Distributional Impact Of Rotavirus Vaccination In 25 GAVI Countries: Estimating Disparities In Benefits And Cost Effectiveness

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Abstract

Background: Other studies have demonstrated that the impact and cost effectiveness of rotavirus vacci-nation differs among countries, with greater mortality reduction benefits and lower cost-effectiveness ratios in low-income and high-mortality countries. This analysis combines the results of a country level model of rotavirus vaccination published elsewhere with data from Demographic and Health Surveys on within-country patterns of vaccine coverage and diarrhea mortality risk factors to estimate within-country distributional effects of rotavirus vaccination. The study examined 25 countries eligible for funding through the GAVI Alliance.

Methods: For each country we estimate the benefits and cost-effectiveness of vaccination for each wealth quintile assuming current vaccination patterns and for a scenario where vaccine coverage is equalized to the highest quintile's coverage. In the case of India, variations in coverage and risk proxies by state were modeled to estimate geographic distributional effects.

Results: In all countries, rates of vaccination were highest and risks of mortality were lowest in the top two wealth quintiles. However countries differ greatly in the relative inequities in these two underlying variables. Similarly, in all countries examined, the cost-effectiveness ratio for vaccination ($/Disability-Adjusted Life Year averted, DALY) is substantially greater in the higher quintiles (ranging from 2–10 times higher). In all countries, the greatest potential benefit of vaccination was in the poorest quintiles. However, due to reduced vaccination coverage, projected benefits for these quintiles were often lower. Equitable coverage was estimated to result in an 89% increase in mortality reduction for the poorest quintile and a 38% increase overall.

Conclusions: Rotavirus vaccination is most cost-effective in low-income groups and regions. However in many countries, simply adding new vaccines to existing systems targets investments to higher income children, due to disparities in vaccination coverage. Maximizing health benefits for the poorest children and value for money require increased attention to these distributional effects.

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1. Introduction

Global and regional level analysis of rotavirus vaccination demonstrates that the impact and cost-effectiveness of vaccination is heterogeneous [1–4]. In general there are greater benefits and better cost-effectiveness ratios in low-income countries and regions, primarily due to higher estimated mortality. At the same time, lower vaccination coverage, along with reduced efficacy and great delays in timing mean that the percent reduction in rotavirus burden would be lowest in these countries [5].

However this global pattern of disparities is likely to be repeated within as well as between countries [6]. Poorer households and poorer regions within a particular country are likely to have high diarrhea mortality risk and lower levels of timely vaccination coverage. This suggests that distribution of the benefit, cost-effectiveness and residual (post-vaccination) rotavirus mortality are also likely to differ after vaccine introduction.

This paper estimates the geographic and socio-economic distributional effects of rotavirus vaccine introduction within a subset of countries eligible for funding by the GAVI Alliance. This includes the distribution of benefits, cost-effectiveness, and residual (post-vaccine introduction) mortality risk. The main research question is 'how do outcomes differ across geographic and socio-economic gradients at the regional, national, and sub-national scales?' Better understanding of distributional effects is essential in tackling the substantial remaining rotavirus mortality burden, even with

vaccination. Distributional effects also have implications for decisions about where to invest first, even among and within GAVI-eligible countries.

Best practices for economic evaluations of health interventions typically require distributional analyses to assess who within a population is more or less likely to benefit. This is based on an understanding that cost-effectiveness is just one criterion in decision-making and other factors, such as who benefits, also need to be considered. While in practice, few vaccine cost-effectiveness studies directly explore these issues, there is evidence that vaccination can have both pro-poor and anti-poor distributional effects. Bishai et al. demonstrated that near universal measles vaccination in Bangladesh reduced disparities in under-5 mortality [7]. Michaelidis et al. found that efforts in reducing disparities in influenza vaccination among elderly minority groups in the US was moderate to highly cost-effective [8]. Human papillomavirus (HPV) vaccination provides a somewhat different scenario. While the burden of cervical cancer is disproportionately borne by poorer women with limited access to prevention and timely treatment, vaccination programs may similarly miss the target population [9,10].

Several approaches have been suggested for addressing distributional and equity concerns in cost-effectiveness. One approach is to explicitly weight outcomes among the poor as higher than those among better off sub-populations through an equity weight [11,12]. In some cases, weights are suggested based on socio-economic status and in other contexts based on the severity of individual conditions [13].

In some contexts there is an equity-efficiency tradeoff where the most impactful or efficient is not the most equitable [14]. Walensky et al. modeled a variety of prevention and treatment approaches for HIV in South Africa, considering the cost-effectiveness and equity of different intervention combinations [15]. Their model included a calculation of the opportunity cost of equity, based on the health improvements that would be forgone in order to select the most equitable solutions. Jehu-Appiah et al. demonstrated the usefulness of a similar modeling approach to quantify the trade-offs between efficiency and equity in health investment priorities in Ghana [16].

One of the simplest approaches to assessing distributional effects is to explicitly estimate costs and impacts for distinct sub-populations. This may include stratifying by age, sex, socio-economic status and/or geographic regions. Coyle et al. provide a general framework for population stratified cost-effectiveness analysis [17] and Sculpher describes the application of the approach in contexts such as the UK's NICE evaluation process [18].

2. Methods

2.1. General model structure

We used an existing country-level rotavirus impact and cost-effectiveness model [1] that has been updated with newly available data [5]. Estimates here are for vaccinating a single birth cohort, including outcomes during their first five years of life. National rotavirus mortality estimates were based on recently published figures [19]. Estimates of inpatient and outpatient visits are also from previously published studies [20].

Vaccine efficacy estimates were based on region and mortality strata [21–23]. Estimates for high mortality countries were based on pooled estimates from recent trials [21] and are described in full detail in Atherly et al. [5]. Efficacy was adjusted for the expected age at which first and second dose would be received in each country, based on DPT1 and DPT2 coverage from DHS surveys [3,24]. This was done by modeling coverage of 1 and 2 doses of vaccine at 0–2, 3–5, 6–8 and 9–11 months. Reported DPT1 and DPT2 coverage among 12–23 month old children was used to estimate the fraction of those that would receive each vaccine at the different age ranges [5]. Vaccination effectiveness was based on the fraction of children at each age with 0, 1, or 2 doses and the expected protection of each, assuming 50% lower efficacy for a single dose in the 2-dose regime. For each age band, the effectiveness was applied to the proportion of rotavirus deaths that would occur during that period. Current SAGE recommendations suggest that children over 8 months or 32 weeks not receive a vaccine in order to avoid potential adverse effects. The model used in this study assumes that children receiving their second DPT dose between 8 and 12 months of age would still receive it [25].

Table 1
Selected Demographic and Health Survey (DHS) country data for the distributional impacts of rotavirus vaccination.

Country by DHS region	Year
Latin America and Caribbean	
Haiti	2006
South and Southeast Asia	
Bangladesh	2007
Cambodia	2005
India	2006
Nepal	2006
Sub-Saharan Africa	
Burkina Faso	2003
Cameroon	2004
Chad	2004
Dem. Rep. of Congo	2007
Ethiopia	2005
Ghana	2008
Guinea	2005
Kenya	2009
Lesotho	2004
Liberia	2007
Malawi	2004
Mali	2006
Mozambique	2003
Niger	2006
Nigeria	2008
Senegal	2005
Sierra Leone	2008
Tanzania	2005
Uganda	2006
Zambia	2007

Medical treatment costs were estimated for inpatient and outpatient visits, using cost-estimates from WHO-CHOICE for facility charges and extrapolations of medication and diagnostic costs from published studies, as described elsewhere [1,3]. Medical costs were in 2010 US Dollars and presented in more detail elsewhere [5]. All costs and DALY estimates were discounted at 3%. Cost-effectiveness estimates are based on a two-dose vaccine with a price of $2.50 per dose.

In the original model we adjusted for a potential differential coverage among children likely to suffer rotavirus mortality [1]. For the current model we eliminated that assumption since we are explicitly modeling the co-distribution of risks and access.

2.2. Socio-economic distribution of immunization benefits at the national level

The distributional impact of vaccination in a given country was modeled by incorporating data on the disparities in vaccine coverage by wealth quintile at the national level and by estimating the distribution of rotavirus mortality risk by wealth quintile. Both of these were estimated using available data (2003 or later) from the most recent Demographic and Health Surveys of the 25 GAVI-eligible countries [26]. Countries were selected based on the availability of data at the time of the analysis. Countries with earlier surveys were excluded given that disparities may change over time due to ongoing efforts to achieve universal coverage. Table 1 shows

Table 2
Selected inputs for estimating the distributional impacts and cost effectiveness of rotavirus vaccination.

Variable	Value	Reference
Health		
Rotavirus mortality	Country-specific	[19]
Hospitalization	0.016	[20]
Distribution of rotavirus mortality by wealth and region	Country-specific	Based on [26]
Vaccination		
Vaccine efficacy		
Severe rotavirus		
High mortality countries	0.57	[5]
Mid-low mortality countries in Asia	0.72	[5]
Latin America and Europe	0.85	[23]
Outpatient visit		
High mortality countries	0.47	[5]
Mid-low mortality countries in Asia	0.70	[5]
Latin America and Europe	0.78	[23]
Sub-national vaccination coverage	Country-specific	[26]
Costs		
Hospitalization	$17–232	[5]
Outpatient visit	$1–13	[5]
Vaccination system cost	$0.50–1.26	[5]
Vaccine price ($/dose)	$2.50	Authors assumption

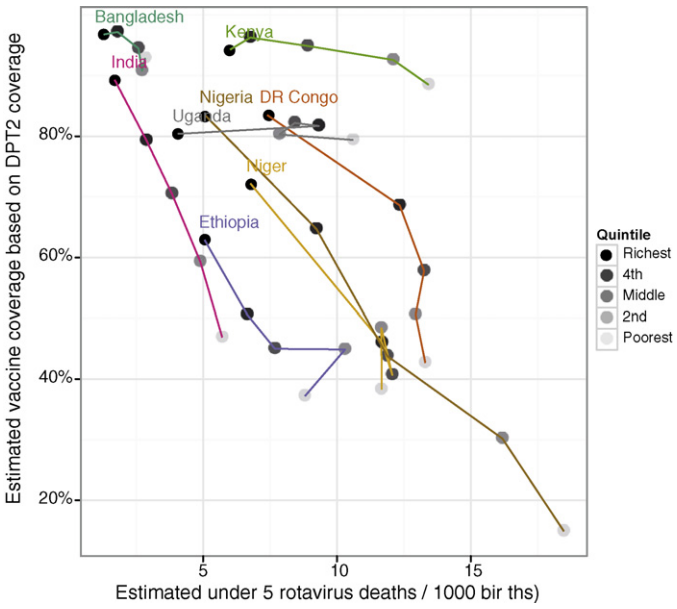

Fig. 1. Estimated vaccination coverage and under-5 rotavirus mortality by wealth quintile in 8 high mortality countries, based on DHS surveys.

the countries and the year of the survey. For immunization coverage, DPT2 coverage was used as a proxy to estimate the distribution of rotavirus vaccination by quintile.

No specific publications were identified with data on the distribution of rotavirus or diarrheal mortality by wealth quintile. As a result, we used alternative proxy measures to estimate the potential distribution of rotavirus mortality across wealth quintiles. We used three proxy measures: post-neonatal infant mortality, less than −2 standard deviations in weight for age *Z*-scores, and less than −3 standard deviations in weight for age *Z*-scores [26]. The first of these was expected to correlate with rotavirus mortality risk as a proxy for health care access, while the latter two were expected to be proxies for physical susceptibility due to their demonstrated association with diarrheal mortality [27]. Post-neonatal infant mortality (between 1 and 11 months of age) was used since it closely corresponds with the primary ages of rotavirus mortality. However it is unclear whether other measures like 1–59 months mortality would be a more appropriate proxy. The rates of low weight for age and post-neonatal infant mortality by quintile were used to estimate the fraction of each outcome that would occur in a given quintile. For each of these proxies, the quintile fraction was applied to the estimated national annual rotavirus deaths to estimate the rotavirus deaths for each quintile. Given the uncertainty as to which proxy would best estimate the distribution, the average of the estimated deaths based on the three proxies were averaged for each quintile, resulting in a single estimate of rotavirus mortality that would occur in each quintile. In addition, we also used each of the proxy measures to conduct a sensitivity analysis of the main outcomes. These are shown as a range in Table 4. Overall model parameters are shown in Table 2 and key inputs for the distributional analysis are shown in Table 3.

Using these estimates of vaccination and mortality distribution for each country, we estimated children vaccinated, rotavirus deaths averted, DALYs averted, net costs and cost-effectiveness by wealth quintile.

2.3. Geographic distribution of benefits

Socio-economic and geographic disparities in health and intervention impact may be highly correlated at the sub-national level, in part due to the geographic clustering of socio-economic characteristics such as wealth and education. In order to explore this, we also estimated the geographical distribution of rotavirus vaccination effects for one country – India. Esposito et al. developed a national model of rotavirus introduction and estimated the benefit and cost-effectiveness for India. They estimate that rotavirus vaccination could prevent about one-third of rotavirus-associated deaths in India, suggesting that improving current vaccine coverage would significantly increase vaccination impact [28]. This model includes estimates of rotavirus mortality and vaccination coverage by state from DHS data [26] using the same method as described above for wealth quintiles.

2.4. Characterizing disparities in risk and benefit

In order to characterize and compare the distribution of key outcomes at the national level, we developed concentration curves and concentration indices [29]. For a given outcome, the concentration curve graphs the fraction of that outcome that occurs within different fractions of the population ranked by wealth; for example, the portion of national vaccinations occurring in the bottom 10, 20, and 50 percent of the population ranked by wealth. The concentration index is a single dimensional number between −1 and 1 that represents the extent to which the concentration curve of an outcome differs from the line of equity where the bottom *x* percent of the population accounts for *x* percent of the outcomes.

2.5. Impact of alternative scaling strategies on benefit and cost-effectiveness

We estimated the health cost due to disparities in vaccination between wealth quintiles within each country by modeling a scenario in which vaccination rates in all quintiles are equal to that of the quintile with the highest coverage.

3. Results

Detailed information is presented for the 8 countries with the highest rotavirus mortality estimates and available distributional data from DHS. Fig. 1 shows the estimated co-distribution of

Table 3
Distributional analysis country-level input values.

Country wealth quintile	DPT2 coverage (%)	Post-neonatal infant mortality	Weight for age (< −2 SD)	Weight for age (< −3 SD)	Rotavirus deaths/1000 births
Bangladesh	94.4	17.4	42.2	10.7	2.25
Poorest	92.9	17.7	50.7	16.8	2.84
2nd	90.8	23.4	45.1	13.0	2.72
Middle	94.5	23.3	46.0	10.9	2.58
4th	97.2	13.5	40.9	7.1	1.80
Richest	96.8	9.0	28.1	5.7	1.29
DR Congo	60.6	53.7	27.3	6.7	11.85
Poorest	42.7	69.6	32.0	6.0	13.30
2nd	50.6	61.6	30.3	6.8	12.94
Middle	57.8	54.2	30.1	8.3	13.26
4th	68.6	51.6	25.1	8.3	12.34
Richest	83.5	31.6	19.1	3.9	7.40
Ethiopia	48.1	39.2	34.9	10.6	7.70
Poorest	37.2	40.8	39.8	13.2	8.80
2nd	44.9	47.4	41.1	17.2	10.30
Middle	45.0	38.5	35.9	10.4	7.69
4th	50.6	39.5	32.5	6.9	6.65
Richest	62.9	29.8	25.4	5.1	5.06
India	69.1	19.2	43.8	14.4	3.81
Poorest	46.9	26.2	60.1	25.5	5.72
2nd	59.3	24.8	52.9	19.6	4.89
Middle	70.5	21.1	44.3	13.2	3.84
4th	79.3	15.2	36.9	9.2	2.88
Richest	89.3	8.9	24.6	4.5	1.70
Kenya	93.3	26.0	18.8	3.7	9.44
Poorest	88.5	26.3	27.9	6.5	13.43
2nd	92.6	31.0	21.7	5.5	12.10
Middle	94.9	26.9	20.9	2.5	8.91
4th	96.3	17.9	12.6	2.9	6.76
Richest	94.3	27.7	10.7	1.0	6.01
Niger	49.1	50.9	42.8	16.6	10.77
Poorest	38.3	47.6	46.1	20.5	11.66
2nd	48.4	54.3	47.7	17.7	11.66
Middle	40.7	55.1	45.4	20.2	12.07
4th	46.0	60.5	45.1	16.8	11.69
Richest	72.2	37.2	29.8	7.6	6.77
Nigeria	47.4	39.1	27.4	9.9	12.17
Poorest	14.9	49.4	40.5	17.9	18.48
2nd	30.2	52.0	35.1	13.6	16.18
Middle	43.8	40.5	26.9	9.0	11.88
4th	64.7	33.9	21.7	6.1	9.24
Richest	83.5	19.6	13.0	2.7	5.07
Uganda	80.8	52.4	15.6	4.1	8.05
Poorest	79.4	68.0	20.6	5.5	10.61
2nd	80.3	59.0	15.6	3.3	7.85
Middle	82.2	54.0	17.0	4.2	8.42
4th	81.7	49.0	16.5	6.1	9.32
Richest	80.4	32.0	8.4	1.5	4.06

under-5 rotavirus mortality and vaccination coverage by wealth quintile for 8 countries. Each line represents a different country and each point in the line represents one wealth quintile in that country. In general coverage was highest and mortality lowest in the richest quintile. However countries varied in the relative disparities for each of the variables.

Fig. 2 shows the benefits (under-5 rotavirus deaths averted per 1000 births) and cost-effectiveness ratio (CER, $/DALY) associated with rotavirus vaccination for each wealth quintile within the 8 countries. Each point in the figure represents a different quintile. In most countries, the CER is highest (least cost-effective) for the richest quintile and the benefit is the lowest, primarily due to lower estimated mortality rates. In poorer quintiles, the benefit tends to go up due to increased mortality, but sometimes goes down due to lower vaccination coverage rates.

Estimates of benefits and cost-effectiveness for the selected 8 countries are shown in Table 4. Detailed information for all 25 countries can be found at the website for the model (http://egh.phhp.ufl.edu/distributional-effects-of-rotavirus-vaccination/). In all countries, the incremental cost-effectiveness ratio was least favorable in the richest quintiles. The largest relative differences in the CERs were in Cameroon, India, Nigeria, Senegal, and Mozambique, where the CER in the richest quintile was 355%, 273%, 265%, 253%, and 227% higher than in the poorest. The differences were lowest in Zambia, Chad, Burkina Faso, Liberia, and Niger (all less than 75% higher).

In addition to the analysis using combined indicators of relative rotavirus mortality, separate analyses were run using each of the individual indicators: post-neonatal infant mortality, less than −2 *Z*-score weight for age, and less than −3 *Z*-score weight for age. The results of these analyses are shown in Table 4 as the range for each outcome. While patterns differed slightly between countries, all three of the individual indicators produced consistent results. The analysis using less than −3 *Z*-score resulted in the strongest equity effects.

Fig. 3 shows the relationship between disparities in input variables (vaccine coverage and mortality) and output variables (benefit and post-vaccination mortality). The figure uses Concentration Index (CI) data on each variable for each country to do this. CI values that are negative are concentrated in the poor and those

Table 4
Estimated distributional effects of rotavirus vaccination – mortality reduction and cost-effectiveness in selected GAVI-eligible countries.

Country wealth quintile	Rotavirus deaths averted		CER ($/DALY)		Rotavirus deaths averted/1000 births		Equity scenario – deaths averted/1000 births		Health cost of disparity (rotavirus deaths not averted)	
		Range		Range		Range		Range		Range
Bangladesh	4084		$140.38		0.98		1.01		143	(132–151)
Poorest	1014	(818–1261)	$111.00	(89–138)	1.22	(0.99–1.52)	1.28	(1.03–1.59)	47	(38–58)
2nd	950	(840–1057)	$115.89	(104–131)	1.14	(1.01–1.27)	1.23	(1.08–1.36)	67	(59–74)
Middle	939	(832–1095)	$121.95	(105–138)	1.13	(1–1.32)	1.16	(1.03–1.36)	27	(24–31)
4th	675	(558–815)	$174.57	(145–211)	0.81	(0.67–0.98)	0.81	(0.67–0.98)	0	(0–0)
Richest	479	(433–558)	$245.06	(210–271)	0.58	(0.52–0.67)	0.58	(0.52–0.67)	2	(2–2)
DR Congo	9970		$28.20		3.22		4.44		4146	(3978–4303)
Poorest	1577	(1265–1820)	$25.09	(22–31)	2.55	(2.04–2.94)	4.98	(4–5.75)	1507	(1209–1739)
2nd	1818	(1699–1908)	$25.79	(25–28)	2.94	(2.75–3.08)	4.85	(4.53–5.09)	1182	(1105–1241)
Middle	2128	(1918–2369)	$25.17	(23–28)	3.44	(3.1–3.83)	4.97	(4.48–5.53)	946	(853–1053)
4th	2351	(2073–2812)	$27.03	(23–31)	3.80	(3.35–4.54)	4.62	(4.08–5.53)	511	(450–611)
Richest	1715	(1608–1920)	$45.11	(40–48)	2.77	(2.6–3.1)	2.77	(2.6–3.1)	0	(0–0)
Ethiopia	5655		$43.38		1.66		2.17		1929	(1845–2048)
Poorest	1001	(910–1093)	$37.89	(35–42)	1.47	(1.34–1.61)	2.49	(2.26–2.72)	691	(629–755)
2nd	1414	(1242–1719)	$32.37	(27–37)	2.08	(1.83–2.53)	2.91	(2.56–3.54)	567	(498–689)
Middle	1057	(1039–1087)	$43.40	(42–44)	1.55	(1.53–1.6)	2.17	(2.14–2.23)	420	(413–432)
4th	1029	(777–1199)	$50.15	(43–66)	1.51	(1.14–1.76)	1.88	(1.42–2.19)	250	(189–291)
Richest	972	(714–1124)	$65.96	(57–90)	1.43	(1.05–1.65)	1.43	(1.05–1.65)	0	(0–0)
India	34,616		$82.98		1.20		1.55		12,917	(12,218–13,979)
Poorest	7064	(6398–8320)	$55.22	(47–61)	1.22	(1.11–1.44)	2.33	(2.11–2.74)	6386	(5784–7522)
2nd	7649	(7181–8086)	$64.48	(61–69)	1.32	(1.24–1.4)	1.99	(1.87–2.11)	3870	(3633–4091)
Middle	7130	(6474–7745)	$82.24	(76–90)	1.23	(1.12–1.34)	1.56	(1.42–1.7)	1901	(1726–2065)
4th	6023	(5075–6699)	$109.51	(98–130)	1.04	(0.88–1.16)	1.17	(0.99–1.31)	759	(640–845)
Richest	3992	(2796–5029)	$186.07	(148–265)	0.69	(0.48–0.87)	0.69	(0.48–0.87)	0	(0–0)
Kenya	5802		$35.38		3.95		4.07		229	(197–258)
Poorest	1566	(1113–1940)	$24.90	(20–35)	5.32	(3.79–6.61)	5.79	(4.13–7.19)	138	(98–171)
2nd	1476	(1329–1718)	$27.62	(24–31)	5.02	(4.53–5.85)	5.22	(4.71–6.09)	59	(53–69)
Middle	1113	(800–1312)	$37.54	(32–52)	3.79	(2.73–4.47)	3.84	(2.77–4.54)	16	(12–19)
4th	858	(803–942)	$49.42	(45–53)	2.92	(2.74–3.21)	2.92	(2.74–3.21)	0	(0–0)
Richest	746	(318–1249)	$55.64	(33–130)	2.54	(1.08–4.26)	2.59	(1.11–4.35)	16	(7–26)
Niger	1934		$31.97		2.37		3.48		995	(961–1041)
Poorest	327	(281–373)	$29.54	(26–34)	2.00	(1.73–2.29)	3.77	(3.25–4.31)	290	(249–330)
2nd	413	(406–424)	$29.55	(29–30)	2.53	(2.49–2.6)	3.77	(3.71–3.88)	203	(199–208)
Middle	360	(339–390)	$28.55	(26–30)	2.20	(2.08–2.39)	3.90	(3.69–4.25)	278	(263–302)
4th	394	(367–429)	$29.48	(27–32)	2.41	(2.25–2.64)	3.78	(3.53–4.14)	224	(209–245)
Richest	358	(260–414)	$50.92	(44–70)	2.19	(1.6–2.54)	2.19	(1.6–2.54)	0	(0–0)
Nigeria	15,300		$28.30		2.59		4.56		14,705	(13,893–15,885)
Poorest	1459	(1217–1747)	$18.60	(16–22)	1.24	(1.03–1.48)	6.93	(5.77–8.29)	6716	(5601–8044)
2nd	2589	(2495–2691)	$21.24	(20–22)	2.19	(2.11–2.28)	6.07	(5.84–6.3)	4570	(4404–4749)
Middle	2758	(2582–2932)	$28.92	(27–31)	2.34	(2.19–2.48)	4.46	(4.17–4.73)	2499	(2341–2658)
4th	3166	(2585–3625)	$37.20	(33–46)	2.68	(2.19–3.07)	3.46	(2.82–3.96)	920	(751–1053)
Richest	2242	(1477–2705)	$67.82	(56–103)	1.90	(1.25–2.29)	1.90	(1.25–2.29)	0	(0–0)
Uganda	3935		$41.48		2.92		2.97		62	(65–71)
Poorest	1017	(1002–1031)	$31.51	(31–32)	3.77	(3.72–3.82)	3.91	(3.85–3.96)	32	(35–36)
2nd	762	(625–879)	$42.55	(37–52)	2.83	(2.32–3.26)	2.89	(2.38–3.34)	16	(15–21)
Middle	836	(815–870)	$39.67	(38–41)	3.10	(3.02–3.23)	3.10	(3.02–3.23)	0	(0–0)
4th	920	(743–1176)	$35.86	(28–44)	3.41	(2.76–4.36)	3.43	(2.77–4.39)	5	(5–7)
Richest	394	(285–477)	$82.31	(68–114)	1.46	(1.06–1.77)	1.50	(1.08–1.81)	8	(6–11)

Note: National level results reflect the results without adjusting for distributional effects.

that are positive are concentrated in the rich. The absolute value of the CI reflects the degree of disparity (values close to 1 and −1 are more inequitable).

Fig. 3a shows the concentration of pre- and post-vaccination rotavirus mortality on the two axes. Pre- and post-vaccination mortality was concentrated in the poor for all countries (negative CI), with countries differing greatly in the extent. The dotted line shows the points for which pre- and post-vaccination is the same. For all countries, post-vaccination results showed disparities that were greater than before vaccination. Again, the extent of this differed widely with some countries substantially below the dotted line. Countries that were close to the line (more equitable benefit) were those with more equitable vaccination coverage (smaller dot).

Fig. 3b shows the distribution of countries in terms of post-vaccination mortality concentration (vertical axis) and vaccination benefit (horizontal axis). For about one-third of countries, it was estimated that vaccination would disproportionately benefit children in better off households (i.e., greater than 0 on the *y*-axis). Countries with larger disparities in vaccination coverage (larger circles) are the most likely to be biased away from the poor. In contrast, benefits are most equitable in countries where underlying rotavirus burden is concentrated in the poor (darker) and yet vaccination is relatively equitable (smaller).

3.1. Health cost of disparity

The health cost of vaccination disparity was estimated by modeling a scenario where coverage in all quintiles was equal to that of the highest wealth quintile. Results were reported as the estimated rotavirus deaths averted per 1000 children, with current coverage and 'equitable' coverage. Table 4 shows the estimated deaths averted for the richest quintile and the poorest quintile (current and equitable coverage), as well as the mortality cost of disparities in coverage for the country as a whole. The health cost

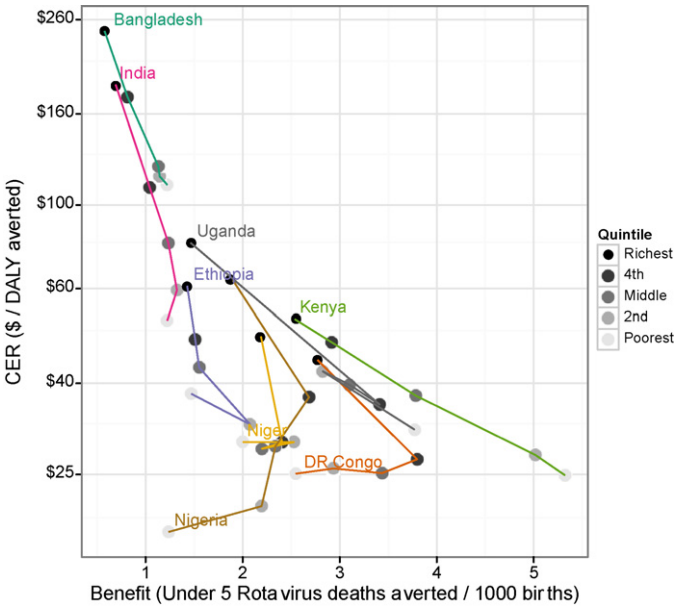

Fig. 2. Estimated benefit (rotavirus deaths averted by 1000 births) and cost-effectiveness ratio ($/DALY) by wealth quintile for 8 high mortality countries.

of disparity for the poor in Chad, Nigeria, DRC, India and Niger is substantial, where equitable coverage could improve mortality reduction among the poorest quintile by 656%, 460%, 96%, 90% and 89%, respectively. In contrast, the potential increase in impact in the poorest quintile, due to more equitable vaccine coverage, was less than 5% in Bangladesh, Uganda, and Ghana. Across the 25 countries, equitable coverage would increase mortality reduction benefits by 89% (range of 88–91% across mortality proxy measures) among the poorest quintile and 38% overall (range of 37–40%).

3.2. *Geographic distribution*

Geographic patterns of disparities were examined by modeling expected outcomes for India by state. Fig. 4 shows the estimated cost-effectiveness ($/DALY averted) and vaccination benefit (DALYs averted/1000 children) by state. Cost-effectiveness and benefits differed substantially among states, from over $250/DALY averted in Kerala to less than $60/DALY averted in Madhya Pradesh. The states with the lowest CERs are those with high pre-vaccination mortality (larger circles). However, many of these same states also have the lowest percent reduction in rotavirus mortality (further to the left), due to low vaccination coverage (lighter color). If national rotavirus vaccination were implemented on top of existing EPI coverage, then the states with the most favorable cost-effectiveness ratios and greatest burden would actually benefit the least.

4. Discussion

Previous analyses have demonstrated substantial variability in vaccination benefit and cost-effectiveness among countries based on geography and economic status [1]. This disparity, in part, is the justification for GAVI investment in low-income countries where benefits are greater and there is better value for money. These investments are also based on rights and fairness principles that children in low-income settings are entitled to these interventions, even if households and national governments cannot afford them. The present analysis demonstrates that there are also strong gradients within countries that should be considered in decisions regarding vaccination programs.

Our analysis focuses on underlying disparities in vaccination coverage and pre-vaccination rotavirus mortality risk, and their impact on vaccination outcomes. Countries differed substantially in their patterns of underlying disparities. In Fig. 1, countries with longer lines had greater differences between quintiles in one or both parameters. Some had greater disparities in vaccine coverage, represented by flatter lines, while others had more disparity in mortality, the steeper lines.

Underlying disparities affect differences in estimated vaccination outcomes. Some countries, such as Bangladesh, Ghana, Uganda and Lesotho, had relatively low disparities in both coverage and mortality risk. This resulted in relatively equitable benefits of vaccination. In countries with high disparities in coverage and mortality risk (e.g., India, Pakistan and DRC) vaccination, in the absence of efforts to reduce these disparities, would result in a further concentration of rotavirus mortality among the poor.

The answer to the question of whether rotavirus vaccination will be equitable depends on both the context and the measure of equity. One option is to consider the distribution of benefits by wealth (or region) – is the estimated mortality reduction greater or lower among poorer households? Based on the analysis of Concentration Indices (Fig. 3), rotavirus vaccination would disproportionately benefit the poor in two-thirds of the GAVI countries considered. An alternative criterion is to ask whether vaccination would increase or decrease the concentration of burden among the poor or marginalized populations. Using this standard, vaccination is unlikely to be equitable unless programs specifically target populations or regions with elevated mortality risk.

It is also important to note that vaccination investments in GAVI-eligible countries target the global poor at a national level, making vaccination available faster to children who would be unlikely to receive it otherwise. However there is a great deal of overlap in economic levels within populations in low and middle-income countries. Countries such as India and Brazil have large economic disparities that are obscured by national income level categories. This means that many upper income children in low-income countries will receive GAVI-funded vaccines while low-income children in middle-income countries will not. Additional analyses could explore the cost-effectiveness and benefit of targeted efforts to increase coverage among poorer or higher risk children in middle-income countries.

4.1. *Increasing cost-effectiveness and equity*

This analysis suggests that the value for money of rotavirus vaccination could be substantially increased. Eliminating differences in coverage between richest and poorest quintiles could increase the number of deaths averted by 89% among the poorest quintile and could increase the overall number of lives saved by 38%. This is equivalent to increasing vaccine efficacy against severe rotavirus infection from 57% to 79%. In countries with near-universal coverage or highly equitable coverage, there is little or no disparity in benefits.

The analysis compares impact and cost-effectiveness with current patterns of immunization and an equity scenario where poorer children have the same coverage as those in the highest quintile. While universal equitable coverage would reduce disparities, an alternative would be to target accelerated introduction or expanded coverage of high-risk children, based on geography or other population characteristics. The cost-effectiveness and impact estimates in Table 4 and Figs. 2 and 4 can be interpreted as the incremental cost-effectiveness of introducing the vaccine into higher risk populations first. The results suggest that it would be most cost-effective to target these children first. Although few countries are considering sub-national introduction, this could be done to target high-risk regions. In order to be most effective, these

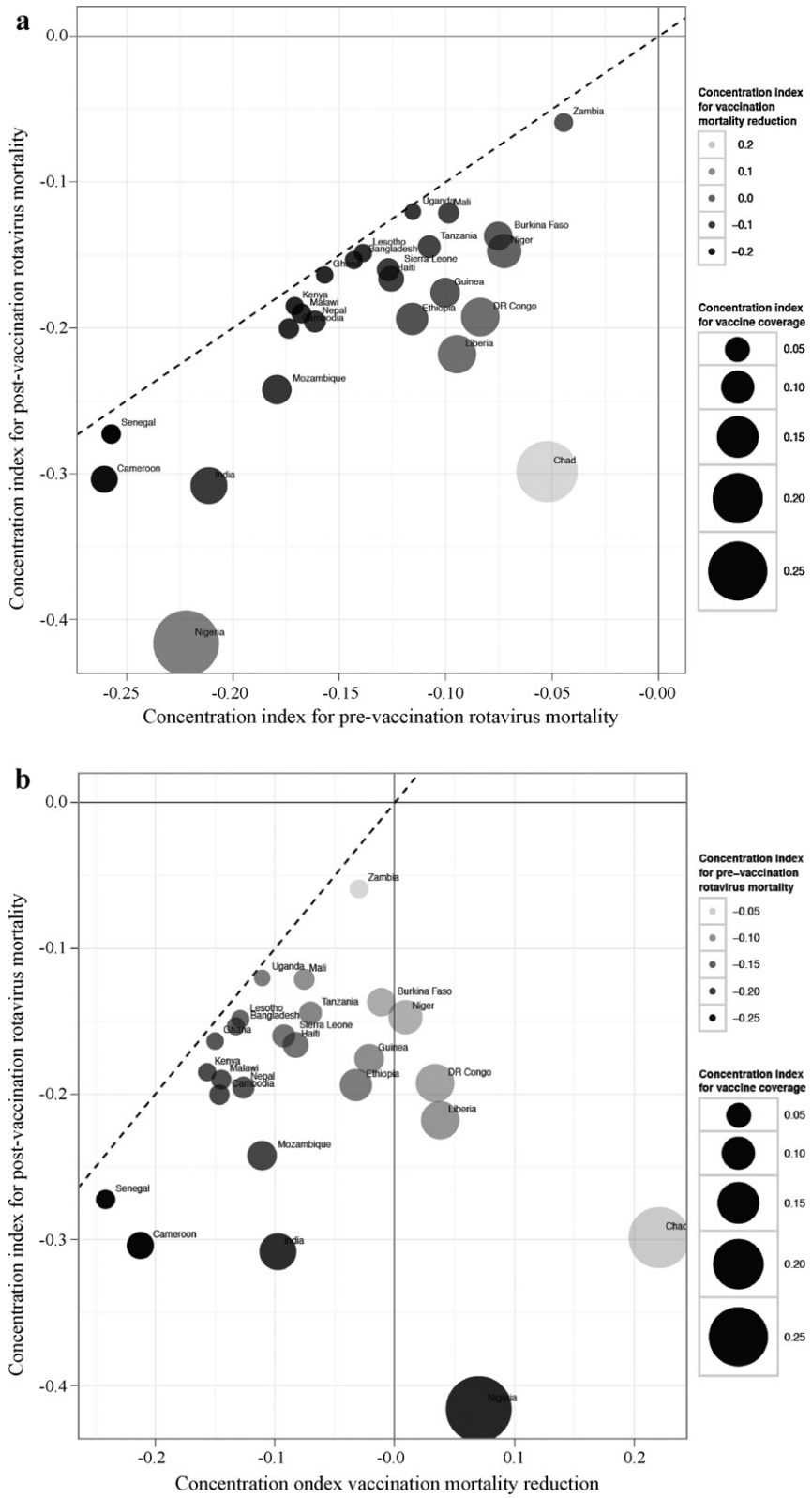

Fig. 3. Disparities and concentration indices for vaccination coverage, pre-vaccination rotavirus mortality, vaccination mortality reduction, and post-vaccination rotavirus mortality for 30 GAVI-eligible countries.

regions would also need to have adequate levels of vaccine coverage. Geographic targeting could also focus on more remote areas where access to timely treatment of diarrhea is lower. For other infections with clear geographic hotspots (e.g., malaria and soil transmitted helminthes) this is a clear strategy for improving value for money [30,31]. Although it can be more difficult to target children based on socio-economic characteristics, there are examples of programs designed to do this, such as conditional cash transfer programs that target low-income communities and households [32,33]. A related approach would be to target based on other risk

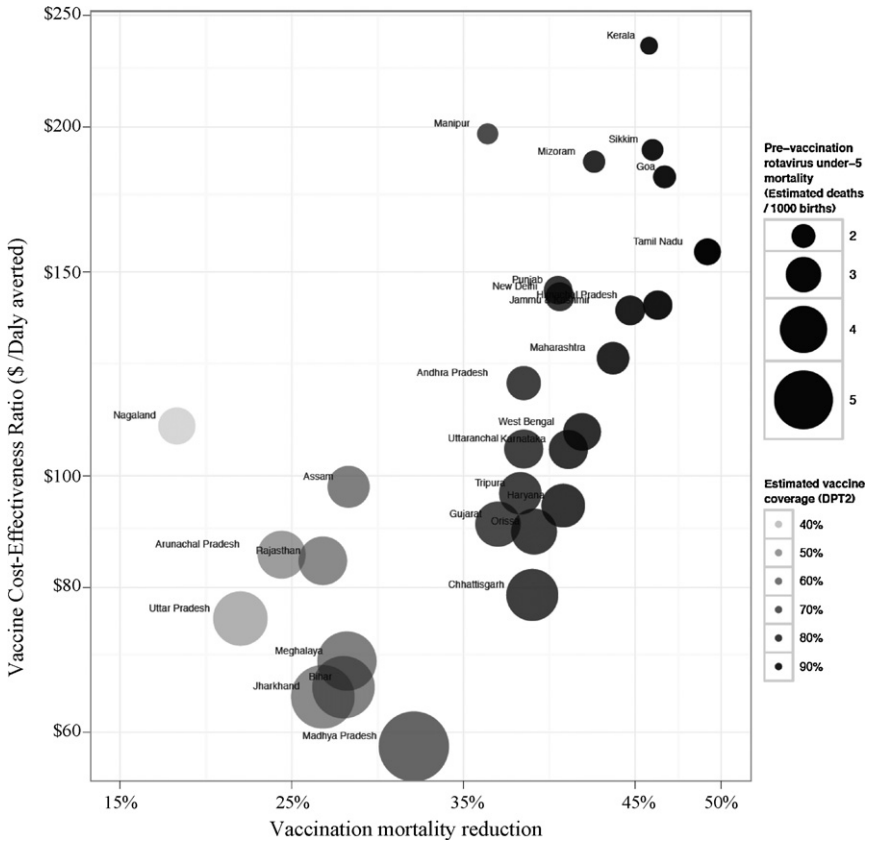

Fig. 4. Geographic disparities in estimated vaccination coverage, pre-vaccination rotavirus mortality, vaccination mortality reduction, and vaccination cost-effectiveness in India.

factors such as nutritional status by coordinating with maternal and newborn nutrition programs. These targeting strategies would increase the likelihood that investments go disproportionately to the areas or children where they provide the greatest value for money. While these targeting strategies would create challenges, the level of potential benefit (a 38% increase in mortality reduction) is too great to ignore.

4.2. Limitations

The current study is a preliminary assessment of the distributional effects and, as such, it has a number of limitations. First, no systematic data are available for directly estimating rotavirus mortality or burden by wealth quintile or sub-national regions. As a result, we aggregated data on post-neonatal infant mortality and low weight-for-age as a proxy measure. It is important to note that there is variability in estimated mortality disparities, depending on which proxy measure is used. For example, in Table 3 post-neonatal mortality is highest in the second poorest quintile, rather than the poorest. This may be the product of higher neonatal mortality among the poorest, differences in reporting biases or other factors. This suggests that better proxy measures, at the level of quintiles or individuals could provide more accurate estimates of disparities. In addition, the analysis only explores one dimension of equity at a time (either socio-economic status or geographic location) without exploring the interaction between them or whether other factors such as maternal education may explain both reduced vaccination and increased mortality risk. As a result, this may underestimate the actual disparities in outcomes.

The current analysis focuses on the differences in impact across socio-economic and geographic groups, however it does not include differences in the costs of reaching different populations or differences in the economic consequences of severe illness, such as medical costs. It is likely that it costs more to reach higher risk children and more to increase coverage among marginalized populations. In particular, there is little available information on the incremental costs of increasing coverage for economically or geographically marginalized children. Future studies should examine the costs of alternative strategies and their resulting cost-effectiveness.

4.3. Other dimensions of disparities

The current model assumes equal vaccine efficacy across wealth quintiles and states within a given country. Clinical trials have demonstrated different levels of efficacy in countries with different income and mortality levels [21,23]. Among other factors, these national level differences may be explained by variability in exposure to other environmental enteric pathogens [21]. Given the substantial within-country disparities in sanitation and water access by region and wealth quintile, it is possible that there would also be disparities in vaccine efficacy at the country level as well, resulting in an underestimation of the actual inequities.

The current analysis assumed that vaccination timing is the same across all wealth quintiles and regions, however this is likely not the case. Patel et al. demonstrated substantial delays in immunizations in 43 low-income countries [25]. It is quite possible that delays are greater among children in the poorer quintiles. Delays could lead to missing opportunities for preventing cases, and given the current SAGE recommendations, could result in more poor children not receiving the vaccine due to the age restrictions.

In addition, Atherly et al. [5] demonstrated that indirect protection through herd immunity might increase the cost-effectiveness of vaccination and reduce the effects of delays or disparities in coverage. If herd immunity occurs it could lead to high of rates of coverage among better off children providing protection to poor

children with lower rates of coverage, thus reducing the disparity in benefit. Although the current analysis did not model the effect of herd mortality or indirect protection, it suggests that their potential impact is likely to depend on the degree of social and geographic mixing associated with the disparities in coverage. If economic and social disparities in coverage are associated (as in the case of India), then indirect protection may be diminished. Even within states or communities, spatial clustering of non-vaccinated children may lead to reductions in indirect protection with poorer unvaccinated children being less likely to be around vaccinated children and thus less likely to receive that indirect protection.

5. Conclusions

The current study represents an initial effort to explore the distributional effects of rotavirus vaccination at the sub-national level. The results demonstrate that rotavirus vaccination is most effective when targeted to low-income populations or geographic regions. Programmatic or funding strategies that accelerate uptake in high-risk subpopulations or regions would increase the cost-effectiveness and impact of national programs.

Earlier this year key international donors including the UK government and the Bill and Melinda Gates Foundation committed billions of dollars to GAVI to expand and accelerate the introduction of new childhood vaccines such as rotavirus. This occurred following the announcement by GSK, one of the rotavirus manufacturers that they would reduce their price to $2.50 per dose for low-income countries. Both of these efforts greatly increase the number of children in low-income countries who will receive the vaccine and the number of deaths that will be averted. However, the current study suggests that these laudable efforts to benefit to the poorest populations and provide good value for money will fall short of their goal without increased attention to the distributional effects on vaccination. Both the cost-effectiveness of vaccination and its impact in terms of deaths averted could be enhanced through greater attention to disparities in risk and in coverage.

Conflict of interest

The authors have no conflicts to declare.

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