Potential impact of introducing the pneumococcal conjugate vaccine into national immunization programmes: an economic-epidemiological analysis using data from India

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Abbreviations:

ABM	Agent-based model
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
cMYP	Comprehensive multi-year plan for immunization
DLHS	District Level Household Survey of India
DPT	Diphtheria, pertussis, tetanus
GAVI	Global Alliance for Vaccines and Immunization
HICs	High-income countries
ICER	Incremental cost-effectiveness ratio
IPD	Invasive pneumococcal disease
LMICs	Low- and middle-income countries

42	NTAGI	National Technical Advisory Group on Immunization
43	NVT	Non-vaccine serotype
44	OOP	Out-of-pocket
45	PCV	Pneumococcal conjugate vaccine
46	PCV7	7-valent pneumococcal conjugate vaccine
47	PCV9	9-valent pneumococcal conjugate vaccine
48	PCV13	13-valent pneumococcal conjugate vaccine
49	RCT	Randomized control trial
50	S. pneumoniae	Streptococcus pneumoniae
51	UI	Uncertainty interval
52	UIP	Universal Immunization Programme
53	VOI	Value of insurance
54	VT	Vaccine serotype
55	WHO	World Health Organization
56	YLL	Year of life lost

ABSTRACT

Pneumococcal pneumonia causes an estimated 105,000 child deaths in India annually. The planned introduction of the serotype-based pneumococcal conjugate vaccine (PCV) is expected to avert child deaths, but the high cost of PCV relative to current vaccines provided under the Universal Immunization Programme has been a concern. Cost-effectiveness studies from high-income countries are not readily comparable because of differences in the distribution of prevalent serotypes, population, and health systems. We used IndiaSim, an agent-based simulation model representative of the Indian population and health system, to model the dynamics of Streptococcus pneumoniae. We estimate that PCV13 introduction would cost approximately $240 million and avert $48.7 million in out-of-pocket expenditures and 34,800 (95% confidence interval [CI] 29,600–40,800) deaths annually assuming coverage levels and distribution similar to DPT (diphtheria, pertussis, and tetanus) vaccination (~77%). Introducing the vaccine protects the population, especially the poorest wealth quintile, from potentially catastrophic expenditure. The net-present value of predicted money-metric value of insurance for 20 years of vaccination is $160,000 (95% CI $151,000–$168,000) per 100,000 under-fives, and almost half of this protection is for the bottom wealth quintile ($78,000; 95% CI 70,800—84,400). Extending vaccination to 90% coverage averts additional lives and provides additional financial risk protection. Our estimates are sensitive to immunity parameters in our model; however, our assumptions are conservative, and if willingness to pay per years of life lost (YLL) averted is $228 or greater then introducing the vaccine is more cost-effective than our baseline (no vaccination) in more than 95% of simulations.

Key words: Pneumococcal disease; Pneumonia; Pneumococcal conjugate vaccine; Streptococcus pneumoniae; cost-effectiveness; financial-risk protection; agent-based model

SUMMARY BOX

What is already known about the topic?

- Streptococcus pneumoniae was responsible for an estimated 105,000 pneumonia deaths in India in 2010, in addition to causing meningitis and other forms of invasive disease.
- The pneumococcal conjugate vaccine (PCV) greatly reduced disease burden in high-income countries (HICs); however, the effectiveness and impact of PCV (including serotype replacement) varied significantly between countries, and it is significantly more expensive than other vaccines in India's Universal Immunization Programme (UIP).
- To circumvent the paucity of information on the vaccine's effectiveness in low- and middle-income countries (LMICs), economic analyses of PCV in LMICs typically assume similar effectiveness as in HICs.

What are the new findings

- The local distribution of dominant serotypes, host population characteristics and behaviour, and vaccination programs, affect the vaccine's effectiveness.
- Despite uncertainty, we project that the vaccine will avert a significant number of deaths, provide financial risk protection for poor populations, and deliver value for the cost as assessed by the World Health Organization's cost-effectiveness guidelines.

Recommendations for policy

- Economic analysis should consider local context and the dynamics of S. pneumoniae transmission and serotype replacement within that setting.
- Given our conservative assumptions and our projections of PCV13 effectiveness and impact in India, we recommend including PCV13 in the UIP, though we caution that

existing data gaps remain and the vaccine's effectiveness should be continuously monitored as it is rolled out.

INTRODUCTION

Streptococcus pneumoniae was responsible for an estimated 393,000 (95% uncertainty interval [UI] 228,000–532,000) child pneumonia deaths globally in 2015, with nearly all mortality occurring in low- and middle-income countries (LMICs) [1]. The introduction of a seven-valent pneumococcal conjugate vaccine (PCV7) in the early 2000s greatly reduced disease incidence and hospitalization in high-income countries (HICs), by reducing invasive pneumococcal disease (IPD), which occurs when S. pneumoniae invades normally sterile sites such as the bloodstream [2]. PCV7 provided protection against the seven most common serotypes causing IPD in the United States at the time, and countries have since adopted expanded PCVs that provide protection against serotypes estimated to cause approximately 70% of IPD globally [3]. Today, 135 countries include a PCV in their national immunization program [4].

In India, an estimated 105,100 (95% confidence interval [CI] 92,100–120,000) of 356,300 (CI 311,600–407,400) under-five pneumonia deaths were associated with S. pneumoniae in in 2010 [5]. In 2016, the National Technical Advisory Group on Immunization (NTAGI) recommended introducing a PCV in the universal immunization programme (UIP), which targets a cohort of 27 million newborns with six vaccines across the country and another two vaccines (against rotavirus and Japanese encephalitis) in a few states. The Indian government had planned to roll out PCV in three states in 2017, but progress remains slow in part due to the relatively high cost of PCV compared to other vaccines already provided under UIP [6–8]. The Global Alliance for Vaccines and Immunization (GAVI) has pledged to support PCV provision until 2021 [9], after which the cost of the vaccine will have to be borne by the Indian government. The affordability and cost-effectiveness of the vaccine is especially important in resource-constrained countries, such as India. Prior analyses in several HICs

136 have found PCV introduction to be cost-saving or cost-effective according to World Health
137 Organization (WHO) or local thresholds [10–13], but retrospective studies in other HICs,
138 such as the Netherlands and Australia, found it unlikely that the PCV7 vaccination
139 programme was cost-effective [14,15].
140
141 In addition to PCV's relatively high cost, the uncertainty regarding the vaccine's potential
142 cost-effectiveness in LMICs stems from uncertainty surrounding its effectiveness in these
143 settings [6,7,14]. The incidence of vaccine serotype (VT) IPD fell markedly in many HICs
144 after the vaccine was introduced, but decreases in overall IPD varied significantly (e.g., IPD
145 decreased by 12% in Navarro, Spain while in the United States it decreased by 77%, see
146 [16]). The increase in the frequency of S. pneumoniae serotypes not covered by the vaccine,
147 also known as serotype replacement, contributed to this variation in overall IPD. In LMICs,
148 evidence on the effect of serotype replacement on overall vaccine effectiveness in the
149 population is lacking. Evidence on PCV from randomized control trials (RCTs) in LMICs
150 demonstrated that PCV7 and PCV9 are highly efficacious at reducing pneumonia and
151 invasive disease [17–19]. But RCTs are not designed to evaluate serotype replacement at the
152 population level.
153
154 Recent observational studies of the introduction of a PCV in South Africa (PCV7 in 2009)
155 and the Gambia (PCV13 in 2011) found that IPD in children under two dropped by 69% (CI
156 62–76) and 55% (CI 30–71) within one year of introduction, respectively. However, both
157 studies found that disease caused by non-vaccine serotypes (NVTs) was increasing, and, in
158 the case of Gambia, overall IPD increased in the final year of the study [20–22]. In South-
159 East Asia, both Bangladesh and Nepal introduced PCVs in 2015, but data on effectiveness
160 and serotype replacement have not been published [4].

Economic analyses of introducing PCV need to consider the dynamics of S. pneumoniae transmission within the context of the setting being analyzed. Local differences in distributions of dominant serotypes, host populations, health system structure, and vaccination programs all contribute to the variation in the vaccine's impact across countries [23]. To estimate PCV outcomes given these factors, models need to consider the colonized—asymptomatic carrier—population, which is the reservoir of transmission. In HICs that introduced PCV, serotype replacement among colonized individuals was higher and more consistent than serotype replacement in IPD. A logical explanation for higher replacement among the colonized individuals than in IPD cases is that NVTs cause less disease than VTs. If this is the case, the variation in reduced IPD across countries may be partially attributable to local differences in the distribution of colonizing serotypes. Other theories have been proposed to explain the higher serotype replacement seen in colonization than in IPD [16], and projecting the dynamics of S. pneumoniae transmission in LMICs with a paucity of data is difficult. Nonetheless, evaluations of PCV introduction need to consider these economic-epidemiological dynamics. They need to project serotype dynamics within the local context, or, at the very least, they should consider that the outcomes may not be the same in high-burden-LMICs instead of current practice that either ignores the disease dynamics all together or assumes similar herd effects and serotype replacement as in low-burden-high-income settings (see [24–28]).

To project trends in under-five pneumococcal infections, including bacteremic and non-bacteremic pneumonia, meningitis, and other IPD, and estimate the potential financial risk protection, cost, and cost-effectiveness of introducing PCV in the UIP, we modelled S.

pneumoniae dynamics in an agent-based model (ABM) of the Indian population and healthcare system.

METHODS

Agent-based simulation model

We adapted our survey-data driven ABM of an in silico population representative of the Indian population, IndiaSim [29–32]. Our simulated population size was approximately 25,000 individuals and 4,300 households. Individuals in the simulation interacted with each other (contacts) and with the healthcare system, getting vaccinated and seeking care. Individuals were either healthy and not colonized, healthy and colonized, or colonized and symptomatically infected. Those symptomatically infected with S. pneumoniae chose whether to seek care. Individuals could also seek care for exogenous infections. Simulations were run with one-week time steps. Demographic and socioeconomic data and healthcare choices at the individual and household levels were drawn from the District Level Household Survey (DLHS-3) of India [33] and from literature on care seeking behaviour in India [34,35]. Additional details on IndiaSim are in the supplementary appendix and in previous publications [30–32]. The model was programmed in C++11 standard and outcomes analysed in R, version 3.2 [36].

Pneumococcal colonization and transmission dynamics

Pneumococcal disease dynamics were included in IndiaSim based on work by Cobey and Lipsitch [37]. We included 15 serotypes that are representative of the serotype distribution in India [38]; we did not model particular serotypes, but a representation of the S. pneumoniae population.

Transmission between individuals could occur when a carrier (or symptomatically infected) individual came into contact with other individuals. The probability of transmission of serotype z depended on the susceptibility of the individual, a function of both current and historical colonizations and infections:

$$q(z,\vec{\theta},\vec{C}) = \left[1-\omega(\vec{C})\right]\left[1-min\left((1-p),\min(1,\sigma\cdot\tau(z))\right)\right], \quad (1)$$

where $\vec{\theta}$ and $\vec{C}$ are indicator vectors of past and current colonization, indexed by z. Current colonization was assumed to reduce susceptibility through competition, described by the term in the first bracket in (1), where $\omega(\vec{C})$ was set to:

$$\omega(\vec{C}) = \begin{cases} 0, & \sum C_i = 0 \text{ (not colonized)} \\ \mu_{max}\left[1-\dfrac{min(\vec{f})-1}{Z-1}\right], & \sum C_i > 0 \text{ (colonized)}, \end{cases} \quad (2)$$

where Z is the number of serotypes in the model, μ_{max} is the maximum scaling down of susceptibility due to strain competition, and $\vec{f}$ is a vector of serotype fitness ranks such that $min(\vec{f})$ is the rank of the most fit carried serotype. Serotype-specific immunity, described in the term in the second bracket in (1), also reduced susceptibility: p is vaccine efficacy for the targeted serotypes, σ is an anticapsular immunity parameter (equivalent for all serotypes), and

$$\tau(z) = \begin{cases} 0, & \theta_z = 0 \text{ (not previously cleared)} \\ 1, & \theta_z > 0 \text{ (previously cleared)}. \end{cases} \quad (3)$$

The duration of colonization in successful transmissions was drawn from an exponential distribution in which the mean was:

$$v(z) = k + [\gamma(z) - k]e^{-\epsilon \sum_i \theta_i} \quad (4)$$

Serotypes were assumed to differ in their fitness, modelled as a reduction in the length of colonization ($\gamma(z)$) [39,40]. Duration exponentially decreased with the sum of past colonizations ($\sum_i \theta_i$), describing the serotype-independent immunity. k is the minimum duration of colonization and ϵ is a fitted shape parameter. Parameterization of colonization and transmission dynamics are based on Cobey and Lipsitch [37], which fits the functions to data from vaccine naïve populations.

If the person sought care (either for S. pneumoniae infection or for an exogenous infection) and was prescribed antibiotics, duration was updated accordingly. Additional details of the dynamics are in the supplementary appendix and the model parameters are presented in Table 1 and in the following text.

Table 1. Parameters

Description	Symbol [§]	Base-case [sensitivity values/distribution]	Source
Disease model			
Number of serotypes	Z	15	
Under-five colonization prevalence fitted to		40%	Authors assumption based on [41–50].
Contact rate	β	Fitted to under-five colonization prevalence	
Immigration force of infection	ω	1e-06	As in [37]
Intrinsic duration of carriage for serotype z	$\gamma(z)$	25-220 days (linearly increasing across serotypes)	As in [37], and based on [51,52]

Description	Symbol [§]	Base-case [sensitivity values/distribution]	Source
Reduction in susceptibility to pneumococcus from carrying the fittest serotype	μ_{max}	0.25	As in [37]
Reduction in susceptibility to a serotype conferred by prior carriage of that serotype	σ	0.5 [0.5, 0.8]	≥ 0.5 based on results for Z = 15 in [37]
Shape parameter for the reduction in duration of carriage dependent on past colonization	ε	0.1 [0.1, 0.25, and 0.4]	Based on [37]
Case-carrier ratio (pneumococcal pneumonia, meningitis, and other invasive pneumococcal disease)		Fitted to disease incidence given colonization prevalence	Based on [53–55,5]
Case fatality rate		Fitted to death rate	Based on [53,54,56,5]
Treatment			
Seek treatment		Wealth quintile I: 48%; II: 51%; III: 60%; IV: 66%; V: 75%	Based on [34,57,35]
Probability seek care at public provider (if seek care)		- Wealth quintile I: 55% [triangular min = 44%, max = 66%, mode = 55%]; - II: 51% [triangular 40%, 61%, 51%] - III: 43% [triangular 35%, 52%, 43%); - IV: 39% [triangular 31%, 47%, 39%]; - V: 26% [triangular 21%, 32%, 26%]	
Receive appropriate treatment at health provider		95%	Authors' assumption
Inpatient meningitis cost			Based on [57–59]
Public providers		\$191 [triangular min = \$134, max = \$248, mode = \$191]	
Private providers		\$275 [triangular min = \$193, max = \$358, mode = \$275]	
In-patient pneumonia cost			Based on [57,59,60]
Public providers		\$93 [triangular min = \$65, max = \$121, mode = \$93]	
Private providers		\$214 [triangular min = \$150, max = \$278, mode = \$214]	
In-patient other pneumococcal disease cost			Based on [57,59]

Description	Symbol [§]	Base-case [sensitivity values/distribution]	Source
Public providers		$76 [triangular min = $53, max = $99, mode = $76]	
Private providers		$194 [triangular min = $136, max = $252, mode = $194]	
Outpatient cost			Based on [57,59]
Public providers		$7.55 [triangular min = $5.30, max = $9.80, mode = $7.55]	
Private providers		$9.47 [triangular min = $6.60, max = $9.80, mode = $12.30]	
Unattended pneumonia cost		$1.05 [triangular min = $0, max = $1.40, mode = $1.05]	[61]
Antibiotics clear colonization or symptomatic infection		50%	Authors assumption based on Van Effelterre et al. 2010 [62–64]
Exogenous antibiotic prescription rate (per day)		0.001327	Based on IMS Health MIDAS database
Vaccine			
PCV13 % of cases		Most common serotypes representing approximately 70%	Based on [38,65].
Per-person vaccine efficacy	p	0.6	As in [37], estimated using [66]
Per-child cost in scenario 1†		$13.60 [triangular min = $6.35, max = $18.95, mode = $13.60]	Based on WHO cMYP tool.
Per-child cost in scenario 2†		$13.50 [triangular min = $6.25, max = $18.85, mode = $13.50]	Based on WHO cMYP tool.

[§]Symbols for Cobey and Lipsitch 2012 model.
†Three doses at $3.30 per dose and training, syringe, wastage costs (5% vaccine wastage rate and 10% syringe wastage rate), and a 25% buffer stock. Ranges for the sensitivity assume $1 to $5 per dose.
Values varied for sensitivity are in brackets.
Costs in 2014 US dollars.

Fitted pneumococcal colonization prevalence

Studies from the past fifteen years found S. pneumoniae colonization prevalence in India ranging from 6.5% to 70.0% in children and infants [41–43,46–50,67,68]. We fit the contact rate (β) so that the colonization levels of children under-five were ~40%.

252 **Pneumococcal disease**

253 Carriers of S. pneumoniae became symptomatically infected—developed bacteremic or non-
254 bacteremic pneumococcal pneumonia, pneumococcal meningitis, or other invasive
255 pneumococcal disease—according to the invasiveness, or case-carrier ratio. The case-carrier
256 ratio represents infections per acquisition event, which we model as a function of the
257 probability of progressing to symptomatic disease in a time-step and the duration of carriage
258 (the number of time-steps). We assumed that VTs were carried for longer than NVTs [40],
259 and therefore VTs case-carrier ratio was greater. We fit the case-carrier and case-fatality rates
260 to estimates of disease incidence and deaths in the literature [56,54]. For more detail see
261 supplementary appendix.

262

263 **Treatment and antimicrobial prescription**

264 Individuals suffering from pneumococcal disease sought care (i.e., went to hospital/clinic and
265 received antibiotics) depending on their household wealth—wealthier individuals were more
266 likely to seek care [34,35]. Similar to Kouyos and others [69], we assumed that rates of
267 colonization were affected by individuals consuming antibiotics exogenously (i.e., for other
268 causes). Antibiotic consumption rates were drawn from IMS Health MIDAS (IMS Health,
269 Danbury, CT, USA) data on antibiotic consumption in India. The treatment costs for
270 pneumococcal disease were based on Tasslimi and other [59] and include care seeking,
271 diagnostics, hospitalization, and medication.

272

273 **Vaccination scenarios**

274 We evaluated three scenarios: (i) no vaccination; (ii) introducing PCV13 at DPT3 (diphtheria,
275 pertussis, tetanus vaccine) coverage levels (approximately 77%) and following the 2+1
276 schedule that India has adopted; and (iii) increasing PCV13 coverage to 90%. We assumed

277 that households that vaccinate with DPT in DLHS-3 continue to do so. We also increase
278 coverage to 2011 estimates [70]; see previous work on rotavirus vaccination [30]. For the
279 extended vaccination scenario, additional households were recruited randomly to increase
280 vaccination coverage rates to 90%.
281
282 The simulated vaccine did not protect against thirteen simulated serotypes. Instead, we
283 assumed the vaccine provided protection against the most common serotypes that contributed
284 70%–75% of disease incidence prior to vaccination [38,65]; this corresponded to 5 to 10
285 simulated VTs, depending on the simulation parameterization. The vaccine was assumed to
286 reduce susceptibility to asymptomatic carriage for VTs [37] as described by equation (1). The
287 vaccine likely further protects against carriers progressing to disease, but due to lack of
288 evidence, we conservatively assumed that the vaccine only affects susceptibility to
289 colonization for covered serotypes and has no further effect on progression to disease (case-
290 carrier ratio).
291
292 Data on immunization costs were from India's comprehensive multi-year plan (cMYP) for
293 immunization [71]. It included costs for the vaccine and syringes—including wastage—and
294 other related costs such as planning, training, transportation, and cold chain equipment.
295
296 **Analysis and outcome measures**
297 The primary outcome tracked was the change in under-five disease burden measured by
298 estimated disease incidence and deaths averted. We report values for non-severe and severe
299 pneumonia, pneumococcal meningitis, and other IPD. We consider both bacteremic and non-
300 bacteremic pneumonia, and the classification of severe pneumonia is based on the WHO
301 definition used in Rudan et al [72] of lower chest wall indrawing, which represents an

302 indication for hospitalization. To measure serotype diversity, we calculated the Simpson
303 index—the probability that two randomly selected serotypes (with replacement) will differ—
304 and compared it to limited data from India. We also estimated the years of life lost (YLLs)
305 averted, the incremental cost-effectiveness (ICER) measured by the incremental cost per YLL
306 averted from a health systems perspective (costs described above), out-of-pocket (OOP)
307 expenditures averted, and the money-metric value of insurance (VOI)—the dollar amount the
308 population would be willing to pay to avert the risk of financial shock from OOP expenditure
309 on treatment [73].
310
311 We ran simulations with fitted values for the contact rate, case-carrier ratio, and case-fatality
312 rate for a 200-year burn-in period, before introducing vaccination and then estimating
313 outcomes for the next twenty years. We report the rounded median present value for the
314 twenty-year intervention timeframe and annual outcomes. For averted burden estimates, we
315 report differences between median values for each scenario; for example, to estimate the
316 deaths averted by the intervention in scenario 1 we subtract the median deaths in intervention
317 scenario 1 from the median deaths in the no vaccination scenario. Costs and expenditures
318 were converted to 2014 US dollars (see supplementary appendix), and we used a discount
319 rate of 3%, consistent with standard practice.
320
321 **Sensitivity Analysis**
322 In addition to the base-case analysis, to assess the sensitivity of our results, we varied the
323 parameters for anticapsular immunity and serotype-independent immunity as described in
324 Table 1 since the interplay between naturally acquired and vaccine acquired immunity likely
325 impacts strain dynamics and serotype replacement. We ran simulations with each parameter
326 set (and fitted contact-rate, case-carrier ratio, and case-fatality rate as described above), in

total running 1,800 simulations, 600 for each scenario. We constructed 95% CIs by drawing 5,000 bootstrap samples (e.g., of size 100 for base-case scenario 1 outcomes) from these simulations for each statistic we estimated. In addition, we explored the sensitivity of the ICERs to the immunity and economic parameters (Table 1); we set immunity parameters as described above and drew 5,000 samples from the joint distribution of the economic parameters. We constructed cost-effectiveness acceptability curves (CEAC) by calculating the proportion of bootstrap samples that had the highest net benefit for each arm, where the net benefit $= \lambda \times \Delta YLL - \Delta costs$ and λ is the willingness to pay per YLL.

RESULTS

Serotype diversity

To compare the serotype diversity in our model to results in Cobey and Lipsitch [37] and to data from India, we measured the Simpson index for our model outcomes and compared it to the 0.93 index calculated from data collected by Manoharan et al [65], which identified 57 different serotypes and five non-typeable isolates. In our no vaccination simulations, the median Simpson index was 0.92 (95% CI 0.90–0.93).

Disease burden

We estimated that introducing PCV13 at current DPT coverage levels would avert a median 481 (95% CI 456–502) non-severe pneumonia cases, 198 (95% CI 185–211) severe pneumonia cases, 3 (95% CI 3–4) meningitis cases, and 16 (95% CI 14–17) other invasive pneumococcal infections per 100,000 children under-five per year in the base-case (Figure 1). This represented a decline of 20.9% (95% CI 19.8%–22.1%) in severe pneumococcal pneumonia cases per year. The number of cases only stabilizes after five years, when it was 25.2% (95% CI 24.2%–26.3%) and 34.2% (95% CI 31.9%–36.7%) lower per year in the DPT

352 and extended coverage scenarios than in the baseline scenario. Cases of non-severe
353 pneumonia, meningitis, and other invasive pneumococcal disease were similarly reduced.
354
355 Our results varied significantly depending on the sensitivity to immunity parameters, which
356 affected the decline in under-five cases caused by VTs and serotype replacement by NVTs
357 (Figure 2A). In DPT vaccination coverage simulations where we set the serotype-specific
358 immunity parameter, which impacts susceptibility, to the base-case value $\sigma = 0.5$ (see
359 equation 1) and increased the impact of serotype-independent immunity on colonization
360 duration from the base-case by setting $\epsilon = 0.25$ or $\epsilon = 0.4$ (see equation 4), the number of
361 cases dropped by 22.6% (95% CI 21.1%–23.9%) and 19.1% (95% CI 17.8%–20.5%)
362 respectively. In simulations where we set the impact of serotype-specific immunity and
363 serotype-independent immunity to the highest in our range ($\sigma = 0.8$ and $\epsilon = 0.4$), the number
364 of cases dropped by 9.8% (95% CI 8.5%–10.9%).
365
366 VT symptomatic infections decreased and NVT symptomatic infections increased after the
367 introduction of PCV13 for most parameter sets; there was no replacement by NVTs when
368 immunity parameters were high ($\sigma = 0.8$ and $\epsilon = 0.4$) (Figure 2B and C). The highest increase
369 in NVTs was in simulations with low immunity parameter values; by the end of expanded
370 coverage simulations, NVT cases increased by 50.8% (95% CI 45.0%–57.0%) and VT cases
371 decreased by 73.1% (95% CI 71.8%–74.2%) among under-fives when immunity parameters
372 were low ($\sigma = 0.5$ and $\epsilon = 0.1$). The decline in VT cases was lower when we increased the
373 anticapsular immunity parameter, σ, than when we increased the serotype-independent
374 immunity parameter, ϵ, and held other parameters at the base-case. For example, when $\sigma =$
375 0.5 and $\epsilon = 0.4$, VT cases decreased by 47.9% (95% CI 46.5%–50.3%), and when $\sigma = 0.8$ and
376 $\epsilon = 0.1$ VT cases decreased by 39.0% (95% CI 36.9%–42.0%) by the end of simulation.

However, the increase in NVT cases was similar in these simulations: when $\sigma = 0.5$ and $\epsilon = 0.4$, NVT cases increased by 12.1% (95% CI 9.2%−17.8%), and when $\sigma = 0.8$ and $\epsilon = 0.1$, NVT cases increased by 12.7% (95% CI 7.8%−20.1%) by the end of simulation. Dynamics over time of VT decline differed when $\sigma = 0.8$, which is higher than the vaccine's serotype-dependent protection, p = 0.6; before stabilizing, VT disease increased slightly after the initial decline.

The estimated median number of deaths averted by PCV13 over twenty years was proportional to symptomatic infections (Table 2). There were 558 (95% CI 457-656) deaths averted per 100,000 under-fives over 20 years in the DPT level vaccine coverage scenario in the base-case, which, extrapolated to the full population, suggests 34,800 (95% CI 29,600–40,800) deaths averted in children under-five per year (the CIs in this case and for other extrapolations to the entire population do not account for uncertainty of the population size). We estimated that an additional 13,800 (95% CI 5,600–19,000) deaths would be averted per year with expanded coverage. However, outcomes for different parameter sets varied significantly: when immunity parameters were the highest in our range ($\sigma = 0.8$ and $\epsilon = 0.4$), the difference in median deaths averted per year was 11,000 (95% CI 5,400–17,100) in the DPT level vaccine coverage scenario and 16,200 (95% CI 10,200–21,900) in the extended vaccine coverage scenario.

Deaths were inversely related to wealth. In the poorest portion of the population, 178 (95% CI 127–226) deaths were averted per 100,000 children under-five over the twenty-year intervention assuming DPT vaccine coverage levels. An additional 55 (95% CI 11–103) deaths per 100,000 were averted when coverage was increased. The deaths averted in wealth

quintiles IV and V, the wealthiest forty percent of the population, were significantly lower than in the poorer population (89 [95% CI 32–122] in quintile IV and 45 [95% CI 19–87] in quintile V) at DPT coverage levels. Expanded coverage in these groups was not significantly different from no effect with an estimated -5 [95% CI -37–42] additional deaths averted in quintile IV and 38 [95% CI -2–60] in quintile V.

Table 2. Twenty year outcomes and present value costs per 100,000 under-fives by wealth quintile (all parameter sets)

	I—poorest	II	III	IV	V—richest	Total
Scenario 1: PCV13 at DPT coverage (76.8%), incremental to the no vaccination scenario						
Deaths averted	178 (127–226)	135 (89–184)	116 (66–151)	89 (32–122)	45 (19–87)	**558 (457–656)**
OOP expenditure averted[§]	$143 (133–154)	$109 (102–120)	$83.7 (71.5–93.4)	$90.7 (80.4–101)	$111 (97.9–122)	**$538 (514–562)**
Money-metric VOI[§]	$78.0 (70.8–84.4)	$36.3 (33.7–39.7)	$20.6 (17.6–23.4)	$16.2 (14.0–17.9)	$8.90 (7.80–10.0)	**$160 (151–168)**
Scenario 2: PCV13 at 90% coverage, incremental to scenario 1						
Deaths averted	55 (11–103)	78 (42–115)	16 (-17–58)	-5 (-37–42)	38 (-2–60)	**186 (100–272)**
OOP expenditure averted[§]	$51.7 (41.2–60.7)	$37.2 (29.5–44.7)	$50.5 (42.1–59.8)	$32.9 ($24.3–$43.4)	$42.2 (33.7–55.6)	**$215 (195–237)**
Money-metric VOI[§]	$27.9 (22.1–33.7)	$12.5 (9.80–15.3)	$13.0 (10.7–14.4)	$5.90 (4.30–7.80)	$3.40 (2.60–4.70)	**$62.6 (55.6–69.6)**

Incremental differences between medians for 20 simulated years in each scenario using base-case parameters: intervention scenario 1 incremental to the no vaccination scenario and intervention scenario 2 incremental to scenario 1. The totals are for a population of 100,000 under-fives. The distribution of under-fives across wealth quintiles is not equal. 95% CI in parentheses were constructed by 5,000 bootstrap samples for each scenario overall all parameter sets.
OOP: Out-of-pocket.
VOI: value of insurance.
[§] Present value discounted at 3% annually; US 2014 dollars; in thousands.

Financial risk protection

We found that introducing PCV13 into the UIP protected households from the risk of expenditure on treatment and hospitalization for pneumococcal diseases. The estimated base-case present value out-of-pocket (OOP) expenditure averted per 100,000 was $538,000 (95% CI $514,000–$562,000) over twenty years at current vaccine coverage levels and an

415 additional $215,600 (95% CI $195,000–$237,000) with expanded coverage (Table 2).
416 Extrapolating to the Indian population, after the fifth year of introducing PCV13 the median
417 OOP expenditure averted would be approximately $48.7 million annually under DPT vaccine
418 coverage levels and an additional $13.9 million with expanded coverage.
419
420 The median OOP expenditure averted was estimated to be highest for quintiles I (in the DPT
421 coverage level scenario, the twenty-year present value was $143,000 [95% CI $133,000–
422 $154,000] per 100,000 under-fives in the base-case), but it showed no clear trend across other
423 wealth quintiles. The money-metric VOI decreased with wealth. The present value VOI was
424 $78,000 (95% CI $70,800–$84,400) in wealth quintile I and $8,900 (95% CI $7,800–
425 $10,000) in quintile V per 100,000 children under-five assuming DPT vaccine coverage
426 levels. Increasing coverage provided additional protection, especially for wealth quintile I.
427
428 **Cost and cost-effectiveness**
429 The present value cost of including PCV13 at DPT levels at $3.30 per dose was
430 approximately $2.8 million per 100,000, and increasing coverage levels to 90% would
431 increase this cost another $1 million. Extrapolating to the population, the cost is
432 approximately $240 million each year under DPT coverage levels and $328 million under
433 expanded coverage. At $1 per PCV13 dose, a similar cost to the rotavirus vaccine, the
434 respective costs are approximately $112 million and $152 million per year. We estimated the
435 median YLLs and calculated the cost per YLL averted. The incremental cost per YLL averted
436 was $144 under DPT vaccine coverage levels in the base-case, and the incremental cost of
437 expanding coverage was $127. In the sensitivity analysis, the incremental cost per YLL
438 averted was highest when immunity parameters where highest, reaching $518 per YLL
439 averted in the DPT vaccination coverage scenario. Figure 3 shows the cost effectiveness

acceptability curves for all simulations (including all parameter sets). When the willingness to pay per YLL averted, λ, is greater than $228, we estimate that introducing the vaccine (scenario 1 + scenario 2) is almost surely (in more than 95% of our simulations) more cost-effective than the baseline scenario. If λ is greater than $325 the extended coverage scenario is almost surely the most cost-effective option.

DISCUSSION

India's recent decision to integrate the pneumococcal vaccine into its UIP is a response to the high pneumococcal disease burden in the country [5]. The current cost of PCV is relatively high and its effectiveness uncertain given the paucity of information on asymptomatic carriage (the main reservoir of the bacteria), the distribution of IPD-causing serotypes in India [74], and the potential changes to the serotype distribution after vaccine introduction. We examined these issues using an ABM. An ABM is helpful in this context as clinical trials are not feasible for predicting how a mass-vaccination at the population level will affect serotype distribution. To that end, we simulated the effect of introducing the PCV13 vaccine into India accounting for differences in population wealth and access to health services.

We found that the introduction of PCV13 is likely to reduce the disease burden of S. pneumoniae. The greatest reduction in disease incidence and mortality is predicted to occur in the first few years after the introduction of the vaccine. This result is similar to other countries' experiences and reflects the significant reduction in the most prevalent serotypes that are linked to the greatest incidence of disease [75–78]. Though colonization levels don't fall as precipitously, the new colonizing serotypes are assumed to have a lower case-carrier ratio, which results in reductions in disease incidence and mortality. Our estimated percent decline in disease incidence is modest compared to some studies in HICs [75–78], as well as

in South Africa [20]. This may be because of our conservative assumption that the vaccine does not explicitly impact disease incidence, but only affects it implicitly by reducing carriage of more fit serotypes. However, other factors contribute to the smaller effect on disease incidence. PCV7 serotypes contributed to a higher percentage of disease incidence in the pre-vaccine era in HICs (and PCV13 in South Africa [20]) than estimates of PCV13 serotypes contribute to disease in India [38,65]. The impact of vaccination may be even smaller if the ABM population is not well-mixed—if we assume individuals are more likely to come into contact with others in their household or region (see supplementary appendix). Because the vaccination coverage is heterogeneous in the DPT coverage scenario (according to existing DPT vaccination reported in DLHS-3) there may be unprotected pockets in the population. These pockets provide a reservoir for PCV13 strains and could propagate outbreaks of IPD with those strains.

The cost of implementing the vaccine is not insignificant, we estimated that it would cost at least $240 million annually, more than double the estimated costs of implementing the rotavirus vaccine that India recently introduced [30]. If PCV13 cost were to drop from $3.30 per dose to $1, a similar cost to the rotavirus vaccine and likely closer to the cost of a conjugate vaccine being developed in India, the annual cost would drop to approximately $112 million. However, including the rotavirus vaccine in the UIP was estimated to reduce the disease and financial burden more than PCV13. The rotavirus vaccine was estimated to avert 44,500 deaths assuming DPT coverage [30], while the estimated number of median deaths averted by PCV13 is approximately 34,800 in our base case.

The estimate of $144 per YLL in the DPT coverage scenario is a range that would be considered cost-effective. If willingness to pay per YLL is over $325, introducing the vaccine

with coverage extended to 90% was the most cost-effective option in over ninety-five percent of our bootstrap samples. The cost-effectiveness ratios in our analysis are in line with other projections in low- and middle-income countries studies [24,25,27], but are higher than studies in Uganda (cost-saving at $0.15 per dose) [26] and in Kenya (mean $47 per disability-adjusted life year at $3.50 per dose) [28]. In addition to assuming different vaccine costs these studies vary significantly from ours. For example, the study in Uganda does not consider serotype replacement, and the study in the Kenya assumes replacement will be similar to the US. In addition, we assumed the vaccine had no impact on the case-carrier ratio. If we altered that assumption the vaccine's effectiveness and cost-effectiveness would be greater.

Our study has a number of limitations. First and foremost, our estimates are uncertain, which is a reflection of the uncertainty in the parameters, particularly the efficacy of the vaccine to reduce the incidence of IPD as well as baseline rates of infection and mortality. Uncertainty is also partially a function of the size of the simulated population, which was ~25,000, with children under five representing 3,000–4,000 members of the population. We chose this population size to focus on a model of serotype dynamics that includes several serotypes. Our analysis does not fully capture the structural uncertainty of the disease model. We vary assumptions on the impact of immunity but maintain a similar model structure across simulations. Additionally, our demographics are based on sampling frameworks of the population. Though representative, they do not fully capture the heterogeneity that exists in a population as large as India. Our model does not currently consider sensitivity to the vaccine dose schedule, and we assume the 2+1 schedule rolled out in India.

Although the introduction of the PCV13 vaccine in India is likely to reduce the disease burden of S. pneumoniae and is cost-effective, the magnitude of the impact is uncertain. Data collection on pneumococcal carriage, disease, and the prevalent serotypes in India and their virulence needs to be strengthened. Filling these gaps while also increasing understanding of pneumococcal dynamics and reducing reliance on assumptions will improve our ability to project the serotypes likely to emerge and their impact on disease in India after introducing vaccination. Continuing surveillance after India introduces PCV will inform these dynamics as well, enhancing effective resource allocation and the success of future initiatives and course corrections. Though we caution that existing data gaps need to be filled, given our conservative assumptions, the disease and financial burdens averted and the relatively low expected cost per YLL saved makes this an intervention worth pursuing.

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FIGURE LEGENDS

Figure 1. Pneumococcal Disease Cases (base-case)

Median pneumococcal disease incidence by year for 5,000 bootstrap samples using base-case parameters. The line representing the no vaccination scenario is the median across all years. The shaded areas represent the 95% CI for each year. The vertical lines with arrows and the corresponding values are the median cases averted after year 5, and the values in parentheses are the 95% CIs.

Figure 2. Sensitivity to immunity parameters

Sensitivity of pneumococcal disease cases, including non-severe and severe pneumococcal pneumonia, pneumococcal meningitis, and other invasive pneumococcal infections, to immunity parameters over 5,000 bootstrap samples. Panel (A) shows estimated cases averted per year for each parameter set. It is calculated by subtracting the median cases in scenario 1 and median cases in scenario 2 from the median cases in the no vaccination scenario for each bootstrap sample. Dots and triangles are the predictions and line ranges are the 95% CIs. The other panels show serotype replacement over time; plotted values are the medians for each year. Panel (B) shows the percent reduction in vaccine type cases of pneumococcal disease and (C) the percent increase in non-vaccine type pneumococcal cases after the introduction of PCV13 to 90% of the population (scenario 2).
ϵ: Serotype-independent immunity shape parameter (see equation 4).
σ: Anticapsular (serotype-specific) immunity parameter (see equation 1).

Figure 3. Cost-effectiveness acceptability curves

Cost-effectiveness from health system perspective. Includes all simulations.

S1 Appendix

S1-1 IndiaSim agent-based simulation model structure

IndiaSim is an agent-based model (ABM) programmed in C++11 standard. The ABM was previously used to analyse the introduction of rotavirus vaccination in the UIP [1], expanding neonatal care by community health workers [2], universal public finance of epilepsy treatment [3], and implement water and sanitation interventions to reduce diarrheal diseases [4] among other analyses. The model is representative of the Indian population at the district level. It was constructed using the District Level Household Survey 2007–2008 (DLHS-3), which includes data on 34 Indian states (Nagaland is excluded), approximately 720,000 Indian households, and 3.4 million individuals. The survey reported information on individual characteristics (e.g., age, and sex) and household socioeconomic status. The survey also includes information health care facilities (e.g., their location and quality) and on households' care-seeking behaviour.

The ABM is structured in 67 patches, describing geographical units. Each patch is the urban or rural region in a state (Andaman and Nicobar's urban region is excluded because of small sample size). Each patch is populated by individuals, grouped into household units (for this analysis approximately 4,300 households were drawn from DLHS-3). Decisions in the model, including healthcare seeking and vaccination ones, are made at the household level. Households decide whether to vaccinate to protect from disease, and they decide whether to seek care when household members exhibit disease symptoms. For more details on the ABM see previous publications [1–3].

S1-2 Disease model

We modelled the dynamics of pneumococcal disease by building on a colonization model by Cobey and Lipsitch 2012 [5]. The model used similar assumptions, but was modified to include infection. At each time-step, a host carrying serotype z transmits to x individuals, where x is drawn from a Poisson distribution with a mean βI_z. β is the effective contact rate, a product of the host's contacts and likelihood of transmission, and I_z is the number of strains of serotype z the host carries. The x individuals the host transmits to are randomly picked from the entire population, where for each individual in the population the probability of being picked is weighted by their location relative to

the host and the parameter for fraction of contacts from within the same household (ρ_h), within the same patch (ρ_p), and neither $(1-\rho_h-\rho_p)$.

Each of the x individuals acquires the strain based on their susceptibility. Similarly to Cobey and Lipsitch 2012 [5], host susceptibility to pneumococcal colonization by strain z is given by:

$$q(z,\vec{\theta},\vec{C}) = \left[1-\omega(\vec{C})\right]\left[1-min\left((1-p),\min(1,\sigma\cdot\tau(z))\right)\right] \quad (1)$$

where $\vec{\theta}$ and $\vec{C}$ are vectors of past and current colonization indexed by z. The term in the second bracket of (1) represents naturally acquired and vaccine serotype-specific immunity. p is vaccine efficacy for the targeted serotypes. σ is an anticapsular immunity parameter (equivalent for all serotypes) and

$$\tau(z) = \begin{cases} 0, & \theta_z = 0 \text{ (not previously cleared)} \\ 1, & \theta_z > 0 \text{ (previously cleared).} \end{cases} \quad (2)$$

Host susceptibility is also a function of the serotypes currently carrying (the strain competition) represented by the term in the first bracket in (1). Competition is represented by

$$\omega(\vec{C}) = \begin{cases} 0, & \sum C_i = 0 \text{ (not colonized)} \\ \mu_{max}\left[1-\dfrac{min(\vec{f})-1}{Z-1}\right], & \sum C_i > 0 \text{ (colonized).} \end{cases} \quad (3)$$

where Z is the number of serotypes in the model, μ_{max} is the maximum scaling down of susceptibility due to strain competition, and $\vec{f}$ is a vector of serotype fitness ranks such that $min(\vec{f})$ is the rank of the most fit carried serotype.

The duration of a new colonization in a host is drawn from an exponential distribution with a mean

$$v(z) = k + [\gamma(z)-k]e^{-\epsilon\sum_i \theta_i} \quad (4)$$

where k is the minimum duration of colonization, $\gamma(z)$ is a serotype specific intrinsic colonization duration, and ϵ is a fitted shape parameter (see in [5] for fit). Duration exponentially decreases with the sum of past colonization, describing the non-specific immunity.

Carriers of strain z can become infected with the daily likelihood $\eta(z)$, which was equivalent across serotypes in our simulations, and infected individuals die according to the case-fatality rate.

S1-3 Simulation and fitting

Our estimates are based on a 20 year simulation time frame (in discrete time-steps of one week) for the three scenarios: the baseline scenario without PCV; scenario 1 with PCV13 coverage at households that also get DPT vaccination (approximately 77%); and scenario 2 with 90% PCV13 coverage. Each scenario was simulated using 6 different parameter sets: under-five colonization prevalence was set to 40%; the serotype specific immunity parameter, σ, was set to 0.5 or 0.8; and the non-specific immunity parameter, ϵ, was set to 0.1, 0.25, or 0.4; vaccination and treatment costs in public and private providers were also varied. These parameters are described further in the disease model section and the choice of their values is described in Table 1.

To initialize our populations' carriage and immunity distributions, we ran each parameter set for a 200 year burn-in period with no vaccination. We fit the simulations to three indicators: under-five colonization prevalence, the observed number of pneumococcal infections, and the number of deaths. Two sources estimated pneumococcal pneumonia, pneumococcal meningitis, and other invasive pneumococcal disease cases and mortality in India in the early 2000s [6,7], and two other studies have estimated these values for pneumococcal pneumonia in 2010 [8,9]. To achieve the fit, we did a parameter sweep, altering the contact rate (β), the daily rate of infection (for carriers), and the case fatality rate; we drew 100 samples for each of the 6 parameter sets using Latin Hypercube Sampling (LHS). We simulated each of the samples 10 times for a total of 6,000 simulations.

The best fits from the simulations used to initialize our populations were used as the starting point for simulations we used in the analysis. For this analysis, all three scenarios were simulated 100 times from each of the starting points using their respective values for σ, ϵ, and the fitted parameters. We then ran a total of 1,800 simulations (3 scenarios, 6 parameter sets, and 100 runs of each).

S1-4 Estimating outcomes

We estimated outcome measures and 95% CIs by drawing 5,000 bootstrap samples.

Incremental government expenditure and private, out-of-pocket expenditure averted

We considered cost of care-seeking, diagnostics, and treatment, including hospitalization and medication. These costs are out of pocket in all scenarios. Government expenditure is for introducing and including the pneumococcal conjugate vaccine in India's Universal Immunization Programme (UIP). These costs are from India's comprehensive multi-year plan (cMYP) for immunization [10] as described in the manuscript.

Using the outputs from IndiaSim we calculated the present day incremental values for both government costs and out-of-pocket (OOP) expenditure averted for each scenario. All costs were converted to 2014 US dollars using the Internal Revenue Service yearly average currency exchange rates [11] and GDP deflators [12].

Years of life lost (YLLs) and cost per YLL

We calculated the years of life lost YLLs averted using IndiaSim outputs on deaths due to pneumococcal infections. We also calculated the dollars-per-YLL averted. Costs included OOP expenditure and costs to the government for including the vaccine in the UIP. We discounted at 3% assuming uniform age-weights.

Money-metric value of insurance

We estimated the financial risk protection of averting out-of-pocket expenditure on care and treatment for individuals with pneumococcal infections. To estimate this we calculated the money-metric value of insurance, using a constant relative risk aversion utility function. For more information on this calculation please see Verguet et al. 2015 [13] and the appendix in Megiddo et al. 2016 [3].

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