$0.37–23.48 million in annual health system costs (Table 3). The annual economic burden due to PCV10-, PCV13-, PCV15-, and PCV20-unique serotypes across all 13 markets was \$25.39 million, \$62.79 million, \$30.18 million, and \$95.14 million,

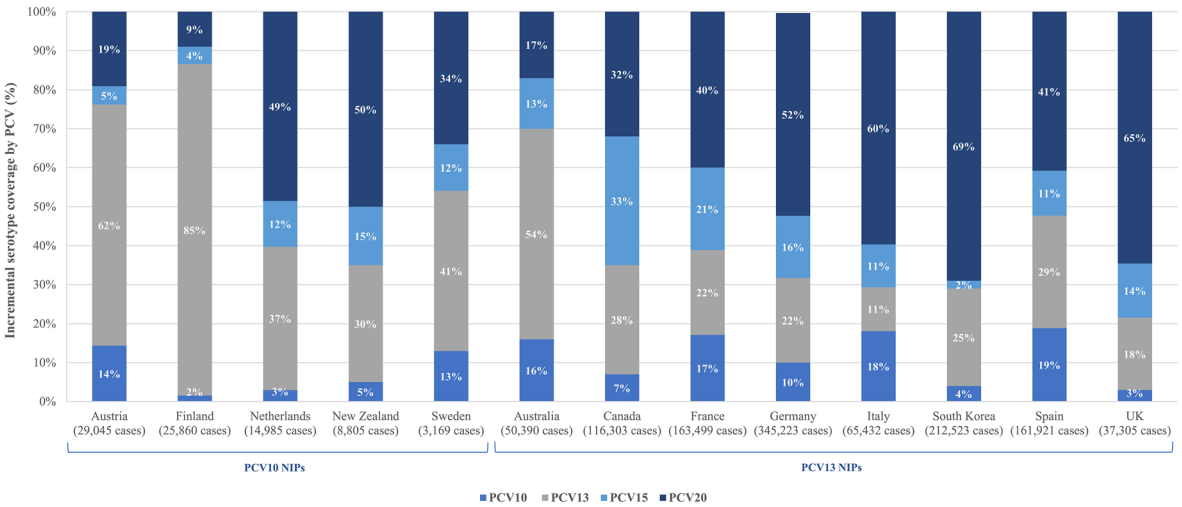

Fig. 4 Proportion of PCV20-type disease burden covered by PCV10, PCV13, PCV15, and PCV20 in children < 5 years in 13 selected countries. Figure represents the relative PCV serotype coverage (%) of total pneumococcal disease cases (caused by PCV10, PCV13, PCV15, PCV20 serotypes) by country, exclusive of non-PCV20 type disease. *NIP* national immunization program, *PCV* pneumococcal conjugate vaccine, *UK* United Kingdom

respectively. Across countries and outcomes (i.e., IPD cases, PNE cases, and OM cases), the highest annual economic burden was mostly reported for OM cases due to the high prevalence of OM as compared to other pneumococcal disease outcomes.

Sensitivity Analysis

A sensitivity analysis was performed to assess the impact of including cross-reactive serotypes 6C with PCV13, PCV15, and PCV20, as well as 15C with PCV20. The analysis was conducted for Australia, Austria, Canada, Finland, France, Italy, Netherlands, New Zealand, South Korea, Spain, Sweden, and UK, which reported IPD cases caused by either serotypes 6C or 15C (see Tables S2 and S3 in the supplementary material for details). Among these countries, serotype coverage of 6C and 15C ranged from 0.3% to 8.5% and from 0% to 9.5%, respectively.

In Austria and Finland, countries with PCV10 NIPs, the remaining PCV20-type disease burden (inclusive of cross-reactive serotypes) due to PCV13-, PCV15-, and PCV20-unique serotypes was 63–86% (22,078–23,536 cases annually), 4% (1162–1374 cases annually), and 8–22% (2324–7605 cases annually), respectively. In the other PCV10 markets, i.e., Netherlands, New Zealand, and Sweden, the remaining PCV20-type disease burden differed from Austria and Finland, with disease cases due to PCV13-, PCV15-, and PCV20-unique serotypes estimated to be 33–47% (1814–6390 cases annually), 10–14% (369–1763 cases annually), and 33–48% (1263–7272 cases annually), respectively. Compared to the base case, the inclusion of 6C and 15C in PCV13 serotype coverage increased the number of cases caused by PCV13-unique serotypes by 7–39% in the five PCV10 markets, while 17% and 37% more cases were caused by PCV20-unique serotypes in Sweden and Austria, respectively.

In the 7 PCV13 NIPs (Australia, Canada, France, Italy, South Korea, Spain, and UK), the remaining PCV20-type disease burden (inclusive of cross-reactive serotypes) attributable to PCV13-unique serotypes was 11–29% (7777–57,218 cases annually); it was relatively higher in Australia at 52% (28,456 cases annually). An incremental 2–28% vaccine-preventable cases (4087–38,327 cases annually) were due to PCV15-unique serotypes, and most of the remaining cases, i.e., 21–71% (11,412–171,652 cases annually) were

Table 3 Annual economic burden of disease attributable to PCV serotypes, in children < 5 years in 13 selected countries (reported in millions of $USD)

	PCV10 NIPs					PCV13 NIPs							
	Austria	**Finland**	**Netherlands**	**New Zealand**	**Sweden**	**Australia**	**Canada**	**France**	**Germany**	**Italy**	**South Korea**	**Spain**	**UK**
Population < 5 years old	435,133	255,924	861,472	305,930	595,076	1,572,293	1,921,944	3,739,757	3,926,397	2,572,948	1,909,183	1,967,261	3,957,956
Total costs ($M)													
PCV10-serotypes	1.298	0.063	0.350	0.066	2.600	1.467	1.583	1.739	4.361	4.313	0.593	6.742	0.213
PCV13-serotypes	6.885	3.536	4.724	0.464	10.659	6.400	7.489	3.941	14.089	6.977	4.448	17.035	1.533
PCV15-serotypes	7.313	3.719	6.124	0.663	12.944	7.573	14.552	6.085	21.384	9.598	4.745	21.129	2.528
PCV20-serotypes	9.038	4.086	11.899	1.325	19.588	9.067	21.432	10.141	44.865	23.805	15.420	35.696	7.138
IPD costs ($M)													
PCV10-serotypes	0.030	0.002	0.022	0.006	0.034	0.284	0.128	0.161	0.172	0.037	0.002	0.315	0.022
PCV13-serotypes	0.158	0.132	0.297	0.039	0.140	1.240	0.606	0.365	0.555	0.060	0.018	0.797	0.157
PCV15-serotypes	0.168	0.139	0.385	0.055	0.170	1.467	1.177	0.563	0.842	0.083	0.020	0.988	0.260
PCV20-serotypes	0.207	0.152	0.748	0.110	0.257	1.757	1.733	0.938	1.766	0.206	0.063	1.669	0.733
PNE costs ($M)													
PCV10-serotypes	0.876	0.010	0.100	0.042	0.423	0.813	0.452	0.274	2.534	3.431	0.092	1.894	0.125
PCV13-serotypes	4.648	0.569	1.352	0.293	1.735	3.549	2.138	0.622	8.187	5.551	0.691	4.786	0.903
PCV15-serotypes	4.937	0.599	1.753	0.419	2.107	4.200	4.154	0.961	12.426	7.636	0.737	5.936	1.489
PCV20-serotypes	6.101	0.658	3.405	0.837	3.188	5.028	6.118	1.601	26.071	18.940	2.396	10.029	4.203
OM costs ($M)													
PCV10-serotypes	0.392	0.050	0.228	0.019	2.143	0.369	1.003	1.303	1.655	0.844	0.499	4.532	0.066
PCV13-serotypes	2.079	2.835	3.705	0.132	8.784	1.611	4.746	2.954	5.347	1.366	3.739	11.452	0.473
PCV15-serotypes	2.208	2.982	3.987	0.189	10.667	1.906	9.221	4.561	8.116	1.879	3.988	14.204	0.780
PCV20-serotypes	2.729	3.726	7.745	0.378	16.143	2.282	13.581	7.602	17.029	4.659	12.961	23.998	2.201

PCV10-serotypes: 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F; PCV13-serotypes: PCV10 serotypes + 3, 6A, and 19A; PCV15-serotypes: PCV13 serotypes + 22F and 33F; PCV20-serotypes: PCV15 serotypes + 8, 10A, 11A, 12F, 15B. The data for economic burden are inclusive of direct healthcare costs only

$M Million USD, *IPD* invasive pneumococcal disease, *NIP* national immunization program, *OM* otitis media, *PCV* pneumococcal conjugate vaccine, *PNE* pneumonia, *UK* United Kingdom

attributable to PCV20-unique serotypes. Across the PCV13 NIP countries, 3–8% (up to 13% in UK) additional cases were caused by PCV13-unique serotypes and 11–38% (up to 49–50% in France and Canada) additional cases were caused by PCV20-unique serotypes with the inclusion of 6C and 15C as compared to the base case.

DISCUSSION

This study presents an analysis of the potential vaccine-preventable pneumococcal clinical and economic disease burden due to serotypes contained in currently licensed and investigational PCVs among children under 5 years of age in countries with PCV10 or PCV13 NIPs. To our knowledge, this is the first multi-country assessment of the vaccine-preventable disease burden of investigational vaccines, as measured through avertable disease cases and deaths and direct health system costs. The results of this analysis demonstrate that there is a substantial unmet need due to serotypes not covered within currently licensed PCVs among countries considered in this study. Notably, between 46% and 77% of remaining pneumococcal disease is due to PCV20 serotypes among the 13 countries included in this analysis. This corresponds to approximately 1.23 million cases, 160 deaths, and $214 million in direct medical costs annually across included countries. These findings align with the reported impact of non-PCV13 serotypes on clinical and economic burden in recent studies; several publications have discussed the remaining disease burden of IPD [58, 59] and OM [60, 61] driven by non-PCV13 serotypes in children under 5 years of age. Extrapolating our findings of clinical and economic disease burden to a global scale, the need for broader PCV serotype coverage is evident.

Of note, the heterogeneity between serotype distributions across countries observed in our study depended primarily on whether PCV10 or PCV13 was used in the NIP. In countries with PCV10 NIPs (i.e., Austria, Finland, Netherlands, New Zealand, and Sweden), PCV10 serotypes contributed to only 2–14% of the remaining PCV20-type disease burden (excluding non-PCV20 serotypes). Most of the remaining PCV20-type disease (30–41% in Netherlands, New Zealand, and Sweden and 62–85% in Austria and Finland) is attributable to PCV13-unique serotypes, predominantly caused by serotypes 3 and 19A, which are contained in PCV13 but are left uncovered by PCV10. In countries using PCV10, serotype 19A has been observed to increase in both the proportion of disease and in the absolute number of cases [56]. For this reason, disease caused by PCV15- and PCV20-unique serotypes make up a smaller proportion of remaining disease in these countries, corresponding to an additional 4–15% and 9–50% of remaining PCV20-type disease, respectively. Both Sweden and New Zealand had lower proportions of PCV13-unique serotypes compared to the other PCV10 NIPs, potentially due to partial protection of PCV13 from its use in several counties in Sweden, and residual impact of the previous PCV13 NIP implemented in New Zealand from 2014 to 2017.

In countries using PCV13 as part of their current NIP at the time of data availability (i.e., Australia, Canada, France, Germany, Italy, South Korea, Spain, and UK), the remaining burden of PCV15- and PCV20-unique serotypes was higher than in countries using PCV10. In these countries with PCV13 NIPs, a smaller proportion of disease attributable to serotypes contained in currently licensed PCVs was identified, with a substantially greater proportion of disease preventable by investigational PCVs; notably, 2–33% of PCV20-type disease burden is due to PCV15-unique serotypes and 16–69% is due to PCV20-unique serotypes. Both investigational PCVs will provide substantially more protection than current PCVs, with PCV20 addressing a markedly greater disease burden compared to PCV13. Australia had the highest remaining burden of PCV13 serotypes among PCV13 NIPs, which may be due to the prior use of the $3 + 0$ schedule compared to other countries which utilize a booster dose in either a $2 + 1$ or $3 + 1$ schedule. As of July 2018, Australia has made the decision to move to a $2 + 1$ schedule, thus serotype distributions may change in future years [52].

This juxtaposition between the burden of disease in PCV13 and PCV10 NIPs is important for several reasons. First, countries that introduce a higher-valent PCV observe an analogous increase in the proportion of disease due to non-vaccine serotypes. In countries with PCV10 NIPs, this increase has largely been due to serotype 19A, given its high invasiveness and propensity for carriage, transmission, and antimicrobial resistance [56]. Meanwhile, in countries using PCV13, disease attributable to the incremental serotypes above those covered by PCV10 (i.e., PCV13-unique serotypes) has largely been reduced, and consequently the largest share of residual disease is due to non-PCV13 serotypes. Therefore, unlike PCV10 NIP countries, PCV13 NIP countries experience greater variability in the disease-causing serotypes. Importantly, while the serotype distribution has shifted, the overall incidence of disease has consistently declined over time with the introduction of higher-valent PCVs regardless of serotype replacement. In the UK, for example, incidence of IPD pre-PCV13 NIP (2008–2010) was 21.6 per 100,000 in children under 2 years of age, but fell to 13.9 per 100,000 in 2016/2017 despite the increase in non-PCV13 serotype disease (7.7 per 100,000 in 2008–2010 vs. 12.3 per 100,000 in 2016/2017) [11]. This serotype replacement phenomenon is likely due to an "unmasking" of non-PCV13 serotypes in carriage after widespread introduction of a PCV into pediatric NIPs, as less invasive circulating serotypes have the opportunity to cause disease, albeit at lower levels than pre-PCV13 [27].

Second, the burden of disease as estimated across the included countries in this analysis not only varies due to the choice of PCV in the NIP, but also by the population's PCV uptake, the duration of PCV use, dosing schedules, and host, pathogen, and environmental epidemiologic variability. Data availability also varies by country, with different years of data being used as model inputs that could impact interpretation and comparability of disease burden estimates across countries. Consequently, consideration of each of these factors is important for interpretation of PCV serotype coverage and disease burden estimates; thus, results should be interpreted individually for each country. In the subset of countries selected, most countries reported data at least 5 years after PCV NIP introduction, which typically corresponds to high population PCV uptake, and have utilized a $2+1$ dosing schedule. Therefore, aside from choice of PCV in the NIP, differences in PCV serotype coverage and disease burden estimates can also be explained by special NIP characteristics, such as differences in regional PCV NIPs or switching from PCV13 to PCV10 and vice versa. Specifically, each country has implemented the vaccine in different manners and at various times across the last decade. In Spain, Italy, and Canada, there is a national recommendation for PCV in children, but implementation is on a regional basis as compared to national implementation, and in Spain a PCV NIP was not introduced until 2015/2016 with low PCV13 uptake until recent years [62]. Additionally, in some countries where multiple vaccines are used in clinical practice (i.e., Canada, Germany, Italy, South Korea, and Sweden), there may be suboptimal overall protection of all vaccine serotypes at a national level.

Two recent studies by Hu et al. quantified the additional economic burden of PCV15 serotypes in the United States [63] and Europe [64] and found directionally similar results to our study; however, they did not include the burden of the five additional serotypes contained in PCV20. By omitting the incremental burden of PCV20-unique serotypes from their calculations, Hu et al. overestimates the burden of PCV15-unique serotypes and consequently misrepresents the vaccine-type burden of pneumococcal disease by only using PCV15-type disease as a denominator. These studies also considered pre-PCV incidence of both PCV7 and PCV13-unique serotypes, while we only considered the most recent serotype coverage and burden of disease to characterize the remaining burden of vaccine-preventable pneumococcal disease rather than historical estimates. Although it is beneficial to show the overall value of a PCV program, this methodology does not reflect the current burden of disease which is perturbed by decades of PCV use. Estimating the current pneumococcal

disease burden is important when policymakers must characterize which vaccines will provide robust serotype coverage and decrease the disease burden in their country, given that serotype epidemiology has changed over time and current disease rates are not analogous to pre-PCV incidence and serotype distributions. However, it remains essential that investigational higher-valent vaccines continue to protect against serotypes contained in currently licensed vaccines and avoid removing vaccine pressure, given that uncovered serotypes can rebound and cause significant disease. Such resurgence was observed in Belgium following the switch from PCV13 to PCV10 in their NIP, which resulted in a significant increase of serotype 19A disease [65–67].

Despite the significant disease burden estimated in this study, there are several limitations in this analysis that may contribute to an underestimation of the total vaccine-preventable pneumococcal disease. First, not all IPD cases are laboratory-confirmed (because a blood culture may not be sought or the patient may have already been treated with antibiotics), serotyped (because it may not be standard practice), or required to be reported to national surveillance, contributing to the likely underestimation of IPD burden. Additionally, there are variations in pneumococcal IPD serotype distributions across 0- to 5-year-olds; however, we present this evidence as a monolith due to inconsistently reported age strata across markets. Second, although real-world effectiveness studies have determined that PCV use has a larger impact on non-specific, all-cause PNE [18, 21, 68] and OM [14, 15, 17] incidence, results conservatively estimated the pneumococcal-specific non-IPD burden. Moreover, the proportion of all-cause non-IPD due to pneumococcus is consistently underreported because of the lack of a robust diagnostic tool to identify the causative disease pathogen in children with PNE or OM [69, 70]. Many of the countries in our analysis conservatively assumed only 20% of PNE and OM were attributable to *S. pneumoniae*, despite observed reductions in OM and PNE in children as high as 41% [14] and 47% [18] after PCV13 introduction, respectively. This suggests that such a narrow definition of disease burden could be underestimating the potential impact of higher-valent PCVs in the future. Third, this study did not include vaccine-preventable disease burden across all age groups resulting from the extended benefits of infant vaccination among unvaccinated individuals. By providing direct protection to children under 5 years of age against serotypes contained in the vaccine, transmission of disease is disrupted through the reduction of nasopharyngeal carriage, and older populations also observe reduced pneumococcal disease incidence [11, 71, 72]. Therefore, the total vaccine-preventable disease burden due to infant vaccination could be significantly broader than the scope of this assessment. Fourth, this study only considered direct healthcare costs per disease event in calculating the economic burden attributable to incremental PCV serotypes. However, many other costs are attributable to these outcomes, including long-term sequalae costs, as well as indirect costs to society incurred from additional pneumococcal disease cases, such as the hours of lost productivity to patients, parents, and/or their caregivers, which when considered in the analysis would substantially increase the incremental economic burden averted by higher-valent PCVs.

Finally, an important limitation of this study is that the epidemiologic inputs included in the model were derived prior to the coronavirus disease 2019 (COVID-19) pandemic. Government lockdowns and the implementation of social distancing have been observed to drastically decrease the burden of respiratory illnesses along with pneumococcal disease. For example, in England, IPD incidence in the 2019/2020 epidemiologic year was 30% lower compared to 2018/2019 across all ages, with significant reductions during the February to June 2020 lockdown period [73]. Further years of surveillance data will be needed to understand the full impact of government lockdown measures on the circulation of pneumococcal disease, both in terms of the incidence of overall disease, as well as potential changes in underlying serotype epidemiology. However, several models have indicated that, with relaxed social distancing and consequent disease circulation, the incidence of pneumococcal disease may return to

pre-COVID levels by 2023–2024, suggesting that our results are indicative of the burden of disease at the onset of expected higher-valent PCV implementation [74, 75].

CONCLUSION

The clinical and economic burden of pneumococcal disease is largely driven by serotypes not covered by the PCV currently included in a country's NIP. Countries with PCV10 NIPs have a higher proportion of current vaccine-preventable disease burden than PCV13 countries, with disease primarily caused by serotypes contained in PCV13. Residual disease in countries with PCV13 NIPs is primarily attributable to non-PCV13 serotypes. Investigational PCVs with broader serotype coverage could reduce the clinical and economic burden of pneumococcal disease through breadth of coverage and by targeting serotypes that cause severe clinical outcomes. The incremental PCV20 serotypes contribute to a substantial proportion of annual pneumococcal disease cases, deaths, and direct health system costs that would not be prevented by current or other investigational lower-valent PCVs.

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