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Estimating the economic impact of pneumococcal conjugate, *Haemophilus influenzae* type b and rotavirus vaccines in India: National and state-level analyses

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ABSTRACT

Background: To support vaccine decision-making we estimated from the societal perspective the potential health impact and costs averted through immunization with three vaccines – *Haemophilus influenzae* type b (Hib), pneumococcal conjugate vaccine (PCV) and rotavirus vaccine (RVV). Methods: Based on variability in disease burden, strength of health system and economic status, we selected four states in India: Bihar, New Delhi, Maharashtra and Tamil Nadu. We used secondary data sources to estimate the number of under-5 deaths averted from Hib, pneumococcus and rotavirus in each state and back-calculated the total cases averted. We synthesized available data to estimate the disease burden, treatment cost, caretaker productivity loss and vaccine coverage in each state. A Delphi Survey and roundtable among Indian experts was conducted to reach consensus on model inputs. Results: By scaling up coverage of Hib, PCV and RVV, India could save over US$1 billion (uncertainty range: US$0.9–US$2.4 billion) in economic benefits and avert more than 90,000 needless child deaths each year. An estimated US$1 billion (US$0.9–US$2 billion) or 88% of the total amount of cost savings would be attributable to lost productivity due to premature pneumococcal death. Another US$112.8 million (US$105–297 million), or 10% of the total cost would be accounted by costs related to loss of productivity due to disability as a result of these diseases. Treatment costs of Hib, pneumococcal disease and rotavirus gastroenteritis, would account for US$8.4 million (US$4–12 million) or <1% of the total costs of these diseases. Finally, caretaker productivity loss from seeking care would represent US$1.5 million (US$ 1–4.9 million). Cost savings varied by vaccine, coverage scenarios and states. Conclusions: Hib, PCV and RVV vaccine introduction in India can result in immediate benefits to the government and households in terms of savings.

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1. Introduction

An estimated 5.9 million children died globally in 2015 before completing their first five years of life [1]. With an estimated 1.09 million deaths in this age group, India's share is higher than any other single country [2]. Ten percent of these deaths are due to diarrhea and 13% are due to pneumonia. Diseases like diarrhea, pneumonia and meningitis cause substantial short and long-term morbidity in terms of unnecessary illness and hospitalization, hamper physical and cognitive development and interfere with the future productivity and well-being of affected children [2–5].

Studies from India have consistently shown rotavirus to be the leading cause of moderate-to-severe diarrhea causing 40% of diarrhea-related hospitalizations among children <5 [6–8], and more than 50,000 deaths in the same age group [1,5–7]. One study estimated that in 2011, rotavirus caused 870,000 hospitalizations, more than 3 million outpatient visits and over 11 million diarrhea episodes in children < 5 years of age [9]. In another study, an episode of moderate-to-severe diarrhea increased the risk of all-cause death by 8.5 times [5].

The pneumococcus and *Haemophilus influenzae* type b (Hib) are the leading bacterial causes of pneumonia and meningitis [10], causing more than 70,000 and 40,000 deaths from all causes, respectively [5]. Together rotavirus, pneumococcus and Hib account for more than 10% of under-five deaths in India. Preventing deaths from pneumonia and diarrhea is hence a high priority in India.

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Highly effective vaccines against these pathogens are already in use in India with important documented impact on reducing associated morbidity and mortality. The pentavalent vaccine (DTP-HepB-Hib) was introduced in India as part of the routine immunization program in January 2013 in a 3 + 0 schedule [11]. The rotavirus vaccine (RVV) was introduced three years later (March 2016) in a phase program with a 3 + 0 schedule, while the 13-valent pneumococcal conjugate vaccine (PCV-13) was introduced in May 2017 as part of the phase program with a 2 + 1 schedule [3]. While coverage rates for the 13-valent PCV were not available, WHO/UNICEF Estimates of National Immunization Coverage (WUENIC) coverage rates for RVV and pentavalent vaccines were reported in 2017 at 13% and 99%, respectively [11].

According to the Government of India Planning Commission, PCV vaccine prevented an estimated 28,104 deaths, 661,674 cases and 69,487 hospitalizations each year while Hib vaccine prevented 26,163 deaths, 921,069 cases and 106,443 hospitalizations, assuming the same DPT3 coverage [12]. Post-marketing surveillance of new rotavirus found a small increased risk of intussusception in some studies (1–6 excess cases of intussusception per 100,000 children vaccinated) [13–15], but a recent review by WHO's Global Advisory Committee on Vaccine Safety confirmed that the benefits of RVV outweighed the risks [15].

In this paper, we estimated the potential health gains and costs savings from three vaccines in India: Hib, PCV and RVV.

2. Material and methods

2.1. Review and synthesis of the economic evidence

A review and synthesis of the available published and gray literature was conducted with a particular focus on state level data. References with relevant economic data were included to assess the potential benefits of Hib, PCV and RVV vaccination to the health care system in India. Relevant studies were identified, including general economic papers, cost of illness (COI) studies, economic evaluations at the national and sub-national level. Official reports from India containing information about costs of pneumonia, meningitis and diarrhea were also identified. All papers were published in English from beginning of 2003 to the end of 2017. An additional search was made to update the literature thru end of 2018. Much of the published work and some of the completed study reports in the public domain were obtained from the PubMed-MEDLINE, Bireme-MEDLINE, Bireme-LILACS, SciELO, and the COCHRANE Library databases. Manual bibliographic searches revealed additional articles.

Articles that were not true economic evaluations (e.g., reviews of applied studies, commentaries, or editorials without original data) were excluded, as were some articles that substantially replicated results from other articles. Due to the limited range of published studies originating in India, studies from neighboring countries and studies containing only abstracts and emerging work in the process of being published were also considered. The selected studies were reviewed in terms of their country or state of evaluation, publication year, vaccine strategies assessed, study design, method of evaluation, cost measures, perspective and period of analysis. Appendix 1 provides the findings of the search strategy.

2.2. Expert feedback by phone or in-person

To augment information from the literature, we worked closely with more than 30 Indian stakeholders, including epidemiologists, clinicians, health economists, donors, and policy experts, to determine the best source of state-level and national level data and gain expert advice on the model inputs. Most of the interviews were completed by phone, three experts responded to interview questionnaires by email and four additional interviews were in-person meetings.

We developed five interviews per syndrome (pneumonia, meningitis, diarrhea) to solicit input from key stakeholders, assess data availability, and agree on the model assumptions and sources of these assumptions. Appendix 2 is an example of the epidemiology survey specific to Hib. This survey, like the others, contained specific questions about key epidemiological assumptions that were considered in the model i.e., annual deaths due to pneumonia, meningitis and diarrhea; proportion of deaths attributable to these syndromes; and case fatality ratios (CFRs). For each of the assumptions, a general description about the assumption and the sources leading to that assumption were given. Surveys were sent to experts three weeks prior to the interview or meeting.

2.3. Roundtable discussion

To lay the groundwork for the introduction of new vaccines in India, experts from various disciplines convened on November 19, 2013 in New Delhi, India. At this meeting the model and assumptions were discussed, data needs were identified, and expert advice was sought on how to utilize the results of the state and national-level analysis, discuss the types of data that were most useful for generating future economic evidence. This meeting was part of a broader exercise in collaboration with expert partners from India to examine the potential health impact and costs averted through immunization with three vaccines and supplemented other efforts by India and international stakeholders to answer key economic questions regarding these vaccines. Based on discussions at the roundtable, we compiled a series of recommendations that served as the basis for the present analysis.

The work of the experts at the roundtable culminated in the issuance of the following: (i) validation of the model structure and the model inputs; (ii) agreement that there was sufficient evidence to move forward with running the model and generating a report; (iii) delineation of some of the key gaps in syndrome and pathogen-specific epidemiologic data; (iv) health costs and health care seeking patterns for pneumonia, diarrhea and meningitis; (v) draft of proceedings document; and (vi) guidance for future research to be targeted at obtaining this information.

2.4. Model overview

We estimated the disease cost averted by each of the target vaccines by leveraging modeling work developed for Decade of Vaccines Economics (DoVE) [16]. We used India state-level projections on disease burden from peer-reviewed literature and other sources. Because the available data was not entirely India-specific we obtained guidance from local experts at the roundtable discussion on the use of these data.

We modeled the annual health and economic benefits of Hib, PCV and RVV vaccines for a 10-year period (2018–2029) at the national level and in four states in India (Bihar, Delhi, Maharashtra and Tamil Nadu). These states were chosen because of their disease burden, health system strength and health priorities and the need for economic benefit data to support vaccine programs (Fig. 1). We used the current DPT3 coverage as one of the indicators of health system strength in these states.

The analysis generated new evidence in four categories: (i) treatment and transportation costs due to diarrhea, pneumonia and meningitis; (ii) caretaker wages lost as a result of a child's illness with diarrhea, pneumonia and meningitis; (iii) productivity losses that occur due to premature death; and (iv) productivity

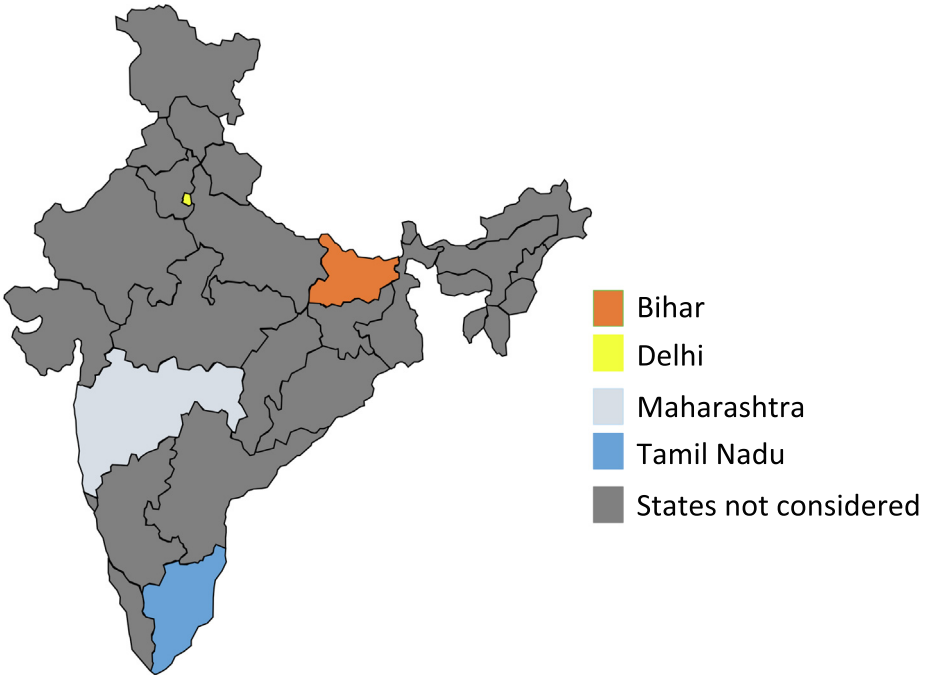


Fig. 1. States considered in the analysis.

losses that occur due to disability (particularly as a result of meningitis).

2.5. Model inputs

The model described above required country-specific data on the epidemiology of the disease, the economic costs associated with different outcomes, and vaccine efficacy. While some of these data were available, the quality and representativeness were severely limited for others.

The principal inputs to the model included epidemiological information on cases and deaths due to diarrhea, pneumonia and meningitis, treatment costs and productivity losses and information about vaccine efficacy. We considered the most up to date, available demographic, epidemiological and clinical data to capture the effects of vaccination compared to no vaccination in a single year at a national and state level in India (Table 1).

Deaths averted were calculated by multiplying the deaths of specific syndromes (pneumonia, meningitis, and diarrhea) and etiology, by the vaccine efficacy, serotype coverage and vaccine coverage rates. Coverage assumptions were modelled for three theoretical scenarios: achievement of DTP3 coverage levels (72%), achievement of 80% coverage, and achievement of 90% coverage for all three vaccines (Hib, PCV, RVV).

Cases averted were estimated by dividing estimated deaths averted using the CFRs. Indian experts at the roundtable agreed that the back-calculation approach was appropriate because cases in India are considered to be largely underestimated. Appendix 3 provides a conceptual diagram for estimating cases averted from deaths averted by a vaccination program using Hib as an example. The solid blue arrows in Appendix 3 represent disease processes. We back-calculated cases averted (red boxes) using circled parameters and equations, represented by dotted red arrows. We used the same methodology to estimate the pneumococcus- and rotavirus-related cases averted. However, for pneumococcal pneumonia and meningitis, efficacy was multiplied by serotype coverage and immunization coverage.

To estimate treatment costs averted, we considered India- and symptom-specific care-seeking, the point of care amongst care-seeking cases, and the cost (including duration) of care for inpatient and outpatient (hospital and health center) treatment (Appendix 4). Lost caretaker wages were calculated by assuming a caretaker loses wages of a half-day for each outpatient treatment visit and full-day wage loss of each inpatient day. Daily wages were derived from India-specific average wage estimates [17]. Productivity losses from death were calculated through net present value formulae applying a conventional discount rate of 3% to account for time preferences. Long-term sequelae estimations were derived primarily from meningitis-related disability calculations. We assumed 21% of health care was public and the remaining 79% was private based on expert opinion.

We performed deterministic sensitivity analyses (DSA) to identify assumptions that are most influential on results. We considered key parameters in the DSA including disease burden estimates (including mortality rates, case fatality rates), average bed days, outpatient visits, care-seeking behavior, cost of medicine and diagnostics, hospitalization rates, labor participation and transportation costs. We used @Risk software to report the results of the DSA.

3. Results

3.1. Review and synthesis of the economic evidence

The literature search yielded a total of 118 papers, of which only 13 economic papers were relevant to the India context (Table 2). Two of these papers evaluated the cost-effectiveness of Hib vaccination [18,20] and 5 the cost-effectiveness of RVV [19,23,24,25,26]. In addition, there were 5 other papers that estimated the costs of more than one strategy or the cost of treating more than one syndrome [17,21,22,27,28].

Cost-effectiveness analysis was the most common type of economic evaluation reported, followed by cost analysis papers, which quantified the cost of treating an event (e.g. diarrheal treatment,

Table 1
Summary of model inputs: State and national level.

	Model parameters	National value (range*)	Bihar	Delhi	Maharashtra	Tamil Nadu	Source
Demo-graphics	Total population	1,236,344,631	103,804,637	16,753,235	112,372,972	72,138,958	[2]
	Birth rate per 1,000 population	21	27	17	17	16	[21]
	1–59-month child mortality per 1,000 live births	23	27 (25–34)	24 (12–26)	15 (5–27)	11 (8–16)	[21]
	Deaths in 1–59 months	592,511	80,421	3,808	11,246	10,313	[1]
Syndrome-specific (Diarrhea)	% of deaths due to diarrhea in 1–59 months	22.8% (19–29%)	East 23% (18–28%)	Central 23% (18–28%)	West 16% (13–19%)	South 23% (18–27%)	[2]
	Diarrhea deaths in 1–59 months	135,048	19,301	914	2,699	2,475	[1]
	Rotavirus diarrhea hospitalizations	39.20% (35–53%)					[13]
	CFR of rotavirus diarrhea	6.8% (3.4%-13.6%)					[14–16]
Vaccine impact- rotavirus	DTP 3 coverage	72% (60–90%)	59% (55–90%)	80% (60–90%)	86% (60–90%)	79% (60–90%)	[22]
	Rotavac efficacy against severe rotavirus diarrhea	56% (45–60%)					[23]
Care-seeking and length of stay in hospital – diarrhea	Children with diarrhea who seek care in last 2 weeks	76% (61–91%)	73.7% (59–88%)	77.1% (62–93%)	77.9% (62–93%)	73.5% (59–88%)	[21]
	% severe diarrhea cases seeking care are hospitalized (public sector)	8% (6–10%)					[21]
	% severe diarrhea cases seeking care are hospitalized (private sector)	24% (19–29%)					Expert assumption
	Diarrhea cases seeking care outpatient visit, 2° hospital-urban (%) – public sector	92% (74–100%					Expert assumption
	Diarrhea cases seeking care outpatient visit, 2° hospital-urban (%) – private sector	76% (71–91%)					Expert assumption
	Diarrhea inpatient bed days (public sector)	2 (1–4)					[21]
	Diarrhea inpatient bed days (public sector)	2.6 (3–6)					[21]
	Diarrhea inpatient bed days (private sector)	4 (3–6)					Expert assumption
Treatment Costs for Diarrhea, US$, 2018	Inpatient cost per bed day (secondary hospital) – public sector	$57 ($45–$68)					[21]
	Inpatient cost per bed day (secondary hospital) – private sector	$246 ($197–$296)					[21]
	Outpatient visit cost (primary health center-rural) – public sector	$2					[21]
	Outpatient visit cost (primary health center-rural) – private sector	$8 ($6–$9)					[21]
	Outpatient visit cost (secondary hospital - urban) – public sector	$4 ($3–$8)					[21]
	Outpatient visit cost (secondary hospital - urban) – private sector	$9 ($6–$13)					[21]
Economic Factors	India average inflation rate from 2012 to 2014	0.0872					[24]
	Average US dollar/India Rupee exchange rate	63.469					[25]
Productivity loss (applies to all syndromes and pathogens)	Average daily wage	$4 ($3–$5)	$3 ($3–$5)	$5 ($4–$6)	$4 ($3–$5)	$6 ($5–$7)	[26]
	Minimum daily wage	2.387					[27]
Demographics: Pneumonia and meningitis	Total deaths pneumonia/meningitis	182,464	28,720	1,360	4,016	3,683	[1]
Sydrome-Specific (Pneumonia, Meningitis	% deaths due to pneumonia in 1–59 months	25.34%	30% (24–35%)	30% (24–35%)	26% (21–31%)	18% (15–22%)	[1]
	% deaths due to meningitis in 1–59 months	5.45%					[28]
	Pneumonia deaths in 1–59 months	150,169	25,329	1,199	3,542	3,248	[1]
	Meningitis deaths in 1–59 months	32,295	3,391	161	474	435	[1]
Pathogen-specific (Hib)	% pneumonia deaths due to Hib	20.7% (17–25%)					[28]
	CFR of Hib pneumonia	2% (0.5–4)					[5]
	% meningitis deaths due to Hib	31% (30–40%)					[29]
	CFR of Hib meningitis	44% (17–62%)					[28]
Vaccine impact (Hib)	DTP 3 coverage	72% (60–90%)	59% (55–90%)	80% (60–90%)	86% (60–90%)	79% (60–90%)	[22]
	Hib conjugate vaccine efficacy against all invasive forms of Hib disease (3 doses)	93% (83–97)					[30]

Table 1 (*continued*)

	Model parameters	National value (range*)	Bihar	Delhi	Maharashtra	Tamil Nadu	Source
Pathogen-specific (Spn)	% pneumonia deaths due to Spn	33% (26–40%)					[28]
	% pneumonia deaths due to Spn	36% (29–43%)					[4]
	CFR of Spn pneumonia	3% (1–5%)					[4]
	% purulent meningitis deaths due to Spn	20% (17–44%)					[29,31,32]
	CFR of Spn meningitis (treated and untreated)	57% (25–71%)					[4]
Vaccine impact (Spn)	DTP 3 coverage	72% (60–90%)	59% (55–90%)	80% (60–90%)	86% (60–90%)	79% (60–90%)	[22]
	Proportion of IPD in <5-year-old PCV13 serotypes in Asia	74% (67–79%)					[33]
	PCV efficacy for vaccine type IPD	80% (58–90%)					[34]
	PCV 13 efficacy for vaccine type IPD in India	59% (39–71%)					Calculation
Care-seeking and length of stay in hospital – pneumonia and meningitis	% children with acute respiratory infections/ fever in last 2 weeks who seek treatment	77.4% (62–93%)	78.8% (63–95%)	88.9% (71–100%)	84.6% (68–100%)	84.8% (68–100%)	[21]
	% of children with meningitis taken to health care facilities	100%	73%	91%	73%	78%	Expert assumption [35]
	% care-seeking pneumonia cases that are hospitalized (public sector)	10% (5–40%)					Expert assumption
	% care-seeking pneumonia cases that are hospitalized (private sector)	40% (20–80%)					Expert assumption
	% care-seeking meningitis cases that are hospitalized (public/private sector)	100%	100%	100%	100%	100%	[35]
	Pneumonia and meningitis cases seeking care at outpatient visit in 2°hospital in urban area (%) (public sector)	10% (5–40%)					Expert assumption
	Pneumonia/meningitis cases seeking care at outpatient visit in 2° hosp., urban (%) (private sector)	40% (20–80%)					Expert assumption
	Pneumonia inpatient bed days (public sector)	4.10 (3–5)					[32]
	Pneumonia inpatient bed days (private sector)	5.5 (3–10)					Expert assumption
	Meningitis inpatient bed days (public sector)	13.6 (10–15)					[36]
	Meningitis inpatient bed days (private sector)	16.6 (10–19)					Expert assumption
Treatment Costs-Pneumonia and Meningitis (US$, 2018)	Pneumonia inpatient treatment cost $ (secondary hospital) -public sector	$96.72 ($77–$116)					[36]
	Pneumonia inpatient treatment cost $ (secondary hospital) - private sector	$246.43 ($197–$296)					[36]
	Pneumonia outpatient visit cost $ (Primary level health center in rural area) -public sector	$3.30 ($3–$4)					[36]
	Pneumonia outpatient visit cost $ (Primary level health center in rural area) -private sector	$12.89 ($10–$15)					[36]
	Outpatient treatment (secondary hospital in urban area) - public sector	$4.23 ($4–$8)					[36]
	Outpatient treatment (secondary hospital in urban area) -private sector	$13.92 ($4–$15)					[36]
	Meningitis inpatient treatment cost $ (tertiary hospital) -public sector	$775.08 ($620–$930)					[36]
	Meningitis inpatient treatment cost $ (tertiary hospital) -private sector	$858.71 ($687–$1,030)					[36]

* A parenthesis is used when a range is included or when a range is available.

diarrheal episode in the hospital and in outpatient settings) or the cost of treatment. One study applied the extended cost-effectiveness analysis framework to estimate the financial risk protection (FRP) afforded and health gains resulting from RVV by income group [29]. No additional studies with relevant economic data of the benefits of Hib, PCV and RVV vaccination to the health care system in India were found when we updated the literature thru the end of 2018.

Table 3 provides a summary of the economic papers reviewed including the setting in which the study took place, the choice of outcome measures, the study perspective, the comparators and the study findings. We found the outcomes measured varied

Table 2
Number of interventions evaluated by type of economic evaluation method.

Economic study type	Number of papers	Hib vaccine	Rotavirus vaccine	Other/combined interventions*
Cost-effectiveness analysis	7	2	3	2
Cost analysis	5	–	–	5
Extended cost-effectiveness analysis	1	–	1	–
Totals	13	2	4	7

* Other/combined interventions include studies that estimate the costs of more than one strategy (e.g. zinc and copper supplementation in the treatment of acute diarrhea) or studies that estimate the cost of treating more than one syndrome.

substantially across studies [17–29]; however, many of the papers chose to consider cost per case or death averted and cost per hospital event averted as their primary outcome measure. In one of the papers, variations in vaccine coverage and risk proxies by state were modelled to estimate geographic distributional effects. The paper that applied the extended cost-effectiveness analysis framework to estimate the FRP afforded and health gains resulting from RVV by income group assessed the consequences of RVV policy by looking at the direct household financial implications, (protection against financial risks, and the distributional consequences across population strata.

The types of interventions evaluated also varied across studies [17–29]. The search found 4 papers that presented RVV economic impact estimates, 2 Hib vaccination impact papers and 7 considered the economic impact of disease or other interventions (e.g. zinc and copper supplementation, hospital and outpatient treatment). No published PCV economic impact estimates were found in India.

We found a relatively strong mix of methodologies [17–29]. Of the cost-effectiveness analyses identified, 4 presented the incremental cost-effectiveness ratios (ICER) in units of cost per Disability-Adjusted Life Years (DALYs) averted and a combination of other outcome measures including cost per life years gained (LYG), cost per death averted. One paper presented the ICER in terms of cost per cases and deaths averted and an additional paper presented it in units of cost per LYG.

In terms of study perspective, 4 papers considered the healthcare system and societal perspectives, 1 considered the household and healthcare perspective, 3 took into account the societal perspective only, 4 took on the healthcare system perspective only. One paper did not specify the study perspective [17–29].

For those studies that looked at the vaccine economic impact, all concluded that vaccination programs are cost-effective. The results of these studies, however, were not generalizable [17–29]. The potential economic impact of vaccination depended on several factors, including vaccine coverage, vaccination costs, vaccine efficacy and effectiveness, disease incidence, serotype distribution, length of vaccine protection, time since vaccination, age of vaccinated group, and lost future wages from children who die of vaccine preventable diseases. Factors limiting the accuracy of these economic studies included lack of understanding of the healthcare system, publication bias, and validity of data used to determine the values of key variables. These studies did not include estimates of indirect effects.

In terms of cost, we found that Hib pneumonia and meningitis and rotavirus diarrhea incurred a substantial cost to the healthcare system or society [17–29]. The biggest cost component of the cost of treatment was hospitalization, followed by opportunity costs associated with missed work. In the published literature, sources of cost data were generally methodologically deficient, not generalizable to other populations, and did not reflect the true economic costs of disease. Despite their methodological differences, all the papers reinforced the importance of performing economic evaluations on the basis of local settings.

3.2. Annual health benefits

Fig. 2 shows the health benefits of improved rates of vaccination in a single year based on the 90% theoretical vaccine coverage scenario for Hib, PCV, and RVV vaccines from the public health sector perspective in India with 827,093 annual cases averted and 35,130 annual deaths averted. Health benefits varied by state with Bihar averting more cases (397,901) and deaths (13,560) than any of the other states (Table 4).

Health benefits also varied by vaccine coverage scenarios. For the public sector, assuming a coverage scenario of 72%, Hib vaccine could prevent 27,626 annual pneumonia and meningitis deaths and 767,757 annual cases of the same syndromes. The annual number of pneumonia and meningitis deaths and cases averted due to PCV vaccination was lower than for Hib vaccine, 25,796 and 716,891, respectively. Similarly, RVV could prevent 21,236 annual diarrheal deaths and 713,226 annual diarrheal cases (Appendix 5). When a coverage scenario of 90% was assumed (Appendix 6), health benefits were higher with 34,533 annual deaths averted due to Hib vaccine and nearly 1 million annual cases averted, 32,245 deaths averted due to PCV vaccine and 26,545 annual deaths prevented due to RVV. The annual health and economic benefits resulting from Hib, PCV and RVV vaccine in the private sector in India, based on a 72% and a 90% vaccine coverage scenario, are presented in Appendices 7–8.

Across the three vaccines, the majority of the deaths averted were attributed to Hib vaccination with reported 37%, followed by PCV vaccination with 34% and RVV with 29%. In terms of annual cases averted, Hib vaccination was the largest contributor of cases averted with 40%, followed by PCV with 32% and RVV with 28%. This is consistent across vaccine coverage scenarios. In contrast, when health benefits were projected for 10 years (2018–2029), RVV was the largest contributor for cases averted, followed by PCV and Hib vaccination (Fig. 3).

3.3. Cost savings and gains in caretaker labor productivity

Table 4 summarizes the economic benefits expressed in terms of treatment savings and gains in labor productivity by state with $156 million in total cost savings for Bihar; $18.7 million in Maharashtra; $14.9 million in Tamil Nadu with and $7.5 million for Delhi. The total cost savings and gains in labor productivity were estimated at $1.1 billion in the four states. The largest contributor of these costs was lost productivity due to premature death averted with $949.5 million, followed by lost productivity due to disability averted with $112 million, the total treatment costs with $8.4 million, $1.6 with total transportation costs averted and lost caretaker wages with $1.5 million. Cost savings varied by vaccine (Fig. 4) with Hib vaccine contributing 42% of these savings from the public health sector perspective. Followed by PCV vaccine with 34% of the total savings and RVV with 24%.

Cost savings also varied by coverage scenarios and health (public, private) sector (Appendices 5–8). Assuming a coverage scenario of 72% (Appendix 5), Hib vaccination could result in US$329.5

Table 3
Summary of economic papers reviewed.

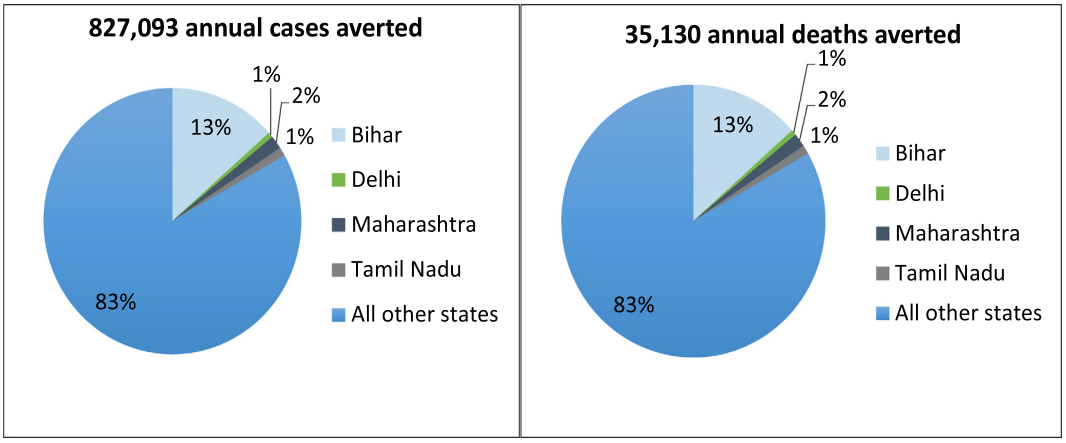
Reference	Location	Setting in India	Outcome measures	Perspective	Comparators	Findings
Anand et al. [17]	Haryana Delhi	Urban, rural; Public and private sector, primary, secondary, tertiary	Costs of pneumonia, diarrhea, meningitis	Healthcare Society	No comparator considered (economic burden study)	Cost of diarrhea up to US$9.5 (public sector), US$5.5 (private sector) depending on level of healthcare; mean total cost of pneumonia US $183 (public sector), US$110 (private sector) depending on level of healthcare; mean total cost of meningitis US $420 (public sector), US$174 (private sector) depending on level of healthcare
Clark et al. [18]	All India	National and state level	Cost per LYG, cost per DALYs averted	Healthcare		
Societal	Hib vaccination vs. no vaccination	US$192 to US$1,033 per DALYS averted (discounted) (government perspective);				
US$155 to 939 per DALYs averted (discounted) (societal perspective)						
Esposito et al. [19]	All India	Nationally representative	Cost per DALY or death averted	Healthcare system	National RVV versus no vaccination	US$21.41 per DALY averted (@ US$1 price); cost saving (@ US$0.15 price); US$0.00 (@US$0.28 price); US$200.21 (@US$ 7 price)
Gupta et al. [20]	Haryana	Public and private sector	Cost per DALY averted, cost per LYS	Healthcare Societal	Hib vaccination vs. no vaccination	US$819 per DALY averted, US $885 per LYG, YS$115 per Hib case averted, US$26,004 per Hib death averted (government perspective); US$277 per DALY averted, US $300 per LYG, US$39 per Hib case averted, US$8,809 per Hib death averted (societal perspective)
Madsen et al. [21]	Vellore	Secondary, tertiary level, private sector	Costs of hospitalized childhood pneumonia	Healthcare provider	No comparator considered (economic burden study)	Total cost to health care provider for one episode of hospitalized childhood pneumonia treated at secondary level was US$ 83.89 and US$ 146.59 at tertiary level. Hospital costs comprised 74% and 56% of the total cost, respectively. Mean household expenditure on secondary level was US$ 41.35 and at tertiary level was US$ 134.62.
Mendelsohn et al. [22]	Vellore	Public sector	Cost of rota-virus diarrhea and all-cause diarrhea	Healthcare system	No comparator considered	US$80.80 at large referral hospital, US$40.60 at smaller community hospital resulting in 5.8% and 2.2% of the annual household income in referral and community hospitals, respectively
Patel et al. [23] Maharashtra	Nagpur Peri-urban					
Mixed	Cost per diarrhea, death averted	Societal	Zinc 40mg Zn sulfate and 5mg Cu sulfate vs 50mg ORS	Mean cost of treating a child with acute diarrhea was US $14, 66% of which incurred by government and 34% incurred by the families; in terms of cost-effectiveness, interventions were cost-saving		
Patel et al. [24] Maharashtra	Nagpur Peri-urban					

(*continued on next page*)

Table 3 (*continued*)

Reference	Location	Setting in India	Outcome measures	Perspective	Comparators	Findings
Mixed	Cost of averting an hour of diarrhea	Societal	2 mg/kg/d of zinc vs. 2 mg/kg/d of zinc, 0.2 mg/kg/d copper vs. placebo	Increased cost of Rs 74.3 for averting an hour of diarrhea in the zinc supplemented group and Rs 169.2 in the Zn +Cu group, as compared with placebo. Total cost of diarrhea was Rs 952.6 for placebo, Rs 1,495.2 for zinc, Rs 1,657 for zinc and copper		
Rheingans et al. [25]	All India	Nationally representative	Cost per DALY averted	Not specified	RVV versus no vaccination	Cost per DALY averted US $82.98 (@2.50 per dose)
Rose et al. [26]	All India	Nationally representative	Cost per life year saved	Healthcare Societal	RVV vs no vaccination	US$ 165 per life year saved
Sowmyanarayanan et al. [27]	All India	Nationally representative	Cost of hospitalized diarrheal episode	Healthcare		
Household	No comparator considered (economic burden study)	Mean total cost of hospitalization per diarrheal episode at US$66 for any cause diarrhea and US$53.75 for rotavirus diarrhea. Mean expenditure for diarrheal episode for non-profit referral hospital and private hospitals were 6,634 Rs and 6,071 Rs, respectively. For non-profit low-cost/concessional hospital and government hospital were 1,869 Rs and 233 Rs, respectively.				
Tate et al. [28]	All India	Nationally representative	Hospital and outpatient costs	Healthcare	No comparator	India spends Rs 2.0–3.4 billion (US$ 41–72 million) annually in medical costs to treat rotavirus diarrhea
Verguet et al. [29]	All India	Nationally representative	Household expenditure averted	Societal	National RVV versus no vaccination	Household expenditure averted US$ 1.9 million (at US$2.50/dose). Total financial risk protection afforded decreased to $15,000, which would be among the bottom income quintile (27%)

millions of cost savings to the public sector in a single year, while RVV could result in annual savings to the public sector of US$216.5 million. A 72% uptake of the PCV vaccine could result in even higher cost savings to the public sector at US$309.8 million annually. When a 90% coverage scenario was analyzed (Appendix 6), the total annual cost savings for a single year were higher at US$411.9 million (Hib vaccine), US$387.3 million (PCV vaccine), and US $270.7 million (RVV).



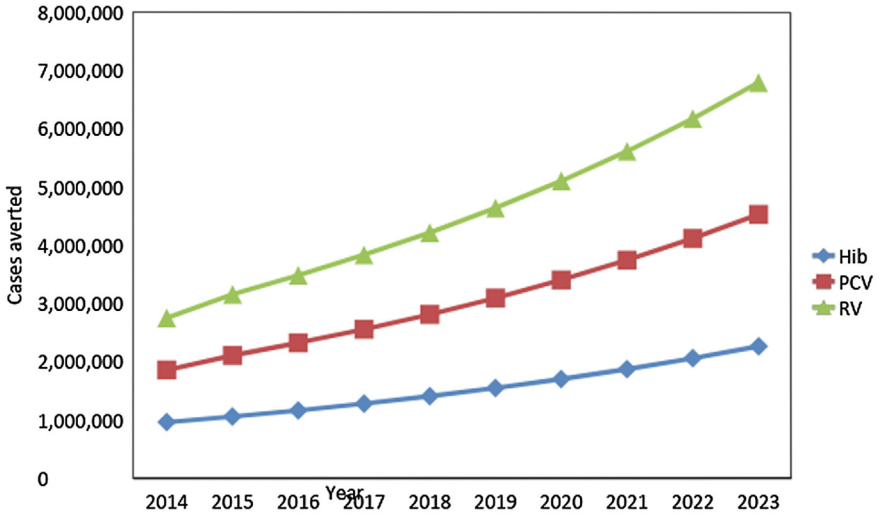
*This is based on a 90% vaccine coverage scenario from the public health sector perspective.

Fig. 2. Annual health impact of vaccine scale-up in selected states*.

Table 4
Annual health and economic benefits by state.*§

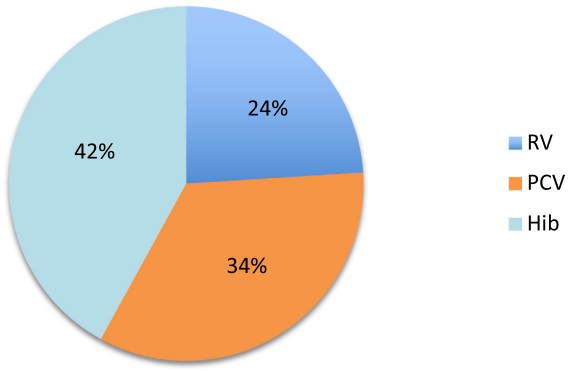
Diseases	Mortality and morbidity averted			Costs of illness averted (millions, US$ 2018)				
	Total deaths averted	Total cases averted	Total treatment costs averted	Total transportation costs averted	Lost caretaker wages averted	Lost productivity due to premature death averted	Lost productivity due to disability averted	Total costs averted
India	93,323	2,747,342	$8,364,346	$1,642,547	$1,506,369	$945,510,553	$112,819,528	$1,069,843,346
Bihar	13,560	397,901	$1,241,083	$237,970	$219,945	$137,388,561	$17,573,581	$156,661,141
Delhi	645	17,923	$62,739	$11,318	$10,475	$8,537,617	$839,006	$7,461,155
Maharashtra	1,598	46,474	$157,746	$27,820	$26,274	$16,194,684	$2,200,606	$18,661,141
Tamil Nadu	1,307	39,004	$114,213	$23,288	$20,771	$13,245,316	$1,495,078	$14,898,578

* Combines rotavirus vaccine (RVV), *Haemophilus influenzae* type b (Hib) and pneumococcal pneumonia and meningitis.
§ This is based on a 90% vaccine coverage scenario (US$ 2018, public sector).



*This is based on the period 2018-2029 for vaccines against rotavirus (RV), pneumococcal disease (PCV) and *Haemophilus influenza* type b (Hib) in India

Fig. 3. Cumulative health benefits by vaccine and year in India*.



*Corresponding to the public health sector

Fig. 4. Proportion of total savings from Hib, PCV and RVV vaccine scale-up (2018–2029)*.

Of the total annual savings of the PCV vaccine, the majority was attributable to averted productivity loss (Table 4). Loss of productivity resulting from morbidity accounted for 12% of the total cost. Caretaker productivity loss from seeking care represented the smallest portion of total costs of disease. Most importantly, lost productivity due to premature pneumococcal death was estimated at 85% of total costs averted. These economic benefits were realized by saving 32,245 lives and 959,696 annual cases of pneumococcal pneumonia and meningitis at 90% vaccine coverage. The rapid uptake of immunization against Hib and rotavirus in India could yielded similar results.

Vaccines against pneumonia were the largest contributor to the total costs of illness estimates, representing approximately 76% of the annual costs averted. This was followed by meningitis with 20% annual costs averted and diarrhea with 4%. Across the three vaccination programs and coverage scenarios, the majority of the cost savings were attributable to averted lost productivity due to premature death (Table 4). This may have implications for the recent declines in childhood mortality and advocacy.

3.4. Differences across states

There are notable differences in both health and economic benefits across states. The greatest savings to the public sector were realized in the state of Bihar where the burden of disease was high. Table 4 shows the economic impact of Hib, PCV and RVV vaccine scale-up combined in selected states in India based on 90% vaccination coverage. Of the states studied, Bihar maintained the highest economic benefit to the public sector from higher burden of disease, at $156.7 million. This was followed by Maharashtra at US$18.7 million, Tamil Nadu at US$14.9 million and Delhi at US $7.5 million.

The economic burden of disease varied widely among the selected states in India. For example, in Bihar, 75% of all treatment costs averted were due to either Hib or PCV. In Tamil Nadu this proportion was 65%. Vaccines against pneumonia had the greatest economic benefits in treatment costs saved in all but Tamil Nadu, where pneumonia was second to diarrhea. Specifically, pneumonia vaccines averted almost 75% of all treatment costs in Bihar.

Annual estimates of lost productivity resulting from severe meningitis disability also varied among the states. Bihar maintained the largest savings at US$156.7 million (Table 4). Lost productivity due to premature death averted contributed the most to the savings at US$137.4 million, followed by lost productivity due to disability averted at US$17.6 million.

3.5. Deterministic sensitivity analyses (DSA)

DSA evaluated the influence of specific inputs on the health and economic benefits of vaccination by varying these inputs across plausible ranges. The analyses identified important uncertainties about the assumptions that are likely to influence the estimates of the vaccine impact. In general, the model was most sensitive to estimates of CFRs, proportion of syndromic deaths attributable to Hib, Spn, and rotavirus, and estimates of vaccine impact on disease. The level of influence of key parameters on total costs averted varied depending on the vaccination program and vaccine coverage scenario.

The tornado diagrams in Figs. 5–7 show the effect of each variable on the output, based on a 90% vaccine coverage scenario. The bars to the right indicate that the output was influenced toward higher values (e.g. total costs averted), whereas the bars to the left indicate that the output was influenced toward lower levels. The widest bars at the top of the tornado diagram indicate the variables that had the most impact on the model outputs.

For the Hib vaccination (Fig. 5), CFR estimates caused the greatest variation, causing an increase in the cost savings results. Other key parameters that were sensitive to the total costs averted included estimates of the pathogen specific (or etiologic) proportion of deaths due to pneumonia and proportion of pneumonia deaths.

For PCV vaccination (Fig. 6), the parameters that were most sensitive to the total costs averted included vaccine efficacy, proportion of deaths due to disease and CFR estimates. The first three top bars lean more toward the right indicating that the outputs for PCV vaccination were influenced toward higher total costs averted.

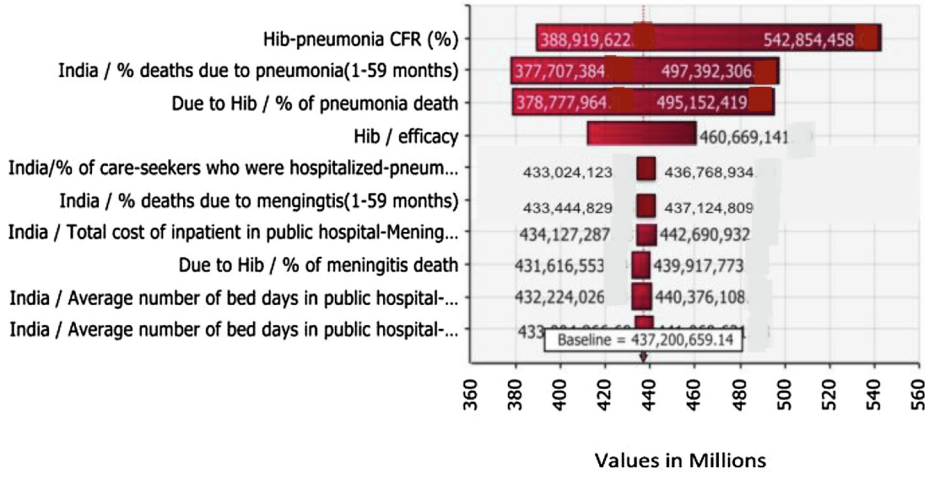
For rotavirus (Fig. 7), DSA showed that the proportion of deaths due to diarrhea and the proportion of deaths due to rotavirus as well as the size of the birth cohort were most sensitive to the total costs averted.

4. Discussion

Our study notes that more than $1.1 billion costs (uncertainty range: US$0.9-US$2.4 billion) can be saved as a result of vaccines such as Hib, PCV and RVV. The economic and disease impact can vary widely by state, vaccine and coverage levels. The evidence of the present evaluation suggests that introducing or scaling up immunization against Hib, Spn and rotavirus in India can also result in immediate benefits to the government and households in terms of preventing over 93,323 annual deaths and 2.7 million annual cases. Saving the lives of over 90,000 children translates into savings the lives of 260 children every day in India and 1 child every 6 min. Similarly, preventing 2.9 million cases of illnesses means almost 8,000 cases per day or 6 cases every minute are avoided. Immediate economic benefits can also be demonstrated from averting treatment costs. For example, although the overall treatment savings of US$8.3 million were considerable for pneumonia, meningitis and diarrhea, gains from increased productivity due to the PCV vaccine were far greater, reaching US$946 million, or 88% of the total costs. These findings underscore the importance of looking beyond treatment cost savings.

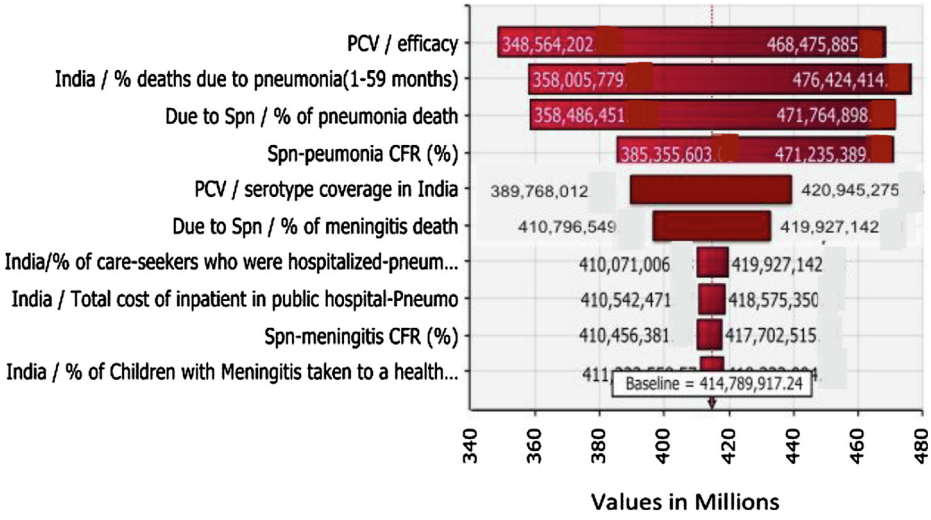
The study revealed differences in the epidemiology of the disease and cost estimates that play an important role in vaccine decision-making. Costs saving estimates within states were due to cost differences and variation in utilization patterns. The disease costs attributable to Hib, Spn and rotavirus increased with disease burden. This explained the higher costs in the state of Bihar. While costs were lower in states like Delhi and Tamil Nadu, the relative impact of these costs were still substantial in these states. Improved estimates of epidemiological burden, state-level treatment costs, and societal costs may provide improved estimates of the epidemiological and economic burden of the vaccine-preventable diseases in question.

A number of important limitations need to be borne in mind when interpreting the results of this study. The key is related to the availability of country- and state-specific epidemiological and



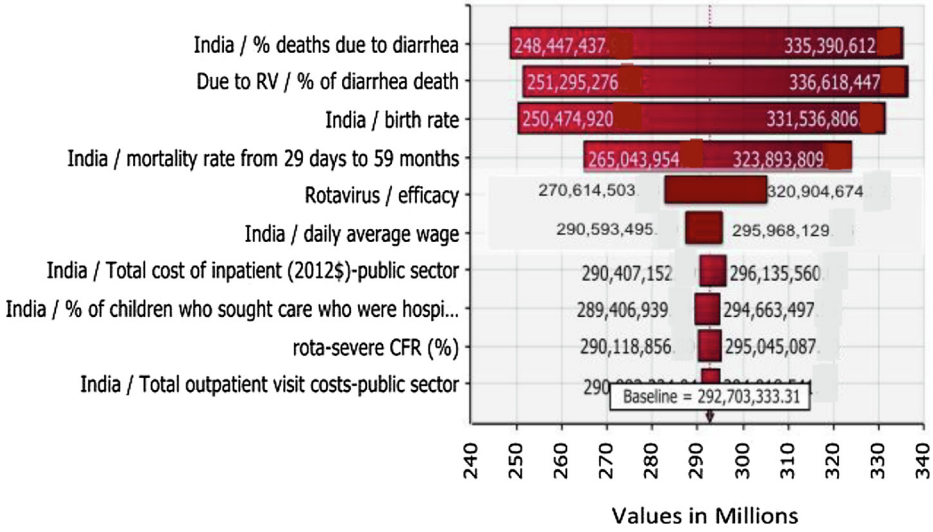
*This is based on a 90% vaccine coverage scenario from the public sector perspective (in Rs 2018)

Fig. 5. Tornado diagram showing the influence of key parameters on total costs averted due to Hib vaccination in India*.



*This is based on a 90% vaccine coverage scenario from the public sector perspective (in Rs 2018)

Fig. 6. Tornado diagram showing the influence of key parameters on total costs averted due to PCV vaccination in India*.



*This is based on a 90% vaccine coverage scenario from the public sector perspective (in Rs 2018)

Fig. 7. Tornado diagram showing the influence of key parameters on total costs averted due to RV vaccination in India*.

cost estimates and, specifically estimates of CFRs of children under 5 years, and the distribution of mortality by disease in this age group. Likewise, there was uncertainty around the estimates of vaccine efficacy. Estimates of health benefits were likely to be underestimates as a result of these data limitations. These estimates were the largest contributors of uncertainty in the current analysis.

The current analysis did not consider the programmatic costs of improving vaccine delivery, as the goal was to evaluate the economic benefits of vaccines. The health care-seeking data (i.e. public versus private) and treatment costs at the state level was limited. Moreover, there was uncertainty on who incurred the costs of health care in India. It was not possible to identify with certainty who were the beneficiaries of cost savings or increased productivity. In the current analysis we assumed that 21% of health care is public and the remaining 79% is private based on expert opinion. Our annual treatment cost estimates for pneumonia, meningitis and diarrhea were not comparable to the results of previous economic studies largely due to differences in methodology.

The greatest gap in evidence emerged in measuring vaccine benefits. No papers that measure the household benefits to avert catastrophic health expenditures were available in India at the time of the analysis, and none that measured the value of lives saved and the labor productivity loss averted due to vaccines. Measures of societal benefits from vaccines, including GDP gains, disease outbreaks averted, life expectancy gains, changes in population and fertility and benefits of human capital investment, were also not available.

Overall the assumptions behind the reported health and economic benefits of Hib, PCV and RVV vaccination varied greatly from previously published studies, making direct comparisons of the costs and benefits of vaccination difficult. The current analysis did not include benefits of increased productivity from better cognition or improved child development/health, educational

achievement or economic returns from reduced fertility, pain or suffering. Other study limitations related to the exclusion of costs borne by families for treatment of disease in less formal settings. Treatment costs borne by families in less formal settings included treatment at home or by traditional healers.

We were not able to address the cost of procuring and distributing vaccines or to estimate the cost-effectiveness ('value for money') of these vaccines and these vaccines may not be affordable. Even a vaccine that provides good value for resources invested may have prohibitive financial requirements that make it difficult for countries like India to adopt these vaccines. More primary data need to be collected to strengthen the assumptions in this area.

While there is established and growing evidence about the health benefits of these three vaccines worldwide, there was paucity of information regarding the economic benefits of vaccines in India. In terms of costs, limited data are available in India on the opportunity costs incurred by households to become vaccinated, costs of enhanced surveillance and training incurred by the health system, and research and development costs that were not fully offset by vaccine prices. As for treatment savings, there was limited information on costs saved and breakdowns between who benefits from these treatment savings, and little consensus on how to model societal level treatment costs.

Another important limitation was the assumption that there was even distribution of the risk of death across the population when applying vaccination coverage. In reality, vaccines would most likely reach those at the least risk of dying given health care infrastructure unless concerted efforts are made by the government to reach those in the greatest need (or those who have the least access to health care).

Few studies have been published that show the relative value of vaccines against Hib and rotavirus in India, and some that show the relative value of these vaccines across states in India. This is the first study to quantify systematically the level of economic benefits of vaccines against Hib and pneumococcal pneumonia and meningitis and rotavirus diarrhea for India and in 4 states in India. The results can be used by country-level and state-level stakeholders to assess the returns on investment in immunization against three important diseases in India.

5. Conclusion

Expanding the use of immunization against Hib, Spn and rotavirus could save US$412 million in the treatment of these diseases, including US$3.9 million in treatment costs. Adding long-term productivity gains resulting from lost productivity due to premature deaths were estimated to reach US$327 million. This analysis provides both national and state-level decision makers with estimates of the tangible monetary benefits that could be accrued by increasing investments in Hib, PCV and RVV immunization. This evidence underscores the importance of vaccines against these childhood diseases to support continued immunization against these childhood diseases as India prepares to transition from Gavi support and begins to bear the immunization program costs.

Authors' contributions

DC guided the study design and conducted the analysis. TL conducted the searches and abstracted data from literature and developed the model with guidance from DC. DC conducted the analysis. DC also wrote the manuscript and created the tables and figures. NA provided review of the manuscript.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.09.084.

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