Modeling Possible Inclusion of Pneumococcal Conjugate Vaccine into the National Immunization Program for Infants in India

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ABSTRACT

Background: India is home to up to 28 million infants born annually, and yet to a large extent these children do not benefit from the protection provided by a pneumococcal conjugate vaccine (PCV) immunization program. The Government of India, with support from Gavi, The Vaccine Alliance (in short, Gavi), has committed to a pilot implementation of PCV. There are few public health impact evaluations available for India, and equally limited epidemiologic data.

Objectives: To estimate the potential impact of an infant pneumococcal vaccination program in India. Methods: Using a well-established pneumococcal disease impact model parameterized with local data to the extent possible, we calculated the potential impact of introducing an infant PCV program in India. The model considered direct vaccine protection by PCV10 or PCV13, focusing on children younger than 5 years, while varying vaccine uptake according to the implementation method (i.e., state-level programs [Gavi funding] or a government-supported national immunization program [NIP]).

Results: With state-level PCV13 programs comprising 25% uptake across the country, approximately 1.9 million cases of pneumococcal disease and approximately 77,000 deaths could be prevented annually. An NIP with PCV13 could prevent approximately 7.6 million cases of pneumococcal disease and approximately 0.3 million pneumococcal deaths annually, compared with no vaccination, considering 100% vaccine uptake. These results are likely to have underestimated the additional potential benefits of herd effects in unvaccinated children and adults. Conclusions: Incorporation of PCV into an Indian vaccination program for infants is predicted to have a substantially positive health impact. Gavi funding of state-level programs is an important step toward achieving the full benefits of an NIP in India.

Keywords: India, national immunization program, pneumococcal conjugate vaccine, pneumococcal diseases.

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Introduction

Pneumococcal disease, although vaccine-preventable worldwide, continues to be a major cause of morbidity and mortality [1], and can result in multiple outcomes ranging from self-limiting illness, with full recovery, to sequelae or death. It can present as noninvasive pneumococcal disease (e.g., nonbacteremic pneumonia), acute otitis media [AOM], sinusitis, and bronchitis) or invasive pneumococcal disease (IPD) (e.g., meningitis, bacteremia, pneumonia, and sepsis) [2].

In 2010, up to 1.9 million children worldwide were estimated to die from pneumococcal diseases each year, mostly in low- and middle-income countries [3,4], with 66% of this burden disproportionately falling on 10 countries in Asia and Africa. In a World Health Organization (WHO) report published in 2011 inclusive of data up to 2008 for Southeast Asia, it was estimated that 99,400 children younger than 5 years ("under-five") would die because of pneumonia and 3,800 children because of meningitis; also, globally 5% of all-cause child mortality (476,000; range 333,000–529,000) in HIV-negative under-five children was because of pneumococcal (Streptococcus pneumoniae) infections [5]. Almost all (99.9%) child pneumonia deaths occur in developing and least developed countries, with most occurring in sub-Saharan Africa and South Asia. Of all pneumonia deaths, 47.7% occur in the least developed countries, most of which are eligible to receive support for the purchase of vaccines and improvement of their immunization programs through Gavi, The Vaccine Alliance (in short, Gavi) [6]. According to a recent estimate from 195 countries, pneumococcal pneumonia was the most common etiology of lower respiratory tract infections or deaths in under-five children, leading to an estimated 55.8% (95% uncertainty interval 32.5–75.0%) (58.7% in India) of lower respiratory tract infections, and of 392,965 deaths (95% uncertainty interval 228,367–532,281) (82,448 deaths in India) [7].

Conflicts of interest: All the authors are employees of Pfizer.

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India presents the largest birth cohort in the world and represents 27% of the global burden of pneumococcal disease [8]. According to WHO’s Child Health Epidemiology Reference Group estimates for 2010 in India, pneumonia caused 397,000 of the yearly total of 1,682,000 deaths in under-five children [9]. Considering that a pneumococcal etiology of about 5% to 35% for pneumonia has been estimated across different studies, the annual under-five mortality in India caused by pneumococcal pneumonia is estimated to range from 19,850 to 138,950 deaths per year [9].

In contrast to surveillance systems in countries where IPD is reportable and monitored by health authorities, much less is known of the burden of IPD in India. The proportion due to IPD was found to be 10.58% in Indian children hospitalized with suspected invasive bacterial disease (IBD), and 24% of all bacterial pneumonia cases were due to S. pneumoniae [10]. In India, pneumonia is the leading cause of death for postneonatal children, contributing about 27.5% of the total under-five mortality [11]. Data available on the incidence of acute bacterial meningitis in India are rare; a single prospective, population-based study conducted among under-five children estimated the annual burden of acute bacterial meningitis to be 53 per 100,000 [12]. Although hospital-based [13] studies highlight the prevalence of IPD among Indian children, there has been no nationally representative study of IPD incidence. Pneumonet, a 2-year-long hospital-based surveillance study, which attempted to close this knowledge gap, was conducted at three hospitals in Bengaluru, South India. The incidence of IPD in under-five children was estimated to be 17.8 cases per 100,000, with the highest burden of 49.9 cases per 100,000 among 6- to 12-month-olds [14]. The most prevalent serotypes found to cause IPD in Indian children were (in order) 6A, 6B, 1, 19F, 19A, 14, 5, 7, 9V, 33, and 17 [15,16].

Two pneumococcal conjugate vaccines (PCVs) are licensed for use in children in India. PCV13 contains poly- or oligosaccharides from 13 serotypes (4, 6B, 9V, 14, 18C, 19F, 23F, 1, 3, 5, 6A, 7F, and 19A) of S. pneumoniae, conjugated to genetically detoxified diphtheria toxin, CRM197. A 10-valent PCV (PCV10) uses recombinant protein D, tetanus toxoid, or diphtheria toxoid as the carrier protein and contains 10 serotypes (4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, and 7F) of S. pneumoniae [17].

Although more than 90 serotypes of the pneumococcus are known, PCVs were designed to address the most predominant causes of IPD morbidity and mortality, which also tend to be the most virulent and antibiotic-resistant strains. PCVs have been shown to reduce invasive disease and noninvasive disease, as well as nasopharyngeal acquisition of vaccine serotypes [18]. On the basis of the substantial burden of pneumococcal diseases globally and the growing resistance to antibiotics, the WHO recognized in 2007 the efficacy, safety, and cost effectiveness of PCVs and recommended their inclusion in childhood national immunization programs (NIPs) [19].

With the largest birth cohort in the world, India needed inclusion of PCVs in the national childhood immunization schedule. Recently, Gavi announced that it would fund a statewide pneumococcal vaccine pilot program in India [20,21]. In view of the current situation, and in the context of only partial local epidemiology data, the present study was intended to estimate the potential impact of an infant pneumococcal vaccination program in India.

### Methods

#### Model Structure

A well-established decision-analytic model designed in Microsoft Excel was used to estimate the potential impact of implementing an infant pneumococcal vaccination program in India with a 2 + 1 schedule [15,22,23]. To summarize, infants entered the model with or without vaccine protection, dependent on assumed vaccine uptake rate, and then could fall into one of the following mutually exclusive health states: no disease, AOM, severe pneumonia, pneumococcal bacteremia, pneumococcal meningitis, or death. The risk of disease was based on the local incidence without PCV adjusted by the effectiveness of the vaccine evaluated, which depended on local serotype coverage estimates. The model then evaluated the impact of a respective vaccination program (PCV10 or PCV13) on the number of the incidence of IPD in under-five children as well as on the associated death or sequelae prevented. Outcomes were calculated over a 1-year period considering only direct protection afforded by vaccination, occurring during a steady state.

#### Vaccination Program Implementation

In 2015, India’s National Technical Advisory Group on Immunization recommended a phased introduction of PCV into India’s NIP using a 2 + 1 dosing schedule at age 6 and 14 weeks, with a booster dose at age 9 months [24]. At the same time, the Indian Academy of Pediatrics recommends an infant pneumococcal vaccination schedule consisting of a 3 + 1 schedule at age 6, 10, and 14 weeks, followed by a booster dose to be completed between age 12 and 15 months [25].

Although the indirect effects of infant PCV programs of reducing disease in unvaccinated persons of all ages in the population are well documented, in this analysis we limited the impact to direct protection of under-five children. Because the analysis was for a steady-state year, under-five children were assumed to be previously vaccinated and directly protected by vaccination. Developed countries with well-established programs maintain national coverage rates between 80% and 95% [26]. Given the potential for variation in vaccination implementation among the large population in India, scenarios around levels of the vaccination rate (i.e., vaccine uptake) were tested including scenarios that reflect 1) regional (state-level) PCV implementation through Gavi funding (10%, 25%, or 50% national uptake) or 2) full NIP (75% or 100% national uptake).

#### Epidemiologic Inputs

The model was adapted using data from the published literature. The population estimate in India was based on age-specific data (for year 2011) published by the United Nations Statistics Division [27]. Pneumococcal disease data (i.e., age-specific pneumococcal disease incidence, case-fatality rates, and life expectancy data in under-five children) were collected from studies by Farooqui et al. [28] and Thomas [29]. The incidence of pneumococcal bacteremia and meningitis was calculated on the basis of the assumption that 80% of IPD cases are bacteremia and 20% are meningitis. Farooqui et al. [28] used a mathematical model to estimate the number of severe pneumonia episodes, pneumococcal pneumonia episodes, and pneumonia deaths in under-five children in India in 2010. They predicted an incidence (cases per 1000) of severe pneumonia of 30.7 and of IPD of 4.4 in under-five children [28]. Prevalence data for AOM obtained from Rupa et al. [30] were used as a proxy for incidence (Table 1).

Thomas [29] assessed the characteristics of IPD, including serotype prevalence, in six hospitals in India over a 4-year period among patients with suspected pneumonia, pyogenic meningitis, septicemia, or localized pus-forming lesions. Case-fatality rates for pneumococcal bacteremia and meningitis in under-five children were 21% and 34% (Table 1), respectively [25]. Menigitis carries a risk of neurological sequelae or hearing loss; detailed data were collected on the probability of hearing loss from a meta-analysis by McIntyre et al. [31] and on neurological sequelae due to meningitis from Pomeroy et al. [32] in children and
infants in the United States [32]. Hearing loss has been reported as one of the most common sequelae (33.9%), and 19.7% had multiple impairments. In a random-effects meta-analysis, all-cause risk of a major sequel, including cognitive deficit, bilateral hearing loss, motor deficit, seizures, visual impairment, and hydrocephalus, was twice as high in the southeast Asian regions (21.6% [95% confidence interval 13.1%-31.5%]) as in the European region (9.4% [95% confidence interval 7.0%-12.3%]; overall $I^2 = 89.5$%; $P < 0.0001$) [33].

Nisarga et al. [14] estimated the incidence of pneumonia and IPD from 224,966 at-risk under-five Indian children in three geographic zones in Bengaluru, South India (Table 1), and they obtained vaccine-specific serotype coverage data for 9,950 children [14]. The catchment included total population data for 2001, under-five children population data for January to December 2006, and infant population data for 2006. They analyzed available discharge data from three hospitals to determine the total number of hospitalizations, the distribution of hospitalization for syndromes of IBDs (diagnosed using International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM]), and deaths associated with IBD-related syndromes in under-five children [34]. They also analyzed ICD-9-CM discharge data to determine the percentage of under-five children who were admitted with a diagnosis of IBD-associated syndromes of meningitis, pneumonia, and septicemia (ICD-9-CM) and deaths caused by IBD-associated syndromes in this age group. Identification of an appropriate field site and the robust methodology followed by Nisarga et al. [14] to describe the catchment population provide an accurate representation of patient classes [34]. Overall, PCV13 covered 91.7% of IPD in all age groups (Table 1) [14].

A systematic review [35] published during the preparation of this article included results from seven studies, including the one by Nisarga et al. [14]. Three of these studies are conference proceedings [36–38], of which one includes data for surveillance of bacterial meningitis [38]. (Including only conference abstracts runs the risk of all data not being available for this review.) Another study in a smaller sample size included children with suspected meningitis [39]. Balaji et al. [40] used culture-positive isolates, but most cases of clinically suspected IPD do not have cultures obtained or are culture-negative; thus, the full burden of the disease and the predominant serotypes are not clear. In the study by Manoharan et al. [38], surveillance was limited to laboratory-confirmed IPD; therefore, the data cannot provide complete information about the full burden of IPD in India. Another study included in the review does not mention the total children studied and mentions only the numerator value (i.e., number of serum samples analyzed) [41]. The possibility of including studies with positive data has a risk of publication bias.

### Vaccine Effectiveness

Because differences in dosing schedules, timing of doses, underlying pneumococcal epidemiology, and duration of PCV use contribute to variations in the estimates of vaccine effectiveness, results obtained from one setting may not be completely applicable to another. Published values of direct protection against pneumococcal disease were used to estimate vaccine efficacy for PCV7 [42]. The vaccine efficacy for PCV7 was next adjusted to reflect local coverage of additional serotypes included in the higher valent vaccines, and these values were used to estimate vaccine effectiveness [42].

**Effect of vaccination in preventing IPD**

With the direct effect, a vaccinated individual who maintains protective immunity may be directly protected against disease. For instance, on the basis of a randomized, double-blind, placebo-controlled trial, the direct effect of PCV7 against vaccine-serotype IPD led to a 94% protection value [43]. To provide estimates of the direct effect in India for higher valent vaccines, adjustments were made to account for serotype coverage. Specifically, to calculate a vaccine’s direct effectiveness against IPD, vaccine efficacy was adjusted by the proportion of serotypes responsible for IPD in India that would be covered by each of the vaccine formulations. India-specific vaccine effectiveness for PCV10 and PCV13 were extrapolated using the efficacy of PCV7, whereas effectiveness was assumed to be similar for both vaccines only for the serotypes common to both vaccine formulations.

**Effect of vaccination in preventing pneumonia and AOM**

Effects against pneumonia were mostly derived from a clinical diagnosis of community-acquired pneumonia hospitalization. The direct effectiveness of PCV7 in preventing pneumonia confirmed by x-ray [44, 45] was estimated at 25.5%. Direct effectiveness of PCV10 and PCV13 against pneumonia was derived from PCV7 effectiveness, which was adjusted for PCV10 or PCV13 by taking the ratio of PCV7 serotype coverage in India against IPD relative to the PCV10 or PCV13 serotype coverage against IPD. For pneumonia confirmed by x-ray, the resulting direct effectiveness was estimated at 37.0% and 53.1% for PCV10 and PCV13, respectively. Direct effectiveness against AOM was derived in a similar fashion. The direct effectiveness of PCV7 in preventing clinical episodes of AOM was estimated at 7.0% [46–48]. Adjustments based on local serotype coverage resulted in a direct effectiveness of 10.2% and 14.6% in preventing AOM for PCV10 and PCV13, respectively.

### Sensitivity Analysis

A sensitivity analysis was undertaken by varying the serotype coverage used to estimate vaccine effectiveness. This was done using serotype coverage estimates published in a recent systematic review [35]. This analysis led to a vaccine effectiveness for IPD, community-acquired pneumonia (CAP), and AOM, which was based on the reported IPD serotype coverage that ranged from 78.4% to 91.7% for PCV13 and from 63.9% to 67.3% for PCV10 (Table 1) [14].

<table>
<thead>
<tr>
<th>Variable</th>
<th>0–&lt; 5 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population in India [25]</td>
<td>112,806,778</td>
</tr>
<tr>
<td>Pneumococcal bacteremia incidence (per 100,000)</td>
<td>352</td>
</tr>
<tr>
<td>Case-fatality rate [27]</td>
<td>21.0%</td>
</tr>
<tr>
<td>Pneumococcal meningitis incidence (per 100,000)</td>
<td>88</td>
</tr>
<tr>
<td>Probability of hearing loss [28]</td>
<td>13.0%</td>
</tr>
<tr>
<td>Probability of neurological sequelae [29]</td>
<td>7.0%</td>
</tr>
<tr>
<td>Case-fatality rate [27]</td>
<td>34.0%</td>
</tr>
<tr>
<td>Severe pneumonia incidence (per 100,000) [20]</td>
<td>3,070</td>
</tr>
<tr>
<td>Case-fatality rate [26]</td>
<td>10.0%</td>
</tr>
<tr>
<td>AOM incidence (per 100,000)† [30]</td>
<td>29,000</td>
</tr>
<tr>
<td>Serotype coverage</td>
<td></td>
</tr>
<tr>
<td>PCV13 [14]</td>
<td>91.7%</td>
</tr>
<tr>
<td>PCV10 [14]</td>
<td>63.9%</td>
</tr>
<tr>
<td>PCV7 [14]</td>
<td>44.4%</td>
</tr>
</tbody>
</table>

AOM, acute otitis media; PCV, pneumococcal conjugate vaccine.† Prevalence of AOM used as a proxy for incidence given lack of evidence in India.
Results

The results of this analysis demonstrated that implementation of a childhood pneumococcal conjugate vaccination program in India would have substantial health benefits (Table 2). The realization of this impact, nevertheless, will be dependent on the scale on which India implements the program.

Introduction of an NIP with PCV13

If India were to implement an NIP with high uptake (i.e., assuming a 100% vaccination compliance), compared with no vaccination, use of PCV13 in infants could reduce the number of pneumococcal disease cases by more than 7 million cases and 300,000 associated deaths per year (Table 2; Fig. 1). Among pneumococcal meningitis cases, PCV13 could prevent an estimated 6,483 cases of neurological sequelae and 12,040 cases of hearing loss as compared with no vaccination each year. Assuming 75% uptake in India, PCV13 vaccination would prevent each year, as compared with no vaccination, approximately 3.9 million cases of pneumococcal disease and 230,000 pneumococcal deaths, as well as sequelae of pneumococcal meningitis (6,500 cases of neurological sequelae and 12,000 cases of hearing loss).

Introduction of PCV13 through Gavi Funding at a State Level in India

Given that implementing a vaccination program would occur gradually in several states over time, we estimated the impact of programs at different national-level vaccination uptakes. Assuming a 10% uptake, for instance, would represent one state or several small states in India; the model estimates that PCV13 would prevent 762,080 cases of pneumococcal disease and 30,850 deaths per year (Table 2; Fig. 1). With state-level programs leading to 25% uptake across the country, approximately 1.9 million cases of pneumococcal disease and about 77,000 pneumococcal deaths could be prevented per year (Fig. 1).

Comparisons of PCV10 with PCV13

At 10% vaccine uptake, use of PCV13 would prevent 230,944 more cases of pneumococcal disease and 9,349 more deaths per year, as compared with the use of PCV10 (Table 2). Assuming there was an NIP with only one vaccine, a 100% uptake of PCV13 is estimated to prevent each year, as compared with a 100% uptake of PCV10, 1,565,413 more cases of AOM, 603,387 more cases of pneumonia, 140,335 more cases of IPD, and 93,488 more pneumococcal deaths (Table 2).

Sensitivity Analysis

Using the serotype coverage for PCV13 (78.4%) from the Singh et al. [35] review, a 100% uptake would still avert 396,050 cases of IPD, 1,703,708 cases of CAP, and 4,417,869 cases of AOM compared with no vaccination. This corresponded to averting 263,839 pneumococcal deaths each year. Using the review, serotype coverage for PCV10 (67.3%) resulted in the vaccine averting 339,976 cases of IPD, 1,388,392 cases of CAP, 3,600,225 cases of AOM, and 219,074 pneumococcal deaths. Therefore, at 100% uptake, PCV13 was estimated to avert 1,189,033 more cases of

<table>
<thead>
<tr>
<th>Uptake level</th>
<th>Vaccination status</th>
<th>IPD</th>
<th>Pneumonia</th>
<th>AOM</th>
<th>Deaths averted</th>
</tr>
</thead>
<tbody>
<tr>
<td>10% uptake</td>
<td>PCV13 vs. no vaccination</td>
<td>46,309</td>
<td>199,208</td>
<td>516,564</td>
<td>30,850</td>
</tr>
<tr>
<td></td>
<td>PCV10 vs. no vaccination</td>
<td>32,275</td>
<td>138,839</td>
<td>360,023</td>
<td>21,501</td>
</tr>
<tr>
<td></td>
<td>Difference</td>
<td>14,034</td>
<td>60,369</td>
<td>156,541</td>
<td>9,349</td>
</tr>
<tr>
<td>25% uptake</td>
<td>PCV13 vs. no vaccination</td>
<td>115,771</td>
<td>498,020</td>
<td>1,291,410</td>
<td>77,124</td>
</tr>
<tr>
<td></td>
<td>PCV10 vs. no vaccination</td>
<td>80,688</td>
<td>347,098</td>
<td>900,056</td>
<td>53,752</td>
</tr>
<tr>
<td></td>
<td>Difference</td>
<td>35,084</td>
<td>150,922</td>
<td>391,353</td>
<td>23,372</td>
</tr>
<tr>
<td>50% uptake</td>
<td>PCV13 vs. no vaccination</td>
<td>23,1543</td>
<td>996,040</td>
<td>2,582,820</td>
<td>154,248</td>
</tr>
<tr>
<td></td>
<td>PCV10 vs. no vaccination</td>
<td>161,375</td>
<td>694,196</td>
<td>1,800,113</td>
<td>107,504</td>
</tr>
<tr>
<td></td>
<td>Difference</td>
<td>70,168</td>
<td>301,843</td>
<td>782,707</td>
<td>46,744</td>
</tr>
<tr>
<td>75% uptake</td>
<td>PCV13 vs. no vaccination</td>
<td>347,314</td>
<td>1,494,059</td>
<td>3,874,229</td>
<td>231,372</td>
</tr>
<tr>
<td></td>
<td>PCV10 vs. no vaccination</td>
<td>242,063</td>
<td>1,041,294</td>
<td>2,700,169</td>
<td>161,256</td>
</tr>
<tr>
<td></td>
<td>Difference</td>
<td>105,251</td>
<td>452,765</td>
<td>1,174,060</td>
<td>70,116</td>
</tr>
<tr>
<td>100% uptake</td>
<td>PCV13 vs. no vaccination</td>
<td>463,086</td>
<td>1,992,079</td>
<td>5,165,413</td>
<td>305,046</td>
</tr>
<tr>
<td></td>
<td>PCV10 vs. no vaccination</td>
<td>322,750</td>
<td>1,388,392</td>
<td>3,600,226</td>
<td>215,008</td>
</tr>
<tr>
<td></td>
<td>Difference</td>
<td>140,335</td>
<td>603,687</td>
<td>1,565,413</td>
<td>93,488</td>
</tr>
</tbody>
</table>

AOM, acute otitis media; IPD, invasive pneumococcal disease; NIP, national immunization program; PCV, pneumococcal conjugate vaccine.
pneumococcal disease and 44,765 more pneumococcal deaths compared with PCV10.

**Discussion**

Vaccination is one of the most effective ways to promote good health, and consequently it saves about 3 million lives each year globally [49]. It has reduced the burden of many vaccine-preventable infectious diseases, greatly alleviating suffering worldwide [50]. Although the results of this study demonstrate that an NIP with sustained levels of high vaccination uptake would provide the greatest overall health impact, Gavi-sponsored state-level implementation is an important step in achieving improved outcomes and reducing childhood mortality.

The cost effectiveness of NIPs has been well documented to be highly cost-effective in both developed and developing countries [22,23,51,52]. The procurement of vaccine for the Gavi-sponsored program is at the lowest price available in the country with the highest incidence of pneumococcal disease; therefore, the program is likely to be cost-effective or cost saving.

Although the results of this study predict a considerable impact of pneumococcal vaccination in India, there are several important limitations. First, given the 1-year time horizon of the model, the evaluation does not take into account the possible influence of serotype replacement. Some PCV cost-effectiveness studies have included assumptions on serotype replacement; many have not, however, because of the complex nature of pneumococcal disease and the difficulty of modeling interactions between serotypes. Kuhlmann and von der Schulenburg [51] evaluated the cost effectiveness of PCVs in Germany, and it accounted for serotype replacement by modeling the epidemiologic trends in disease over time when programs switch the particular PCV being used. Although assumptions of serotype replacement may seem to better approximate the aggregate impact of vaccination, ongoing PCV13 NIP surveillance systems reveal limited evidence of substantial emergence of nonvaccine serotype IPD in the directly vaccinated cohorts of young children, which does not seem to warrant inclusion of specific serotype replacement in the analysis [53]. Taken together, it is presumed that the steady-state framework approach used in this model would adequately address the longer term implications of pneumococcal vaccination in under-five children, particularly in a PCV-naive country such as India, where the etiology of pneumococcal disease has not yet been affected by the introduction of a vaccination program.

A second important limitation is the absence of indirect vaccine effects in the analysis. Although numerous studies have established the benefits of pneumococcal vaccination in infants, the elderly also suffer from pneumococcal disease [54–56]. Given the density of the Indian population, implementation of a PCV13 vaccination program may provide substantial herd effect because of decreased person-to-person transmission in the population, generated by reduction in carriage of vaccine serotypes. With the implementation of an NIP in India, and after several years of vaccination, those scenarios with high vaccination rates could consequently underestimate the overall impact of vaccination. Surveillance of IPD in the UK NIP 10 years since the introduction of PCV7 and then PCV13 has demonstrated a 25% to 46% reduction in all-cause IPD among unvaccinated individuals older than 15 years [55]. Studies in the US NIP, with sustained high levels of PCV7 vaccination 10 years since introduction, have demonstrated an 18% reduction in all-cause pneumonia in individuals older than 65 years [56].

Direct and indirect herd effects of PCVs are well known. In the United States, indirect effect of vaccination has prevented 2 to 3 times as many cases of IPD as through the direct effect of vaccinating young children [6]. In a systematic review and meta-analysis of data from 242 studies including 9 studies in low- or middle-income countries, the predicted mean time to attaining a 90% reduction in IPD was 9.5 years (95% credible interval 6.1–16.6) with PCV13, suggesting that through herd immunity, a sustained childhood vaccination program will lead to a substantial protection across the whole population within a decade [57]. Indirect protective effects of vaccination have been reported to result in disease reductions across unvaccinated age groups in both high- and low-income country settings [58]. The catchup immunization of about two-thirds of children 12 to 59 months old seemed to lead to herd protection in older age groups in Kilifi, Kenya. This number is similar to the estimate of coverage of children (65%–75%) needed to induce herd protection to PCV13 in Boston, MA [59].

On the basis of the study by Moore et al. [54], it was estimated that for every pediatric case of IPD prevented, two cases are prevented among adults [54]. Extending that same factor to India could result in up to 926,000 cases of IPD averted per year in individuals older than 5 years. Consequently, our study likely underestimates the overall impact of vaccination, given the exclusion of potential indirect herd protection. Further analysis is necessary to estimate the overall impact of indirect effects by an adjustment to disease risk in unvaccinated individuals in the presence of a population-wide vaccination program in India.

Pneumococcal vaccination is a critical public health tool to reduce the burden of pneumococcal diseases in countries such as India, which justifies its inclusion in the country’s NIP. India’s Multi-Year Plan (2005–2010) for Immunization highlighted the need for “accelerated introduction of new and underutilized vaccines against diseases with significant morbidity and mortality in India” [60]. In line with this goal, and the fact that PCVs have been licensed in India since 2006, it is anticipated that they soon will be included in India’s NIP. In this respect, they have been in use in the private sector for almost 6 years with positive acceptance [61].

In India, the National Technical Advisory Group on Immunization drafted a policy that covered all categories of vaccines used in the NIP for the largest birth cohort in the world. The Advisory Group proposed that India can provide about 65% NIP vaccine coverage, although with considerable heterogeneity among the states [62]. Furthermore, the introduction of a new vaccine may actually improve routine immunization coverage by adding training and by increasing awareness and demand among parents. In states such as Uttar Pradesh and Bihar, the current NIP coverage is less than 50% [63].

On the basis of our analysis, a state-level PCV13 vaccination program with 25% uptake across the country would result in approximately 1.9 million cases of pneumococcal disease and about 77,000 pneumococcal deaths averted every year; our analysis was limited to public health impact in children. Because one of the main issues limiting countries such as India from including new vaccines in their NIP is the cost of implementing the vaccination program [64], Gavi is supporting the state-level pilot programs. Although PCVs have been shown to be highly cost-effective and even cost saving in several different settings, including low- and middle-income countries [22,23,51,52], to derive a proper cost-effectiveness analysis to inform the question of value for money, additional data on the costs associated with each disease state and quality of life data in this setting would be necessary. This study suggests that implementing a pediatric immunization program could result in significant cost offsets from disease reduction; further research is, however, necessary to establish the full financial impact of implementing such a program.
Conclusions

Although our results are based only on direct protection, and therefore are likely to underestimate additional benefits of indirect effects in the unvaccinated, incorporation of PCV into the India vaccination program for infants is predicted to have a substantially positive health impact on the population of India. Future vaccination policies may be focused on maintaining herd effects rather than providing direct protection individually. The Gavi funding of state-level programs is an important first step toward achieving the full benefits of an NIP in India.

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