Vaccine 32S (2014) A140–A150

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Estimated impact and cost-effectiveness of rotavirus vaccination in India: Effects of geographic and economic disparities

Richard Rheingans[a,*], John D. Anderson IV[b], Benjamin Anderson[b], Poulomy Chakraborty[b], Deborah Atherly[c], Deepa Pindolia[d]

[a] Department of Environmental and Global Health, Center for African Studies, Emerging Pathogens Institute, University of Florida, Gainesville, FL, USA
[b] Department of Environmental and Global Health, Emerging Pathogens Institute, University of Florida, Gainesville, FL, USA
[c] PATH, Seattle, WA, USA
[d] Department of Geography and Emerging Pathogens Institute, University of Florida, Gainesville, FL, USA

ARTICLE INFO

Article history:

Keywords:
Rotavirus
India
Cost-effectiveness
Equity
Disparities
Vaccination

ABSTRACT

India accounts for 23% of global rotavirus mortality in under-five children, with more than 100,000 deaths from rotavirus annually. Introduction of a vaccine in India is considered to be the most effective intervention for preventing rotavirus mortality. Recent research suggests that there is considerable variation in rotavirus mortality burden across regional, gender and socio-economic subpopulations within India. In addition, there is potential variability in who would likely receive rotavirus vaccine if introduced. We use available household data to estimate heterogeneity in rotavirus mortality risk, vaccination benefits, and cost-effectiveness across geographic and socio-economic groups within India. We account for heterogeneity by modeling estimated three-dose routine vaccinations as a proxy for a generalized rotavirus vaccine, and mortality for subpopulations of children aggregated by region and state, socio-economic status and sex, separately. Results are presented for six geographic regions and for Bihar, Uttar Pradesh, and Madhya Pradesh, three high mortality states accounting for 56% of national mortality estimates. Impact estimates accounting for disparities predict rotavirus vaccine introduction will prevent 35,000 deaths at an average cost of $118/DALY averted (7292 INR/DALY averted). Rotavirus vaccines are most cost-effective for the poor living in high mortality regions and states. Reductions in geographic and socio-economic disparities based on regional estimates could prevent an additional 9400 deaths annually, while reductions in socio-economic disparities in the three highest morality states alone could prevent an additional 10,600 deaths annually. Understanding the impact of heterogeneity can help improve strategies to maximize the benefits of rotavirus vaccination introduction, leading to fewer lives lost as a result of rotavirus disease.

1. Introduction

Diarrheal deaths are the second leading cause of child mortality accounting for 15% of the global under-five child mortality burden [1]. It is estimated that 39% of these diarrheal deaths, which occur mainly in middle and low income countries, are due to rotavirus infection [2]. Realizing the pressing need to prevent childhood diarrheal mortality and morbidity, WHO recommended the introduction of rotavirus vaccines in countries with high population vulnerability, including India [3]. India alone accounts for 23% of global rotavirus mortality, with 100,000 rotavirus deaths annually [4]. Apart from improvements in water, sanitation, nutrition and public health conditions, introduction of a vaccine in India is considered to be the most effective intervention [5,6].

Development of rotavirus vaccines shows potential for significantly reducing rotavirus burden. Initial estimates of health impact and cost-effectiveness of rotavirus vaccine introduction in India showed the vaccine to be cost effective [5,7–9] and protective [10]. However, decisions regarding nation-wide introduction require the best and most recent data on disease burden, vaccine delivery, costs and effectiveness [11,12]. Geographic differences in burden require

* Corresponding author at: Department of Environmental and Global Health, Center for African Studies, Emerging Pathogens Institute, University of Florida, Box 100188, 101 S. Newell Dr, Room 2148, Gainesville, FL 32610, USA.
Tel.: +1 352 294 5110; fax: +1 352 273 6070.
E-mail addresses: rrheing@epi.ufl.edu, rrheing@ufl.edu (R. Rheingans), j5anders@epi.ufl.edu (J.D. Anderson IV), ander88@epi.ufl.edu (B. Anderson), poulomyc@epi.ufl.edu (P. Chakraborty), datherly@path.org (D. Atherly), dpindolia@gmail.com (D. Pindolia).

http://dx.doi.org/10.1016/j.vaccine.2014.05.073

ongoing surveillance to maximize vaccine effectiveness [13] and will be especially important in India.

Recent research suggests that the burden of rotavirus mortality within India differs across states and regions [14]. At the state level, the highest rates of rotavirus mortality are found in Bihar, Uttar Pradesh and Madhya Pradesh, jointly accounting for more than half of rotavirus deaths in India. Regionally, rotavirus deaths are highest in central India, followed by northern, while lowest in western India. In addition to regional heterogeneity, rotavirus mortality rates amongst girls (4.89 deaths/1000 live births) in India are found to be 42% higher than amongst boys (3.45 deaths/1000 live births) [14]. Socio-economic differences play a role as well. Known individual risk factors associated with diarrheal mortality such as being undernourished [15] and scoring low on composite measures of anthropometric failures occur more often in poor households in India [16].

Past research in India has revealed regional, socio-economic and gender disparities in routine immunization rates [17,18]. Socio-economic disparities in burden are found to correspond with disparities in access to routine vaccination, with children belonging to the poorest households having the highest rotavirus deaths and the lowest estimated vaccination rates [7]. Gender-based disparities in rates of childhood immunization have been shown as well; girls are reported to have lower vaccination rates than boys and, similar to rotavirus mortality, there is significant variation across states and regions [19,20]. Moreover, girls at higher birth orders are found to have a greater chance of missing vaccination doses, than boys [21]. These disparities, left unchanged, reduce the potential impact and cost-effectiveness of rotavirus vaccination [7].

The purpose of this study is to use the best available data on rotavirus mortality, health care cost, vaccine access, and efficacy to estimate the impact and cost-effectiveness of rotavirus vaccination across different geographic and socio-economic settings in India. We also examine alternative strategies for increasing the impact of vaccine introduction.

2. Materials and methods

2.1. Overview

We use a spreadsheet-based model developed in Microsoft Excel [22] to estimate the expected health and economic outcomes for one annual birth cohort of children during the first 5 years of life. Due to the known heterogeneity by geography, socio-economic level and gender, we model a series of sub-populations separately. Specifically, we consider six geographic regions (based on Morris et al. [14]), together representing all of India, separately, and independently calculate results for three high mortality states (Bihar, Uttar Pradesh, and Madhya Pradesh). Within each geographic area we group children into five wealth quintiles based on asset index [23]. As a result, the modeling unit of analysis is geographic area × wealth quintile × sex.

Future outcomes are discounted at 3% and costs are estimated in 2013 US dollars.

2.2. Burden of rotavirus mortality

Overall estimates of rotavirus mortality by region, state and sex are taken from Morris et al. [14] (Table 1). However it is likely that there is substantial heterogeneity in rotavirus mortality risk within these groups due to differential nutritional status and access to basic care for diarrheal disease, based on socio-economic status. As a result, we developed an evidence-based individual risk index to estimate the relative distribution of mortality within these region-sex populations.

We used data from the 2005 to 2006 India National Family Health Survey III (NFHS-3) [24] to calculate individual risk index values as well as mean values for each subpopulation, accounting for complex survey design in Stata (version 12) [25]. The risk index assumes that an individual child's risk of rotavirus mortality is a function of the child's nutritional status (as measured by weight-for-age) and the likelihood of receiving rehydration if he/she experiences a diarrheal event. The existing literature suggests that both factors are strongly and quantitatively linked to diarrheal mortality (although not specifically rotavirus mortality) [15,26]. A nutritional risk factor was developed for each child based on their weight for age and a linearized estimate of relative risk from Caulfield et al. [15] (WFA_i). Since data on rehydration is only available for children with an episode of diarrhea in the previous 2 weeks we estimated the individual propensity for receiving rehydration by fitting a logistic regression model to predict rehydration based on age, asset index score, gender and state. We then used the PREDICT function in Stata (version 12) [25] to estimate the propensity for all children ($PrORS_i$). The individual risk factor for rehydration was calculated for each child as the product of their propensity score and 0.07 (β_{ORS}), based on the estimated 93% effectiveness of appropriate rehydration from Munos et al. [26]. For each region (r) wealth quintile (q) and sex (s) sub-population, the mean risk index was calculated based on Equation (1).

$$RVRiskIndex_{r,q,s} = \frac{\sum_i^{N_{r,q,s}} \beta_{ORS} \cdot PrORS_i \cdot WFA_i}{N_{r,q,s}} \quad (1)$$

In order to test this individual risk model, we examined the correlation between state-wide averages generated as described above, with the statewide mortality estimates from Morris et al. [14].

In order to estimate the distribution of rotavirus mortality within geographic-economic-gender subpopulations we combined the risk index and the mortality estimates by geographic area and gender from Morris et al. [14]. The risk index for each wealth quintile was normalized by dividing by the mean risk index for the corresponding geographic area and gender subpopulation (Equation (2)). This ensures that the total mortality for any geographic area and gender is the same as Morris et al. [14], while maintaining an estimated distribution across wealth quintiles based on individual risk factors and quantitative relative risk estimates from the literature. Rotavirus mortality burden is estimated as deaths per 1000 live births.

$$RVBurden_{r,q,s} = \frac{RVMort_{r,s} \cdot RVRiskIndex_{r,q,s}}{RVRiskIndex_{r,s}} \quad (2)$$

All subpopulation means were calculated using appropriate sample weights based on the design of each survey.

Mortality risk was converted into Disability Adjusted Life Years (DALYs) based on standard methods using age weighting and discounting [27,28]. Previous studies have shown that over 98% of DALYs associated with rotavirus diarrhea in low income settings are associated with mortality [29,30], as a result we have not estimated DALYs associated with morbidity from acute cases.

We estimated timing of projected deaths by combining overall rotavirus mortality estimates for each subpopulation and the estimated age distribution of events from Morris et al. [14], combined with additional data from Clark and Sanderson [31,32]. Monthly rates were estimated for the first year of life, and annually for the subsequent 4 years of life. For any subpopulation and period t, mortality burden is estimated in Equation (3), as:

$$RVBurden_{r,q,s,t} = RVTime_t \cdot RVBurden_{r,q,s} \quad (3)$$

where $RVTime_t$ is the fraction of deaths occurring in time period t.

Table 1
Input values, ranges, and references for variables used in the analysis.

Input	Value**	Range	Reference
Rotavirus mortality	Deaths		
National rotavirus mortality rate among children under 5 (deaths/1000 live births)	4.1	3.1–5.7 99% CI; lognormal distribution	[14]
Regional and state rotavirus mortality rate	Various	Lognormal distribution with 99% CI proportional to national estimate	[14]
Risk factors for mortality by sub-group†			[24]
RV vaccine – efficacy			
Full course (three doses) – 1st year	50%	40–60%; triangular	[8,47]
2 Dose – 1st year	25%	15–35%; triangular	Assumption
1 Dose – 1st year	10%	0–20%; triangular	Assumption
Full course (three doses) – Year 2 and later	45%	35–55%; triangular	
2 Dose – Year 2 and later	25%	15–35%; triangular	
1 Dose – Year 2 and later	10%	0–20%; triangular	
Vaccination			
1, 2, and 3 dose coverage (by sub-group)	Various		[34]
Vaccination timing (by sub-group)	Various		[33]
Medical costs			
Mean medical cost per child (US$)	$2.50	$1.25–3.75; triangular	[40,41]
Healthcare utilization by sub-group			[24]
Pharmacy	$0.47		[42]
Healer	$0.47		[42]
Public (in/out patient)	$1.81		[40,41]
Private out patient	$3.04		[41]
Private in patient	$74.98		[40]
Vaccine costs			
Dose (US$)	$1.25	$0.50–$1.50; triangular	Assumption
Administration (US$)	$1.25	$0.50–$1.50; triangular	[8]

† NFHS risk factor index sample size (range across regions) = 8263 1-year-olds; 4363 boys (503–1126) and 3900 girls (430–1017).
** 1 2013 US$ = 61.8 2013 Indian rupees (INR).

2.3. Vaccination coverage and effectiveness

We estimated the coverage of a 'generalized' 3-dose rotavirus vaccine that would be delivered alongside DPT1–3 through a routine immunization program. Vaccine effectiveness was estimated for each subpopulation based on estimated coverage of each of three doses, the expected timing of receiving each dose, and expected efficacy of each dose over time.

Vaccination coverage was estimated by geographic area, gender and wealth quintile. Due to concerted national and state efforts, coverage of routine vaccinations in India is rapidly improving. We used three alternative sources to estimate coverage: 2005–2006 NFHS-3 [24], 2007–2008 District Level Health Survey (DLHS-3) [33], and the 2009 Coverage Evaluation Survey (CES) [34]. A fourth survey, the Annual Health Survey [35–37], was also consulted but it does not provide national estimates and was used descriptively. For the NFHS and the DLHS3, we estimate coverage of DPT1, DPT2 and DPT3 for each geographic area r, sex s and wealth quintile q sub-population.

Vaccination timing was estimated for all three doses using vaccination data for 1-year-olds from DLHS-3. Specifically, for each subpopulation we estimated the proportion of children receiving each dose by the end of each time period t. For any subpopulation, the coverage for each dose d was defined in equation (4) as the product coverage and the likelihood of receiving it by a given period t.

$$Cov_{d,r,q,s,t} = Dose_{d,r,q,s} \cdot Time_{d,r,q,s,t} \quad (4)$$

This model is intended to be generalized, rather than pertaining to a single particular vaccine. As a result, we assumed efficacy that is similar to recent published estimates [10] and assumed the same efficacy in each subgroup. Vaccine efficacy was estimated for 1, 2, and 3 doses to account for incomplete courses and rotavirus events that might occur between doses. During the first year we assumed an efficacy of 50% for a full course, and 10% and 25% efficacy for 1 and 2 doses [5,38]. We also assumed a 10% waning in efficacy (to 45%) during subsequent years [39]. Full assumptions are shown in Table 1.

Vaccination effectiveness and benefit were estimated for each subpopulation by combining information on the coverage and efficacy of each dose by time period with information on the expected burden over time.

$$VacBenefit_{r,q,s} = \sum_{d,t} Cov_{d,r,q,s,t} \cdot VacEff_{d,t} \cdot RVBurder_{r,q,s,t} \quad (5)$$

where $VacEff_{d,t}$ is the incremental protection of each dose d during time period t.

The method described above accounts for the correlation between individual risk and vaccine access at the region-quintile-sex sub-group level, however it implicitly assumes that risk and access are not correlated *within* each subgroup. We tested this assumption by examining the correlation of DTP2 coverage and risk index within each subgroup.

Estimating the expected benefits at current coverage levels, we also estimated the potential benefits if all geographic-economic sub-groups had the same mortality reduction as the highest coverage group (South, middle quintile, 40%). The difference between these potential benefits and expected benefits were defined as the health consequence of coverage disparities.

2.4. Economic outcomes

Patterns of healthcare utilization for diarrheal treatment vary geographically and by socio-economic status. As a result, direct medical costs for rotavirus treatment are expected to vary as well. However, limited data are currently available on the extent of variability. In order to account for this heterogeneity in cost we combined published estimates of overall rotavirus direct medical costs [40,41] per child with an estimate of the relative cost per child in each geographic and economic setting [42] (Table 1).

We estimated the distribution of costs among children based on the pattern of care seeking (NFHS-3) weighted by estimated cost of each treatment type (Table 2). While consistent data are

Table 2
Distribution of treatment sought for diarrheal episodes for children 12–23 months of age by wealth status, setting and region.

	Wealth quintiles					Setting		Region					
	Poorest	Second	Middle	Fourth	Richest	Urban	Rural	North	Central	East	Northeast	West	South
Treatment % (SE)													
None	33.0 (4.5)	29.5 (3.7)	24.8 (3.8)	19.1 (3.5)	15.3 (3.7)	22.7 (2.8)	26.8 (1.9)	19.5 (3.4)	25.4 (2.7)	25.2 (3.7)	46.9 (4.6)	22.8 (3.7)	29.4 (4.2)
Public inpatient													
Hospital	3.6 (1.6)	3.0 (1.4)	9.3 (2.4)	6.6 (1.6)	5.1 (2.2)	10.2 (1.8)	3.4 (0.8)	5.3 (1.6)	4.2 (1.2)	3.6 (1.4)	2.6 (0.8)	4.7 (1.7)	13.2 (3.1)
UHC	0.0 (0.0)	–	–	–	–	–	–	–	–	–	–	–	–
CHC	9.1 (2.4)	6.9 (2.0)	6.7 (2.4)	5.4 (2.0)	5.5 (2.1)	4.5 (1.3)	7.9 (1.1)	4.4 (1.3)	6.1 (1.6)	6.4 (1.5)	3.9 (1.5)	10.3 (2.9)	8.6 (2.6)
Public outpatient													
Dispensary	0.4 (0.0)	0.4 (0.4)	0.8 (0.4)	1.8 (0.5)	1.0 (0.5)	1.3 (0.4)	0.6 (0.2)	8.6 (2.0)	–	0.1 (0.1)	3.7 (2.4)	–	0.8 (0.8)
Mobile clinic	–	0.7 (0.8)	–	0.8 (0.9)	–	–	0.4 (0.3)	–	0.4 (0.4)	–	–	0.9 (0.9)	–
ASHA	–	–	–	–	–	–	–	–	–	–	–	–	–
Sub-centre	2.1 (1.2)	3.0 (1.5)	1.4 (1.1)	0.2 (0.2)	–	–	2.1 (0.6)	–	2.6 (0.9)	1.2 (0.8)	1.7 (1.0)	1.6 (1.1)	–
Camp	–	0.0 (0.0)	0.1 (0.1)	–	–	0.1 (0.1)	0.0 (0.0)	0.2 (0.2)	–	–	0.2 (0.2)	–	–
Anganwadi	1.9 (1.3)	1.3 (0.9)	–	0.8 (0.7)	–	–	1.3 (0.5)	–	0.3 (0.3)	2.2 (1.1)	0.4 (0.4)	0.7 (0.7)	0.8 (0.8)
Other public	–	0.7 (0.8)	–	0.7 (0.5)	–	0.2 (0.2)	0.3 (0.2)	–	–	0.7 (0.6)	2.3 (2.2)	–	–
Private inpatient													
Hospital	3.1 (1.6)	5.0 (1.5)	9.2 (2.8)	14.4 (3.0)	28.6 (4.2)	18.1 (2.6)	7.5 (1.1)	16.2 (3.0)	4.9 (1.2)	4.3 (1.7)	3.1 (1.4)	17.5 (3.4)	29.1 (4.6)
NGO Hospital/Clinic	0.0 (0.0)	0.5 (0.6)	–	–	–	0.0 (0.0)	0.2 (0.2)	–	–	–	0.3 (0.2)	0.7 (0.7)	–
Private outpatient													
Doctor/Clinic	31.8 (5.1)	31.2 (3.9)	34.2 (4.7)	39.5 (4.6)	41.9 (5.2)	35.4 (3.0)	34.8 (2.3)	35.1 (4.1)	42.3 (3.1)	32.0 (4.7)	11.2 (3.4)	38.0 (4.4)	22.4 (3.8)
Paramedic	0.7 (0.8)	0.2 (0.3)	0.6 (0.4)	0.9 (0.5)	0.4 (0.5)	0.2 (0.2)	0.7 (0.3)	5.2 (1.9)	0.6 (0.4)	0.2 (0.2)	0.1 (0.1)	–	–
Homeopathic	1.3 (1.3)	1.5 (1.0)	1.4 (1.2)	0.7 (0.6)	1.3 (1.1)	1.0 (0.6)	1.4 (0.5)	1.3 (0.9)	0.7 (0.5)	2.8 (1.3)	5.2 (3.1)	–	–
Private other	7.8 (2.5)	10.6 (2.7)	7.9 (2.8)	–	0.1 (0.2)	0.1 (0.1)	8.2 (1.3)	0.3 (0.3)	4.4 (1.2)	16.2 (3.3)	0.3 (0.2)	–	–
Pharmacy													
Pharmacy/store	0.7 (0.7)	3.6 (2.0)	2.1 (1.5)	2.3 (1.5)	0.9 (1.1)	0.9 (0.7)	2.3 (0.8)	0.9 (0.9)	2.4 (1.0)	2.1 (1.3)	–	2.5 (2.0)	0.7 (0.7)
Shop	6.0 (2.5)	3.5 (1.3)	4.7 (1.7)	7.4 (2.5)	3.0 (1.6)	7.1 (1.4)	4.2 (0.9)	4.3 (1.7)	6.7 (1.4)	6.2 (1.9)	18.4 (4.7)	0.7 (0.7)	–
Healer													
Traditional healer	1.1 (0.8)	0.6 (0.7)	1.0 (0.8)	–	–	–	0.8 (0.3)	–	0.9 (0.6)	0.3 (0.3)	–	0.7 (0.7)	0.7 (0.7)
Children (*N*)	244	256	274	288	239	481	820	188	335	232	238	165	143

not available for all of these categories we estimated the relative costs based on available published data (Table 1) and applied cost estimates to reported categories of treatment facility or provider in NFHS-3. Relative costs were then rescaled to have a mean of 1 and multiplied by the average cost per child from the literature (to ensure the same mean cost per child). Costs were estimated as a linear function of region, urban/rural, and wealth index, imputed for all children without data using the PREDICT function in STATA 12. The relative cost measure was then applied to the estimated national mean direct medical cost of rotavirus [41] to calculate a mean rotavirus cost by geographic and socio-economic setting.

Averted medical costs ($AvertCost_{r,q,s}$) were then estimated for each subpopulation by combining information on the coverage and efficacy of each dose by time period with information on the expected medical cost over time. All costs were adjusted to 2013 US$ (1US$ = 61.8 Indian rupees, INR).

$$AvertCost_{q,r,s} = \sum_{d,t} Cov_{d,r,q,s,t} \cdot VacEff_{d,t} \cdot MedCost_{q,r,s,t} \quad (6)$$

The incremental cost of the intervention ($IntCost_{q,r,g}$) includes vaccine and administration costs. Intervention costs were estimated assuming a baseline vaccine price of $1.25 (77.3 INR) per dose, wastage of 10% and an incremental administration cost of $1.25 per dose [8]. The cost parameters were varied in the sensitivity analysis (Table 1).

The main outcome measure was the incremental cost-effectiveness ratio ($ICER_{q,r}$), which was estimated for each geographic and economic subpopulation.

$$ICER_{q,r,s} = \frac{IntCost - AvertCost_{q,r,s}}{VacBenefit_{q,r,s}} \quad (7)$$

2.5. Sensitivity and uncertainty analysis

A series of analyses were conducted to assess the impact of uncertainty to predicted outcomes. One-way sensitivity analyses were used to estimate the effect of changes in individual input variables (ranges listed in Table 1). A probabilistic sensitivity analysis (PSA) using Monte Carlo analysis was used to assess the effect of simultaneous changes in multiple input variables. Key input variables were characterized as distributions (Table 1) and a simulation procedure using 10,000 iterations was conducted in Crystal Ball [43] to develop a distribution of estimated impact and cost-effectiveness by region. Lastly, specific scenarios were examined including on-time vaccination, equitable coverage, and full coverage.

In addition, we developed an "Equal risk" scenario where we assumed homogeneous RV mortality risk and treatment costs. We used this scenario to approximate the estimated benefits and cost-effectiveness ratio if inter and intra region disparities were not considered.

3. Results

3.1. Health and medical cost burden by setting

Estimated mortality and direct medical costs are shown for each region-quintile sub-group (Fig. 1a) and state-quintile sub-group (Fig. 1b). In the figures, each line represents a different region or state and each of the dots represent different wealth quintiles. Difference in mortality *among* regions reflects the differences estimated by Morris and colleagues [14]. Within all of the regions, children in poorer households had higher risk of mortality, due to reduced nutritional status and reduced likelihood of receiving rehydration. Conversely, within all regions children in richer households had a higher estimated direct medical cost burden (Fig. 1a and b).

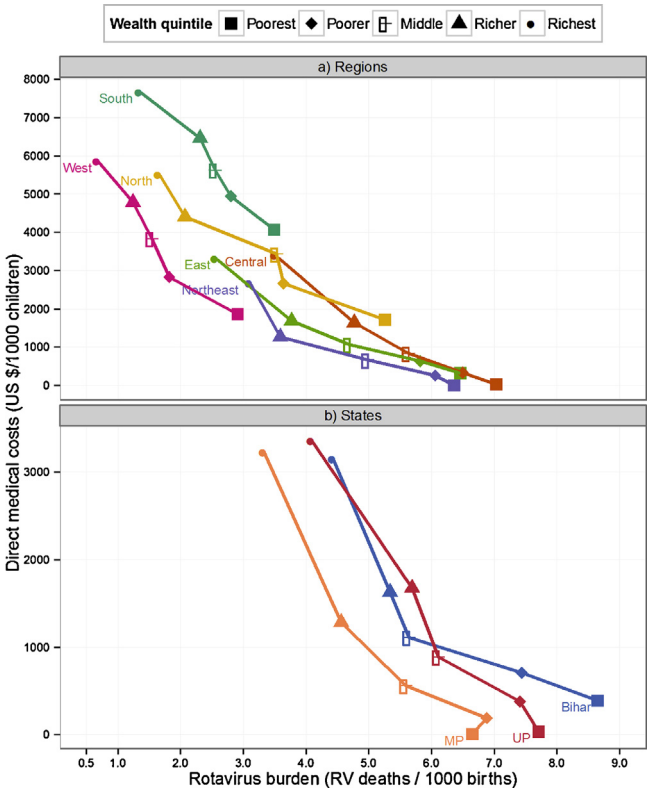

Fig. 1. a–b – Estimated direct medical costs and rotavirus mortality risk by geography and wealth quintile in India (MP = Madhya Pradesh, and UP = Uttar Pradesh).

This difference is driven by an increased likelihood of treatment and in particular increased utilization of private hospitals (Table 2). These differences were observed across the three high mortality states as well.

3.2. Impact of vaccination

We estimate that vaccine introduction will reduce rotavirus disease burden by 30% to 39% depending on the region, with the greatest percent reduction estimated in the South (39%), followed by the North (34%) and West regions (34%), Table 3. The absolute level of benefits (deaths averted per 1000 births) also varied across regions, ranging from 0.55 to 1.66 rotavirus deaths per 1000 births, with the highest benefits estimated in Central, Northeast, and East regions.

Impact varied substantially within regions as well. Fig. 2 shows the estimated effectiveness by geographical region and economic status. For all regions, the highest percent reduction in burden was estimated for the two highest wealth quintiles. The highest and most equitable reduction was estimated in the South, ranging from 38% to 40% across quintiles. Children in poorer households experienced higher mortality risk and lower levels of mortality reduction, particularly in the Central, East and Northeast regions. Estimated average risk for the poor in these three regions is 1.7 times higher with average mortality reductions of 28% as compared to 33% in other regions, respectively.

The estimated health benefits with current coverage and potential coverage are shown in Fig. 3. The highest potential additional benefits are among the high mortality regions and states, and particularly among the poorest quintiles. Nationally, increased coverage would increase benefit estimates by 23%, preventing 9400 additional deaths. In Bihar, Madhya Pradesh and Uttar Pradesh benefit estimates would increase by 55%, 76% and 71%, respectively, preventing 10,600 additional deaths. Among the poorest quintile

Table 3
Estimated impact, costs, and cost-effectiveness of rotavirus vaccination for regions and selected states in India based on data from CES 2009[a].

	Burden (RV deaths/1000 births)	Benefits (RV deaths averted/1000 births)	% Reduction	Costs averted ($/1000 births)	Vaccination costs ($/1000 births)	CER ($/DALY averted)	Equal risk benefits (RV deaths averted/1000 births)	Equal risk CER ($/DALY averted)
National	3.71	1.22	33.7	1089	6821	139	1.40	124
Region								
Central	5.49 (4.45, 6.83)	1.66 (1.32, 2.10)	30.3 (27.0, 33.0)	418 (248, 591)	6367 (3343, 11152)	105 (50, 199)	1.28	129
East	4.66 (3.78, 5.81)	1.40 (1.11, 1.77)	30.0 (27.0, 33.0)	462 (274, 657)	6340 (3336, 10995)	124 (58, 236)	1.28	128
North	3.23 (2.63, 4.01)	1.11 (0.88, 1.40)	34.2 (31.0, 37.0)	1304 (781, 1852)	6841 (3610, 11659)	147 (58, 291)	1.47	120
Northeast	4.82 (3.92, 6.01)	1.54 (1.23, 1.95)	32.0 (29.0, 35.0)	345 (205, 485)	6552 (3451, 11455)	118 (57, 223)	1.36	124
South	2.50 (2.03, 3.11)	0.97 (0.77, 1.22)	38.6 (35.0, 42.0)	2233 (1349, 3169)	7491 (3895, 12947)	160 (46, 349)	1.60	120
West	1.64 (1.33, 2.04)	0.55 (0.44, 0.69)	33.5 (30.0, 36.0)	1372 (811, 1937)	6937 (3655, 11941)	298 (117, 600)	1.44	124
State								
Bihar	6.30 (5.12, 7.81)	1.62 (1.29, 2.04)	25.7 (24.0, 28.0)	398 (236, 564)	5648 (2948, 9812)	95 (44, 181)	1.10	134
Madhya Pradesh	6.20 (4.38, 6.72)	1.44 (0.96, 1.53)	23.3 (20.0, 24.0)	388 (180, 425)	5253 (2573, 8278)	99 (53, 206)	0.97	129
Uttar Pradesh	5.40 (5.02, 7.77)	1.21 (1.14, 1.81)	22.5 (21.0, 25.0)	301 (232, 548)	4825 (2772, 9120)	110 (47, 189)	1.02	134

[a] Lower (5%) and upper (95%) bound estimates from the probabilistic sensitivity analysis in parentheses following means.

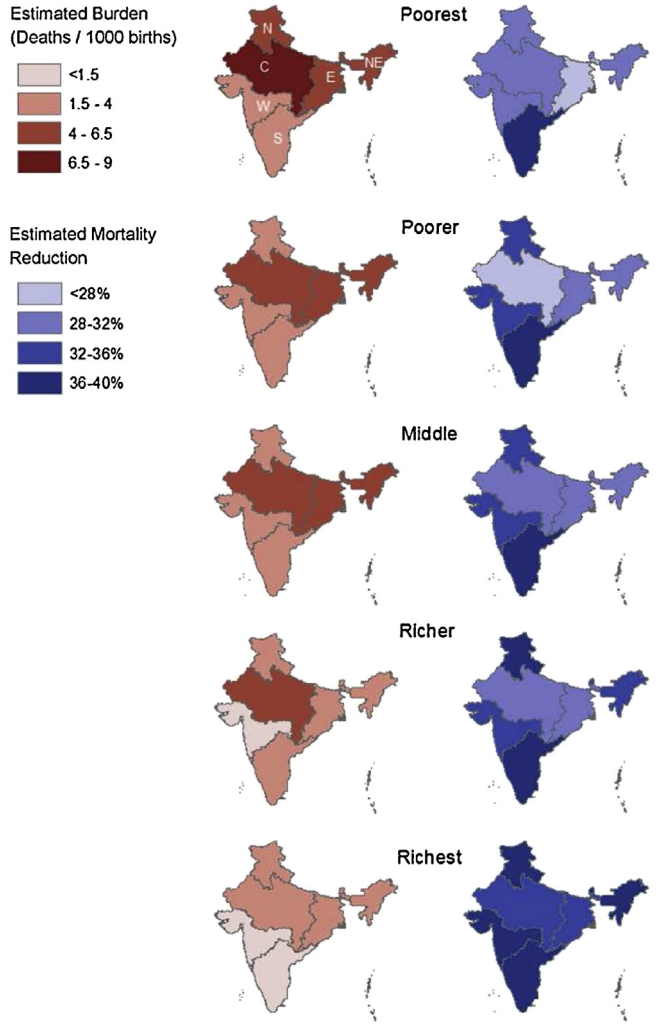

Fig. 2. Maps of estimated rotavirus vaccination effectiveness and burden in India. Region abbreviations: North (N), Central (C), East (E), Northeast (NE), West (W), South (S).

in these states alone, benefits would increase by 72%, 127%, and 121% preventing 3300 additional deaths.

The pattern of higher risk and lower vaccination impact is also reflected in the correlation between key risk factors and variables determining vaccine effectiveness (Appendix A). In the NFHS-3 survey, access to DPT 1, 2 and 3 are inversely correlated with low and very low weight for age, at a national level, as well as within regional-wealth sub-groups. It is also important to note that coverage and wealth are negatively correlated with the probability of receiving ORS. Both of these factors contribute to the underlying heterogeneity in risk and specifically higher risk in marginalized sub-populations.

3.3. Cost-effectiveness of vaccination

The incremental cost-effectiveness ratio (CER) by region ranged from $105 to $298/DALY averted (6489–18,416 INR/DALY averted), with the lowest (most favorable) ratio in the high mortality regions (Table 3). Cost effectiveness also varied within geographic areas as higher wealth quintiles typically had lower incremental costs (due to greater medical costs), yet lower health benefits (due to lower mortality). All ratios at the regional and state levels are substantially lower than the GDP per capita of $1490 in India [44],

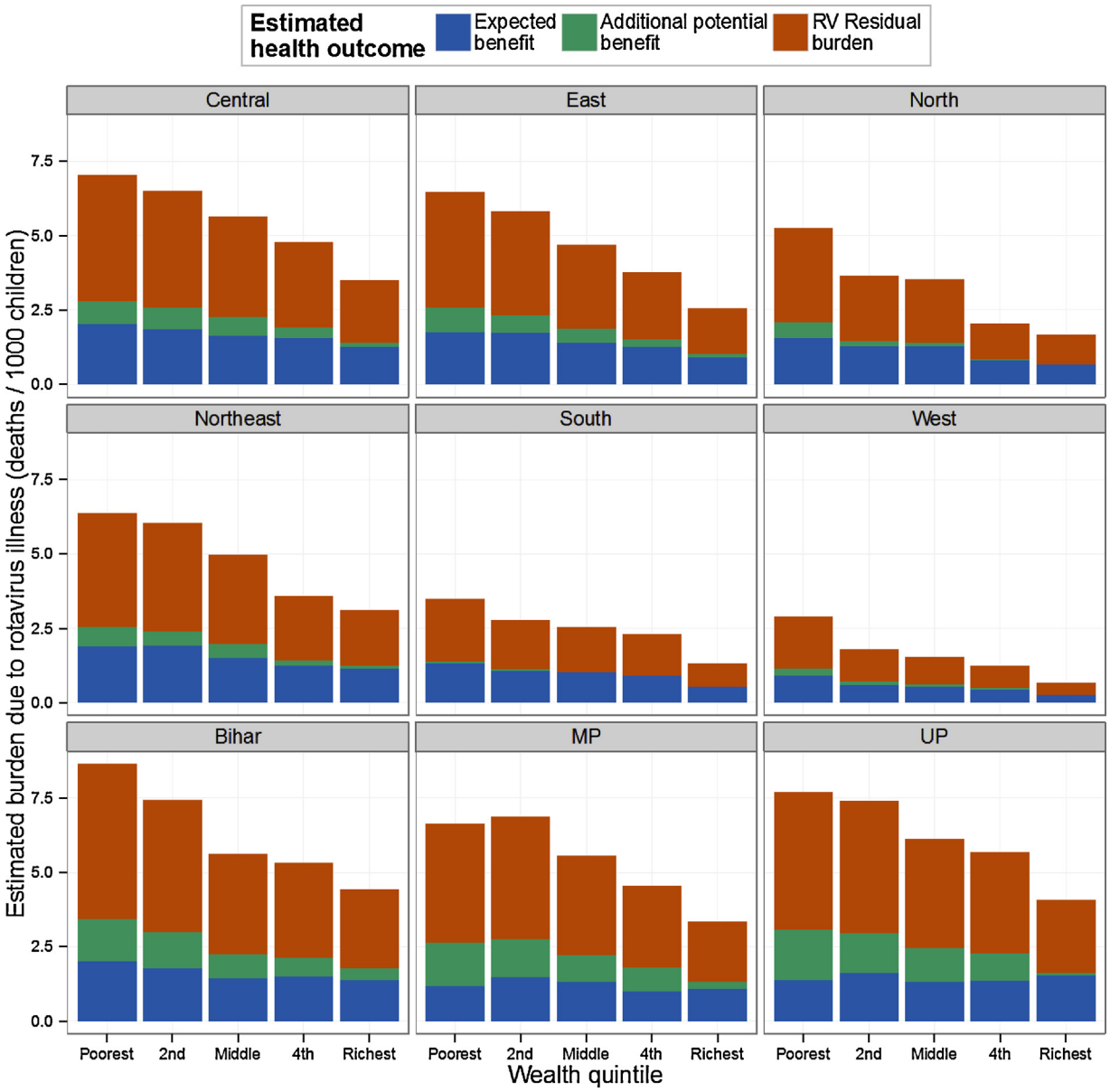

Fig. 3. Estimated potential impact and expected impact of rotavirus vaccination by geography and wealth (MP = Madhya Pradesh and UP = Uttar Pradesh). Additional potential benefit (green) is estimated by calculating the benefit as if all quintiles and regions had the same estimated vaccine effectiveness as the highest quintile (South, middle quintile: 40% effectiveness, see Fig. 2).

suggesting that rotavirus vaccines with the modeled characteristics would be highly cost-effective.

3.4. Sensitivity and uncertainty analysis

One-way sensitivity analysis was conducted to examine the effects of specific input variables on vaccination benefit and cost-effectiveness within each geographic area. The results for the impact on the cost-effectiveness ratio are shown in Fig. 4. For all regions, the variables with the greatest impact were vaccine administration cost, rotavirus mortality, and vaccine price, usually in that order. Mortality uncertainty was most important in higher mortality regions. Other variables had limited impact. The sensitivity analysis for vaccination benefit showed that rotavirus mortality accounted for the greatest uncertainty in impact (results not shown). We also examined the effects of specific scenarios on CER: on-time delivery of vaccine doses and uniform medical costs. On-time delivery reduced the CER in all regions (between 3 and 12 $/DALY averted, 185 and 742 INR/DALY averted). Assuming uniform medical treatment costs, resulted in increased CER in regions with higher healthcare utilization and decreased the CER in regions with low utilization.

The probabilistic sensitivity analysis was used to estimate uncertainty limits around key outcome variables within each geographic region. These are shown in Table 1. A contribution to variance analysis demonstrated that vaccination administration costs and rotavirus mortality uncertainty contributed approximately 50% and 25% respectively to the overall uncertainty of the CER, and rotavirus mortality contributed over 80% of the overall uncertainty of the health impact of vaccination.

The effect of accounting for disparities in mortality risk and costs can be seen in the comparison to the “Equal Risk” scenario in Table 3. Assuming equal RV mortality risks and treatment costs would result in a 15% overestimation of benefit at a national level (1.22 vs. 1.44 deaths averted/1000 births). It also would result in an underestimation of the benefits of introducing vaccination in high

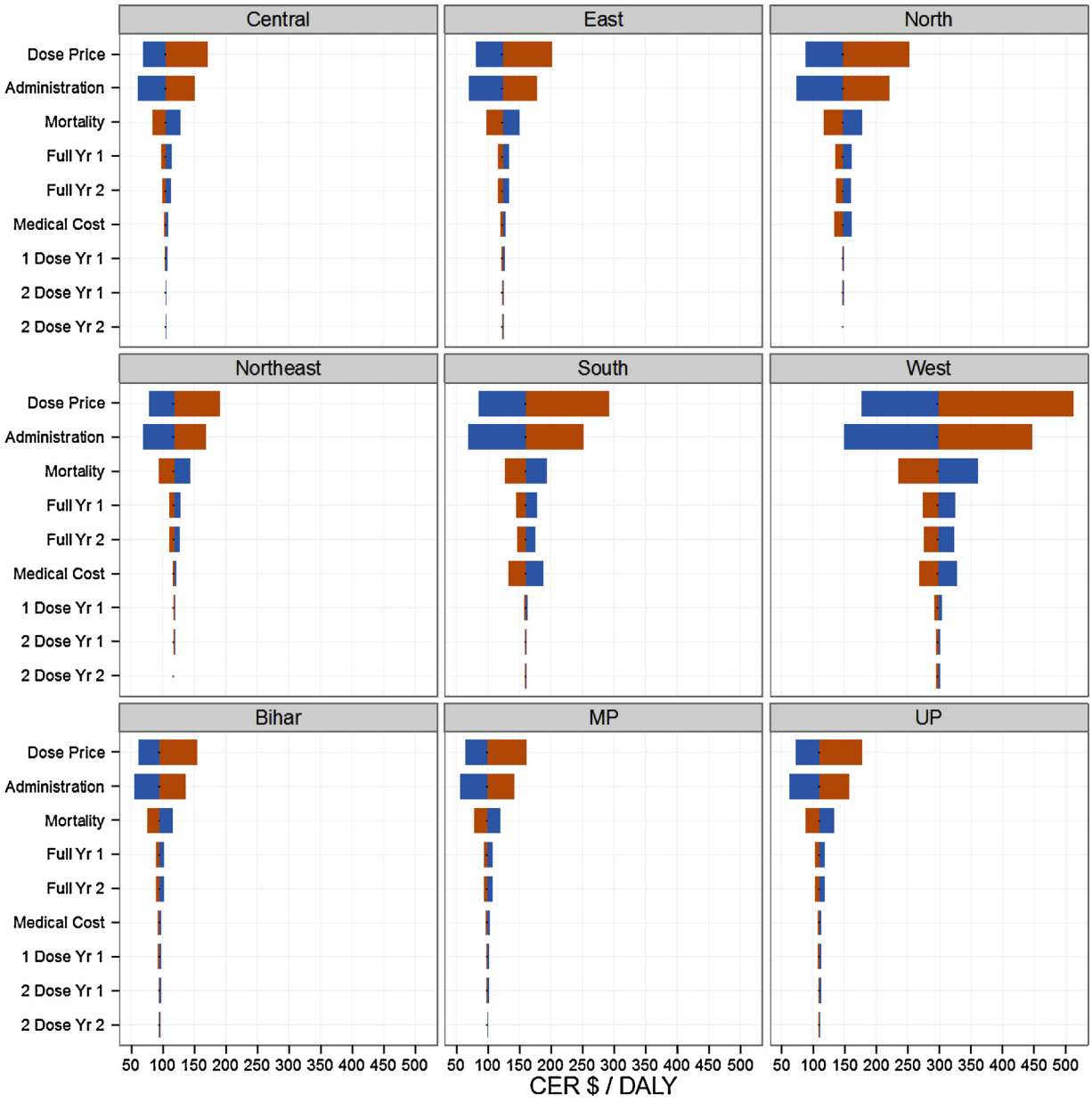

Fig. 4. Tornado plots of one-way sensitivity analysis. Orange bars represent upside (high) estimates while blue bars represent downside (low) estimates for each variable.

mortality regions or states and overestimation of the CER in those areas.

4. Discussion

At a regional level, deaths due to rotavirus are expected to decline by 30–40% in India with the introduction of rotavirus vaccine. Vaccination is estimated to reduce deaths by 23–26% in the states with the highest rotavirus mortality. Among all regions and states evaluated, our current analysis suggests that a vaccination program would be highly cost-effective – consistent with findings of previous analyses [5,7–9].

The greatest potential health benefits of vaccination will come from reaching high rotavirus mortality areas and the poorest households. However, these populations are less likely to benefit given current low coverage estimates. While national vaccination coverage has increased over time in India, further coverage increases in these populations could substantially expand the impact of vaccination. The state level analyses presented here suggest that the greatest benefits may come from focusing on states (or smaller geographic units) with high mortality risk and low coverage of the most vulnerable.

The relationship between healthcare access and disease risk results in clear tradeoffs between economic and health burden across sub-populations. Groups with higher estimated rotavirus mortality tend to have lower healthcare costs. This is not unexpected given that poor access to care contributes to increased risk of mortality (e.g. less likely to receive timely rehydration). In addition, some of the same underlying factors such as geographic distance, lack of access to services, and low household economic resources, can contribute to increased risk and reduced healthcare utilization. The result is an inverse relationship between economic and health burdens among the sub-groups, with some showing greater health burden and others greater economic burden.

This pattern of heterogeneity in economic and health burden leads to alternative rationales for vaccination in different subgroups. In some of the highest mortality states and poorest wealth

quintiles, the primary justification for vaccination is the potential reduction in diarrheal mortality. In contrast, in lower mortality and higher wealth groups, the primary benefit is the potential for averting costs. Of course, in a given population both economic and health benefits occur, but their relative magnitudes will vary.

The current study has several important limitations. The estimates of rotavirus mortality by region are based on Morris et al. [14]. While these are the most recent published estimates by region, the original data is approximately a decade old. Changes in underlying mortality may reduce the differences observed between and within regions. We used a wide range of mortality estimates to address this in our sensitivity analysis. There is also uncertainty in how we estimated rotavirus mortality within regions using risk factors and published risk estimates. Other risk factors not considered here may increase or decrease disparities in rotavirus mortality among economic groups. This analysis only follows one birth cohort and does not account for possible changes in coverage equity in subsequent cohorts as suggested by Victora et al. [45]. The current analysis suggests that healthcare utilization patterns vary across geographic and socio-economic groups, resulting in differences in expected costs and potential cost savings. Although we attempted to account for these differences in utilization, we did not account for potential differences in the cost associated with different levels of care in different settings. For example, the costs of private outpatient or inpatient care might be greater in higher income areas. Additional data on differences in both utilization and unit costs of treatment are needed to develop better estimates. The current model used a relatively crude approach to modeling waning of protection, with uniform protection during the first year of life and reduced efficacy thereafter. A more nuanced model accounting for the timing of vaccination would provide more realistic estimates. Lastly, the results demonstrate that estimated risk and vaccination are correlated across geographic and socio-economic setting (Appendix A). Further analysis shows that there are also correlations between risk and access *within* these sub-groups. However, the current analysis does not adjust for this fact. This correlation, with lower coverage among higher risk children, may result in an overestimate of the benefits of vaccination. Further analysis and more dynamic models may be helpful in better understanding the degree of overestimation.

With few exceptions [46] most economic evaluations of new vaccines do not explicitly consider heterogeneity in economic costs or in the health benefits of vaccination. Evaluations at this level can highlight the effect that disparities may have on the impact of health interventions, and could eventually lead to the development of strategies that will optimize impact. Understanding the effects of heterogeneity could strengthen ongoing and future efforts to improve vaccination coverage, with the aim of maximizing the benefits and improving the equity of vaccine access for rotavirus and other vaccines in India.

Conflict of interest

The authors have no conflicts of interest to declare.

Acknowledgments

This study was funded by PATH's Rotavirus Vaccine Program under a grant from the Bill and Melinda Gates Foundation grant number OPP1068644. We would like to thank Dr. Parvesh Chopra of AC Nielsen and Dr. Satish Gupta, a Health Specialist at UNICEF India, for providing data essential for this work.

Appendix A.

Estimated correlation between DPT doses and likelihood of receiving oral rehydration solution (ORS risk), moderate and severe under-nutrition (−2 standard deviations weight-for-age; WFA −2 sd), severe under-nutrition (−3 standard deviations weight-for-age; WFA −3 sd), and overall rotavirus risk (RV Risk index) calculated for the NFHS-3 (2006–2007).

	Overall			Poorest			Poorer			Middle			Richer			Richest		
DPT dose	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
National																		
ORS risk	−0.34*	−0.35*	−0.35*	−0.25*	−0.28*	−0.23*	−0.31*	−0.32*	−0.34*	−0.35*	−0.33*	−0.32*	−0.30*	−0.32*	−0.31*	−0.26*	−0.25*	−0.26*
WFA −2 sd	−0.13*	−0.14*	−0.16*	−0.12*	−0.12*	−0.13*	−0.08*	−0.11*	−0.12*	−0.06	−0.08*	−0.09*	−0.08*	−0.07*	−0.11*	−0.10*	−0.12*	−0.14*
WFA −3 sd	−0.13*	−0.15*	−0.17*	−0.09*	−0.11*	−0.12*	−0.10*	−0.15*	−0.16*	−0.04	−0.08*	−0.12*	−0.14*	−0.11*	−0.13*	−0.14*	−0.11*	−0.10*
RV risk index	−0.25*	−0.27*	−0.28*	−0.18*	−0.20*	−0.18*	−0.20*	−0.25*	−0.27*	−0.18*	−0.20*	−0.22*	−0.22*	−0.20*	−0.23*	−0.24*	−0.22*	−0.23*
N	8204			1424			1458			1510			1722			2090		
Central																		
ORS risk	−0.31*	−0.32*	−0.34*	−0.28*	−0.30*	−0.20*	−0.15*	−0.11*	−0.15*	−0.30*	−0.27*	−0.26*	−0.30*	−0.29*	−0.30*	−0.25*	−0.25*	−0.31*
WFA −2 sd	−0.08*	−0.11*	−0.12*	−0.08	−0.07	−0.08	−0.06	−0.11*	−0.13*	0.00	0.01	0.00	−0.02	−0.02	−0.02	−0.08	−0.13*	−0.14*
WFA −3 sd	−0.10*	−0.11*	−0.11*	−0.06	−0.05	−0.03	−0.05	−0.12*	−0.11*	0.03	0.05	0.01	−0.12*	−0.09	−0.08	−0.17*	−0.14*	−0.13*
RV risk index	−0.19*	−0.22*	−0.22*	−0.16*	−0.15*	−0.11*	−0.09	−0.17*	−0.15*	−0.06	−0.05	−0.07	−0.17*	−0.14*	−0.15*	−0.24*	−0.25*	−0.25*
N	2125			355			364			360			425			621		
East																		
ORS risk	−0.35*	−0.39*	−0.36*	−0.30*	−0.32*	−0.28*	−0.31*	−0.38*	−0.43*	−0.32*	−0.32*	−0.27*	−0.30*	−0.34*	−0.31*	−0.25*	−0.24*	−0.21*
WFA −2 sd	−0.11*	−0.14*	−0.16*	−0.09	−0.11	−0.12	−0.06	−0.10	−0.12	−0.04	−0.10	−0.15*	0.00	0.02	−0.02	−0.12	−0.12	−0.13
WFA −3 sd	−0.14*	−0.17*	−0.19*	−0.13	−0.20*	−0.18*	−0.09	−0.13	−0.17*	−0.02	−0.10	−0.20*	−0.13	−0.08	−0.13	−0.14	−0.10	−0.06
RV risk index	−0.24*	−0.28*	−0.29*	−0.19*	−0.24*	−0.21*	−0.16*	−0.23*	−0.29*	−0.15*	−0.21*	−0.26*	−0.17*	−0.13	−0.15*	−0.22*	−0.20*	−0.18*
N	1389			231			241			246			279			392		
North																		
ORS risk	−0.21*	−0.22*	−0.21*	−0.19*	−0.14	−0.07	−0.12	−0.08	−0.09	−0.08	−0.07	−0.06	−0.14	−0.26*	−0.18*	0.03	0.01	0.01
WFA −2 sd	−0.16*	−0.15*	−0.15*	−0.13	−0.07	−0.08	−0.05	−0.04	0.01	−0.10	−0.04	−0.03	−0.09	−0.18*	−0.14	−0.04	−0.12	−0.12
WFA −3 sd	−0.15*	−0.14*	−0.17*	−0.11	−0.04	−0.11	−0.16	−0.17	−0.20*	−0.07	−0.04	−0.04	−0.01	−0.15	−0.14	0.03*	0.05*	0.00
RV risk index	−0.22*	−0.22*	−0.23*	−0.14	−0.08	−0.09	−0.15	−0.12	−0.12	−0.14	−0.09	−0.07	−0.06	−0.31*	−0.25*	0.00	−0.03	−0.05
N	1144			234			219			225			240			226		
Northeast																		
ORS risk	−0.13*	−0.17*	−0.15*	0.03	−0.06	−0.04	−0.22*	−0.26*	−0.17	−0.12	−0.14*	−0.14	−0.07	−0.13	−0.17*	−0.09	−0.11	−0.05
WFA −2 sd	−0.12*	−0.11*	−0.17*	−0.01	0.10	−0.18	−0.14	−0.17	−0.21	−0.13	−0.11	−0.07	0.06	−0.01	−0.06	−0.04	0.00	0.01
WFA −3 sd	−0.11*	−0.06	−0.13*	−0.03	0.07	−0.11	−0.18	−0.09	−0.08	−0.12	−0.09	−0.03	−0.08	−0.03	−0.24	−0.01	0.00	−0.06
RV risk index	−0.19*	−0.18*	−0.24*	−0.02	0.07	−0.17	−0.29*	−0.29*	−0.25	−0.21	−0.23*	−0.17	0.02	−0.01	−0.18	−0.13	−0.11	−0.09
N	1481			262			275			278			304			362		
West																		
ORS risk	−0.32*	−0.33*	−0.33*	−0.21*	−0.26*	−0.34*	−0.24*	−0.31*	−0.17	−0.29*	−0.21	−0.18	−0.25*	−0.22*	−0.14	−0.09	−0.12	−0.21*
WFA −2 sd	−0.08*	−0.11*	−0.11*	−0.14	−0.17*	−0.15	0.02	−0.01	−0.02	0.07	0.06	0.12	−0.01	−0.04	−0.10	0.12*	0.04	0.03
WFA −3 sd	−0.10*	−0.14*	−0.13*	−0.04	−0.12	−0.08	−0.04	−0.04	−0.05	0.06	0.02	0.06	−0.10	−0.11	−0.12	0.04*	−0.07	0.00
RV risk index	−0.19*	−0.23*	−0.21*	−0.12	−0.18*	−0.15	−0.07	−0.10	−0.09	−0.01	−0.04	0.07	−0.13	−0.13	−0.12	0.07	−0.06	−0.05
N	928			165			169			187			214			193		

	Overall			Poorest			Poorer			Middle			Richer			Richest		
DPT dose	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
South																		
ORS risk	−0.10*	0.02	0.06	−0.08	−0.02	0.10	0.00	0.15	0.32*	0.00	0.20*	0.26*	−0.04	0.08	0.12	−0.03	0.08	0.11
WFA −2 sd	−0.04	−0.01	−0.06	−0.03	−0.04	−0.05	0.01	0.05	0.04	0.09	0.05	0.03	−0.20*	−0.05	−0.12	0.08*	0.06	−0.04
WFA −3 sd	−0.03	−0.05	−0.12*	0.03	0.05	−0.10	0.00	−0.09	−0.09	−0.04	−0.14	−0.20	−0.11	−0.03	−0.06	0.02*	0.05*	−0.06
RV risk index	−0.08*	−0.03	−0.09*	−0.03	0.00	−0.06	0.01	−0.02	0.00	0.01	0.06	0.03	−0.18	−0.06	−0.10	0.08	0.13*	0.04
N	1137			177			190			214			260			296		
Bihar																		
ORS risk	−0.32*	−0.37*	−0.35*	−0.15	−0.14	−0.18*	0.05	−0.03	−0.04	−0.27*	−0.29*	−0.32*	−0.31*	−0.23*	−0.25*	−0.32*	−0.31*	−0.30*
WFA −2 sd	−0.08	−0.11*	−0.17*	0.07	−0.02	−0.06	−0.02	−0.10	−0.18	−0.04	−0.12	−0.20	0.06	0.20	0.11	−0.12	−0.13	−0.20
WFA −3 sd	−0.11*	−0.13*	−0.19*	0.03	−0.06	−0.11	−0.08	−0.15	−0.20	−0.03	−0.02	−0.19	−0.15	−0.02	−0.13	−0.12	−0.09	−0.04
RV risk index	−0.18*	−0.22*	−0.27*	0.03	−0.05	−0.08	−0.06	−0.17	−0.28*	−0.07	−0.09	−0.23	−0.12	0.06	−0.04	−0.23*	−0.22*	−0.22*
N	420			70			74			77			79			120		
Madhya Pradesh																		
ORS risk	−0.26*	−0.32*	−0.38*	−0.11	−0.21	−0.21	−0.33*	−0.26	−0.23	0.01	0.02	−0.04	−0.12	−0.23*	−0.23*	−0.10	−0.08	−0.08
WFA −2 sd	−0.11*	−0.11*	−0.14*	−0.17	−0.16	−0.12	−0.01	−0.03	−0.16	−0.06	−0.10	−0.11	−0.09	0.01	−0.02	−0.04	−0.02	0.01
WFA −3 sd	−0.08	−0.09	−0.07	−0.07	−0.13	−0.05	0.01	0.06	0.06	0.01	0.07	0.09	−0.12	−0.13	0.04	0.13*	0.15*	0.05
RV risk index	−0.17*	−0.19*	−0.18*	−0.17	−0.15	−0.07	0.02	0.03	0.02	−0.03	0.00	0.00	−0.17	−0.20	−0.11	−0.05	−0.02	−0.01
N	481			77			74			70			85			175		
Uttar Pradesh																		
ORS risk	−0.28*	−0.33*	−0.31*	−0.04	−0.01	−0.02	−0.29*	−0.22*	−0.14	−0.17*	−0.22*	−0.30*	−0.29*	−0.32*	−0.28*	−0.23*	−0.26*	−0.23*
WFA −2 sd	−0.12*	−0.14*	−0.14*	−0.17*	−0.22*	−0.18*	−0.07	−0.08	−0.07	−0.06	−0.03	−0.04	−0.06	−0.06	−0.04	−0.06	−0.12	−0.15*
WFA −3 sd	−0.15*	−0.16*	−0.17*	−0.19*	−0.16*	−0.14*	−0.05	−0.15*	−0.14*	0.02	0.05	−0.06	−0.17*	−0.14	−0.12	−0.31*	−0.28*	−0.24*
RV risk index	−0.20*	−0.22*	−0.22*	−0.20*	−0.21*	−0.16*	−0.08	−0.17*	−0.14	−0.05	−0.05	−0.11	−0.17*	−0.14	−0.14*	−0.27*	−0.28*	−0.27*
N	1044			164			180			175			216			309		

*are statistically significant at a 0.05 level.

References

[1] Black RE, Cousens S, Johnson HL, Lawn JE, Rudan I, Bassani DG, et al. Global, regional, and national causes of child mortality in 2008: a systematic analysis. Lancet 2010;375(9730):1969–87.
[2] Parashar UD, Gibson CJ, Bresee JS, Glass RI. Rotavirus and severe childhood diarrhea. Emerg Infect Dis 2006;12:304–6.
[3] WHO. Rotavirus vaccines:an update. Wkly Epidemiol Rec 2009;84(50):533–40.
[4] Parashar UD, Burton A, Lanata C, Boschi-Pinto C, Shibuya K, Steele D, et al. Global mortality associated with rotavirus disease among children in 2004. J Infect Dis 2009;200(Suppl. 1(Nov)):S9–15.
[5] Esposito DH, Tate JE, Kang G, Parashar UD. Projected impact and cost-effectiveness of a rotavirus vaccination program in India, 2008. Clin Infect Dis 2010;52(2):171–7.
[6] Neogi SB, Hasan H, Sheikh K, Zodpey S. Scope for rotavirus vaccination in India: revisiting the scientific evidence. Ind J Pediatr 2011;78(10):1251–5.
[7] Rheingans R, Atherly D, Anderson J. Distributional impact of rotavirus vaccination in 25 GAVI countries: estimating disparities in benefits and cost-effectiveness. Vaccine 2012;30(Suppl. 1):A15–23.
[8] Atherly DE, Lewis KDC, Tate J, Parashar UD, Rheingans RD. Projected health and economic impact of rotavirus vaccination in GAVI-eligible countries: 2011-2030. Vaccine 2012;30:A7–14.
[9] Rose J, Hawthorn RL, Watts B, Singer ME. Public health impact and cost effectiveness of mass vaccination with live attenuated human rotavirus vaccine (RIX4414) in India: model based analysis. BMJ (Clin Res ed) 2009;339(25(Sep)):b3653–60.
[10] Bhandari N, Rongsen-Chandola T, Bavdekar A, John J, Antony K, Taneja S, et al. Efficacy of a monovalent human-bovine (116E) rotavirus vaccine in Indian infants: a randomised, double-blind, placebo-controlled trial. Lancet 2014; (9935(Jun 21)):2136–43.
[11] Indian Academy of Pediatrics Committee on Immunization (IAPCOI). Consensus recommendations on immunization and IAP immunization timetable 2012. Ind Pediatr 2012;49(7):549–64.
[12] Lodha R, Shah D. Prevention of rotavirus diarrhea in India: is vaccination the only strategy? Ind Pediatr 2012;49(6):441–3.
[13] Bányai K, László B, Duque J, Steele AD, Nelson E. Systematic review of regional and temporal trends in global rotavirus strain diversity in the pre rotavirus vaccine era: insights for understanding the impact of rotavirus vaccination programs. Vaccine 2012;30(Suppl 1):A122–30.
[14] Morris S, Awasthi S, Khera A, Bassani D, Kang G, Parashar U, et al. Rotavirus mortality in India: estimates based on a nationally representative survey of diarrhoeal deaths. Bull World Health Organ 2012;90(10):720–7.
[15] Caulfield L, de Onis M, Blossner M, Black R. Undernutrition as an underlying cause of child deaths associated with diarrhea, pneumonia, malaria, and measles. Am J Clin Nutr 2004;80(1):193–8.
[16] Nandy S, Irving M, Gordon D, Subramanian SV, Smith GD. Poverty, child undernutrition and morbidity: new evidence from India. Bull World Health Organ 2005;83(3):210–6.
[17] Gaudin S, Yazbeck AS. Immunization in india 1993-1999: wealth, gender, and regional inequalities revisited. Soc Sci Med 2006;62(3):694–706.
[18] Mhatre SL, Schryer-Roy A-M. The fallacy of coverage: uncovering disparities to improve immunization rates through evidence. Results from the Canadian International Immunization Initiative Phase 2 – operational research grants. BMC Int Health Hum Rights 2009;9(Suppl. 1):S1.
[19] Pande RP, Yazbeck AS. What's in a country average? Wealth, gender, and regional inequalities in immunization in India. Soc Sci Med 2003;57(11): 2075–88.
[20] Singh PK. Trends in child immunization across geographical regions in India: focus on urban-rural and gender differentials. PLOS ONE 2013;8(9):e73102.
[21] Corsi DJ, Bassani DG, Kumar R, Awasthi S, Jotkar R, Kaur N, et al. Gender inequity and age-appropriate immunization coverage in India from 1992 to 2006. BMC Int Health Hum Rights 2009;9(Suppl. 1):S3.
[22] Microsoft. Microsoft excel. Washington: Redmond; 2011.
[23] Rutstein SO, Johnson K. The DHS wealth index. Calverton, Maryland: ORC Macro; 2004.
[24] International Institute for Population Sciences. Macro international. National family health survey (NFHS-3), 2005-06, vol. I. Mumbai: IIPS; 2007.
[25] StataCorp. Stata statistical software: release 12. College Station, TX: StataCorp LP; 2011.
[26] Munos MK, Walker CLF, Black RE. The effect of oral rehydration solution and recommended home fluids on diarrhoea mortality. Int J Epidemiol 2010;39:75–87.
[27] Murray C, Lopez A. The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. Boston, MA: School of Public Health, Harvard University; 1996.
[28] Prüss-Üstün A, et al. Introduction and methods: assessing the environmental burden of disease at national and local levels. Geneva: World Health Organization; 2003 (WHO Environmental Burden of Disease Series, No. 1).
[29] Parashar UD, Burton A, Lanata C, Boschi-Pinto C, Shibuya K, Steele D, et al. Global mortality associated with rotavirus disease among children in 2004. J Infect Dis 2009;200 (Suppl. 1):S9–15.
[30] Rheingans RD, Constenla D, Antil L, Innis BL, Breuer T. Economic and health burden of rotavirus gastroenteritis for the 2003 birth cohort in eight Latin American and Caribbean countries. Rev Panam Salud Pública 2007;21(4): 192–204.
[31] Sanderson C, Clark A, Taylor D, Bolanos B. Global review of rotavirus morbidity and mortality data by age and region. In: WHO SAGE Meeting. 2012. p. 1–42.
[32] Clark A, Sanderson C. Timing of children's vaccinations in 45 low-income and middle-income countries: an analysis of survey data. Lancet 2009;373(9674):1543–9.
[33] International Institute for Population Sciences (IIPS). District level household and facility survey (DLHS-3), 2007-08. Mumbai, India: IIPS; 2010.
[34] UNICEF. 2009 coverage evaluation survey: all India report. New Delhi: UNICEF; 2010.
[35] Vital Statistics Division. Annual health survey 1010-11 fact sheet: Uttar Pradesh. New Delhi, India: Office of the Registrar General and Census Commissioner; 2011.
[36] Vital Statistics Division. Annual health survey 1010-11 fact sheet: Bihar. New Delhi, India: Office of the Registrar General and Census Commissioner; 2011.
[37] Vital Statistics Division. Annual health survey 1010-11 fact sheet: Madhya Pradesh. New Delhi, India: Office of the Registrar General and Census Commissioner; 2011.
[38] Rheingans RD, Antil L, Dreibelbis R, Podewils LJ, Bresee JS, Parashar UD. Economic costs of rotavirus gastroenteritis and cost-effectiveness of vaccination in developing countries. J Infect Dis 2009;200(Suppl. 1):S16–27.
[39] Lopman BA, Pitzer VE, Sarkar R, Gladstone B, Patel M, Glasser J, et al. Understanding reduced rotavirus vaccine efficacy in low socio-economic settings. PLoS One 2012;7(8):e41720.
[40] Sowmyanarayanan TV, Patel T, Sarkar R, Broor S, Chitambar SD, Krishnan T, et al. Direct costs of hospitalization for rotavirus gastroenteritis in different health facilities in India. Indian J Med Res 2012;136(1):68–73.

[41] Tate JE, Chitambar S, Esposito DH, Sarkar R, Gladstone B, Ramani S, et al. Disease and economic burden of rotavirus diarrhoea in India. Vaccine 2009;27:F18–24.
[42] Rheingans R, Kukla M, Faruque AS, Sur D, Zaidi AK, Nasrin D, et al. Determinants of household costs associated with childhood diarrhea in 3 South Asian settings. Clin Infect Dis 2012;55(Suppl. 4(Dec)):S327–35.
[43] Decisioneering Inc. Crystal ball version 11.0. Denver, CO: Oracle; 2007.
[44] The World Bank. Gross domestic product per capita (current US$). World development indicators 2012 [cited April 2014]; 2014. Available from: http://data.worldbank.org/indicator/NY.GDP.PCAP.CD/countries
[45] Victora CG, Vaughan JP, Barros FC, Silva AC, Tomasi E. Explaining trends in inequities: evidence from Brazilian child health studies. Lancet 2000; 356(9235(Sep)):1093–8.
[46] Verguet S, Murphy S, Anderson B, Johansson KA. Public finance of rotavirus vaccination in India and Ethiopia: an extended cost-effectiveness analysis. Vaccine 2013;31(42):4902–10.
[47] Fischer Walker C, Black R. Rotavirus vaccine and diarrhea mortality: quantifying regional variation in effect size. BMC Public Health 2011;11(Suppl. 3): S16.