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Effects Of Geographic And Economic Heterogeneity On The Burden Of Rotavirus Diarrhea And The Impact And Cost-Effectiveness Of Vaccination In Pakistan

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Abstract

Globally, rotavirus is a leading cause of childhood diarrhea and related mortality. Although rotavirus vaccination has been introduced in many countries worldwide, there are numerous low- to middle-income countries that have not yet introduced. Pakistan is one of the countries with the highest number of rotavirus deaths in children under five years. Although rotavirus infection is almost universal among children, mortality is often a result of poor nutrition and lack of access to health care and other aspects of poverty. We assess the impact and cost-effectiveness of introducing childhood rotavirus vaccination in Pakistan. We use household data from the 2012–2013 Demographic Health survey in Pakistan to estimate heterogeneity in rotavirus mortality risk, vaccination benefits, and cost-effectiveness across geographic and economic groups. We estimate two-dose rotavirus vaccination coverage that would be distributed through a routine vaccination program. In addition, we estimate rotavirus mortality (burden), and other measures of vaccine cost-effectiveness and impact by subpopulations of children aggregated by region and economic status. Results indicate that the highest estimated regional rotavirus burden is in Sindh (3.3 rotavirus deaths/1000 births) and Balochistan (3.1 rotavirus deaths/1000 births), which also have the lowest estimated vaccination coverage, particularly for children living in the poorest households. In Pakistan, introduction could prevent 3061 deaths per year with current routine immunization patterns at an estimated \$279/DALY averted.

Effects of geographic and economic heterogeneity on the burden of rotavirus diarrhea and the impact and cost-effectiveness of vaccination in Pakistan

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A B S T R A C T

Globally, rotavirus is a leading cause of childhood diarrhea and related mortality. Although rotavirus vaccination has been introduced in many countries worldwide, there are numerous low- to middle-income countries that have not yet introduced. Pakistan is one of the countries with the highest number of rotavirus deaths in children under five years. Although rotavirus infection is almost universal among children, mortality is often a result of poor nutrition and lack of access to health care and other aspects of poverty. We assess the impact and cost-effectiveness of introducing childhood rotavirus vaccination in Pakistan. We use household data from the 2012–2013 Demographic Health survey in Pakistan to estimate heterogeneity in rotavirus mortality risk, vaccination benefits, and cost-effectiveness across geographic and economic groups. We estimate two-dose rotavirus vaccination coverage that would be distributed through a routine vaccination program. In addition, we estimate rotavirus mortality (burden), and other measures of vaccine cost-effectiveness and impact by subpopulations of children aggregated by region and economic status. Results indicate that the highest estimated regional rotavirus burden is in Sindh (3.3 rotavirus deaths/1000 births) and Balochistan (3.1 rotavirus deaths/1000 births), which also have the lowest estimated vaccination coverage, particularly for children living in the poorest households. In Pakistan, introduction could prevent 3061 deaths per year with current routine immunization patterns at an estimated $279/DALY averted. Increases in coverage to match the region with highest coverage (Islamabad) could prevent an additional 1648 deaths per year. Vaccination of children in the highest risk regions could result in a fourfold mortality reduction as compared to low risk children, and children in the poorest households have a three to four times greater mortality reduction benefit than the richest. Based on the analysis presented here, the benefits and cost-effectiveness of rotavirus vaccination can be maximized by reaching economically and geographically vulnerable children.

1. Introduction

Rotavirus is a leading cause of childhood diarrhea globally, resulting in mortality, morbidity, and economic impacts on households and health systems [1–3]. While the introduction of new rotavirus vaccines has reduced this health and economic burden in many countries, numerous low- and middle-income countries have not yet introduced them [4–6]. Current estimates indicate

that Pakistan has the third highest number of rotavirus deaths (14,700), exceeded only by India and Nigeria [7]. Recent estimates of diarrheal mortality in Pakistan declined 65% between 1990 and 2015 [8], likely as a result of improvements in water and sanitation at the national level [9]. However, rotavirus mortality estimates have fluctuated and exhibited slower decline, likely because water and sanitation improvements had limited impact on rotavirus transmission due to high fecal shed rates, low infectious dose, and possible respiratory pathways [10–14].

While there are several national estimates of rotavirus diarrheal mortality, they do not address the geographic and economic

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inequality in burden. Although rotavirus is often considered a 'democratic' pathogen because almost all children experience an infection by five years of age, there is great heterogeneity in mortality risk and medical costs induced by infections [7,15], with poorer children being disproportionately impacted. While overall infant mortality in Pakistan declined by 14% between 1991 and 2013, this mortality remained constant for the children in the poorest wealth quintile [16]. In Pakistan, there is substantial heterogeneity in undernutrition and access to diarrheal treatment, both important risk factors for diarrheal mortality [17,18]. Similar inequities in risk are present in India and resulted in substantial heterogeneity in estimated mortality burden and vaccine cost-effectiveness across economic and geographic sub-populations [19].

In addition to health, childhood diarrhea episodes can have an important impact on household economics. In a multi-country study of household costs of managing diarrhea authors found a mean household cost of $4.45 (2011 US$) per episode in Pakistan [20]. While this amount may seem nominal, these costs have broader impacts on households. For example, 12% of households reduced food consumption to cover the costs, 29% borrowed money to pay them, and 14% cut other expenditures. An estimated 28% of respondents stated that treatment costs were a barrier to obtaining treatment for childhood diarrhea. These economic costs are likely to impact the poorest households most severely.

This study assessed the impacts and cost-effectiveness of childhood rotavirus vaccination introduction in Pakistan, while also accounting for differences across geographic and economic populations. Specifically, we focused on: (1) characterizing geographic and economic patterns of diarrhea risk factors and estimating related mortality distribution, (2) characterizing the geographic and economic patterns of vaccination and estimating impact of vaccine introduction, and (3) assessing the cost-effectiveness of vaccination across geographic and economic sub-populations. This study provides important national-level impact and cost-effectiveness estimates as Pakistan prepares to transition from Gavi, the Vaccine Alliance (Gavi) support, most recently projected to be 2020 [21].

2. Methods

2.1. Overview

We used 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 five years of life. We model a series of sub-populations separately by geography and socio-economic status. Our geographic regions of interest are those where data was collected in the 2012–13 Pakistan DHS (2013 PDHS), representing 96% of the total population [16]. We used five regions in our analysis: the four provinces of Balochistan, Sindh, Punjab, and Khyber Pakhtunkhwa (KP) and the Islamabad capital territory (Islamabad ICT). Within each region, we grouped children into wealth quintiles based on an asset index [23]. Thus, the modeling unit of analysis is region by wealth quintile. Future outcomes are discounted at 3% and costs are estimated in 2017 inflation-adjusted US dollars using changes in consumer price indices [24]. All subpopulation means were calculated using appropriate sample weights based on DHS survey design [16].

2.2. Rotavirus mortality burden

Our estimates of rotavirus mortality rates for children under five (CU5) are based on a combination of estimates from the Institute of Health Metrics and Evaluation (IHME) Global Burden of Disease (GBD) study [9,25] and WHO Maternal Child Epidemiology Estimation (MCEE) [7] study. These studies have different approaches and subsequently often have different final estimates. We used the mean rate (deaths/100,000 CU5) of these two estimates as our base case estimates. Annual rates were converted to cumulative rotavirus mortality risk by age five. All statistical analyses and predicted values used as spreadsheet model inputs were calculated accounting for complex survey design in Stata 14 [26]. Maps and figures were created using ArcGIS [27] and *ggplot2* [28] in R [29].

We developed an evidence-based individual risk index to estimate the relative distribution of mortality within region-wealth quintile subpopulations to capture the likely heterogeneity in rotavirus mortality risk among economic and geographic populations after Rheingans et al. [19] (Supplement). We used 2013 PDHS data to calculate individual and mean risk index values for each subpopulation. The risk index assumes that a 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 oral rehydration treatment (ORT) if he/she experiences a diarrheal event.

The risk index for each region-wealth quintile subpopulation was normalized by dividing the mean risk index for the whole population (Eq. (1)). Then, we multiplied it by the overall rotavirus mortality envelope to ensure that the regional total mortality is the same as the average of MCEE and GBD estimates, while maintaining an estimated distribution across wealth quintiles. Rotavirus mortality burden is estimated as deaths per 1000 live births. For each region (r) and wealth quintile (q) sub-population, rotavirus mortality burden was calculated as:

$$RVBurden_{r,q} = \frac{RVMort_{r,} \cdot RVRiskIndex_{r,q}}{RVRiskIndex} \qquad (1)$$

Mortality risk was converted into Disability Adjusted Life Years (DALYs) based on standard methods using age weighting and discounting [30]. We focus on rotavirus mortality in our model, as previous studies have shown that over 98% of rotavirus-associated DALYs in low-income settings are associated with mortality [15,31]. We estimated the timing of deaths by combining overall rotavirus mortality estimates for each subpopulation and the estimated age distribution of events [32,33]. Monthly rates were estimated for the first year of life, and then annually for the subsequent four years. For any subpopulation and period (t), mortality burden is estimated in Eq. (2).

$$RVBurden_{r,q,t} = RVTime_t \cdot RVBurden_{r,q} \qquad (2)$$

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

2.3. Vaccination coverage and effectiveness

Vaccine effectiveness and benefit were estimated using vaccination coverage and timing, dose efficacy over time, and a heterogeneity adjustment for within quintile correlation of vaccine coverage and rotavirus risk (Table 1). We utilized published efficacy estimates [34] and assumed that vaccine efficacy does not vary across subpopulations, despite evidence of variability based on income [35], region [36], and nutritional status [37]. Estimates are based on a two-dose vaccine, as Pakistan is in the early phases of introducing ROTARIX® (ROTARIX is a registered trademark of GlaxoSmithKline Biologicals SA, used under license by GlaxoSmithKline Inc.), delivered alongside DPT1 and 2.

Vaccination coverage for each region (r) and wealth quintile (q) and timing was estimated for both doses using vaccination data for one-year-olds from the 2013 PDHS. For each subpopulation, we estimated the proportion of children receiving each dose by the end of each period (t). We used one-month time periods for the first year and one year intervals thereafter. For any subpopulation,

Table 1
Rotavirus vaccination in Pakistan cost-effectiveness model input parameter values and distributions.

Input	Base case	Range[*]	Ref.
Rotavirus Mortality	Deaths		
National rotavirus mortality rate among children < 5 (deaths/1000 live births)	0.46	0.24–0.68; Triangular	Mean [7,25]
Risk Factors for mortality			[16]
Oral rehydration treatment	93% effective	–	[18]
Undernourished	Relative risk	1–12.5	[17]
RV Vaccine - Efficacy			
Full Course (2 doses): Years 1–2	48.3%	22.3% - 66.1%; Triangular	[34]
Single dose reduced efficacy	50%	25% - 75%; Triangular	Assumption
Reduced efficacy in years 3–5	20%	0–40%; Triangular	Assumption
Vaccination			
Dose 1–3 coverage	Varies by region-wealth quintile		[16]
Vaccination timing			
Medical Costs (2017 US$)			
Mean medical cost per child	$1.21	0.9–1.5; Triangular	[20,41]
Healthcare utilization by sub-group			[16]
Medications (mean)			[20]
All seeking care	$2.18		
Any with cost	$3.35		
Informal care (mean)			[20]
All seeking care	$0.69		
Any with cost	$1.06		
Hospitalization cost (mean)	$0.92		
Rate	0.02		[38]
Cost per episode (4-day stay)	$39.60		[38,41,42]
Outpatient cost (mean)	$0.13		
Rate	0.05		[38]
Cost per episode	$2.52		[38,41,42]
Diarrheal cases that receive formal care	63.7%		[16]
Vaccine Costs			
Vaccine Price			
Full GAVI price (US$/dose)	$2.19	$1.35–$2.19; Triangular	[43]
GoP price (2017–30 average)	$1.49		
Administration (US$)	$1.68	$1.01-$2.35; Triangular	[44]

[*] Range values represent upper and lower values included in uncertainty analyses.

the coverage for each dose (d) was defined in Eq. (3) as the product of coverage and the likelihood of receiving it by a given period (t).

$$Cov_{d,r,q,t} = Dose_{d,r,q} \cdot Time_{d,r,q,t} \qquad (3)$$

Vaccination effectiveness ($VacEff_{d,t}$) and benefit ($VacBenefit_{r,q}$) were calculated by combining information on the coverage, efficacy, expected burden and the heterogeneity adjustment (Eq. (4)). Where $VacEff_{d,t}$ is the incremental protection of each dose d during time period t.

$$VacBenefit_{r,q} = \sum_{d,t} Cov_{d,r,q,t} \cdot VacEff_{d,t} \cdot RVBurden_{r,q,t} \cdot Het_{r,q} \qquad (4)$$

Vaccination benefit estimates accounted for the correlation between individual risk and vaccine access at the region-quintile sub-group level; however, it implicitly assumes that risk and access are not correlated *within* subpopulations. This assumption was tested by examining the correlation between community-level DPT2 coverage and risk index within each subpopulation using Pearson's coefficients (Supplement). The adjustment ($Het_{r,q}$) is defined as the ratio of the mean product of subpopulation DPT2 coverage ($DPT_{r,q}$) and rotavirus risk ($RVRiskIndex_{r,q}$) for the region divided by the product of coverage and risk for each subpopulation (Eq. (5)).

$$Het_{r,q} = \overline{RVRiskIndex_{r,q} * DPT_{r,q}}/RVRiskIndex_{r,q} * DPT_{r,q} \qquad (5)$$

2.4. Economic outcomes

In the absence of data characterizing the patterns of healthcare utilization and related heterogeneity in direct medical costs within Pakistan, we combined published national estimates of rotavirus direct medical costs per child with estimates of the relative cost per child in each subpopulation [20]. We estimated national mean cost per child for rotavirus infection based on average costs for different categories of care and their likelihood (Table 1). Relative cost for subpopulations was calculated based on the utilization rate of public and private, inpatient, and outpatient services, as urban and high economic status households are more likely to seek care, especially inpatient and private care. After Patel et al. [38], we estimated that 2.3% of children will experience a hospitalization, based on surveillance from Karachi, Pakistan [39] and 5.1% will experience an outpatient visit, based on data from India, since estimates for Pakistan were unavailable [40]. We estimated facility costs of $39.6/hospitalization and $2.5/outpatient visit from WHO-CHOICE [41,42]. Costs for medication or informal providers (e.g. pharmacy, healers) were estimated at $2.18/episode [20]. The total mean cost was estimated at $1.21/child in 2017 US$.

Averted (or prevented) ($AvertCost_{q,r}$) costs were estimated for each region (r) and wealth group (q) based on coverage and vaccine efficacy (Eq. (6)).

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

	Burden (RV deaths/1000 births)	RV deaths	RV deaths averted	Benefits (RV deaths averted/1000 births)	% Reduction	Costs averted ($/1000 births)	Vaccination costs ($/1000 births)	GAVI perspective ICER ($/DALY averted)	Average Pakistan perspective ICER ($/DALY averted)	Equal coverage benefits (RV deaths averted/1000 births)	Equal coverage ICER ($/DALY averted)
National	2.28 [1.40; 3.13]	54,761 [33,557; 74,985]	15,304 [7196; 22,928]	0.57 [0.27; 0.86]	29 [16; 37]	2122 [972; 2405]	26,103 [22,576; 29,615]	279 [182; 617]	224	0.96 [0.46; 1.44]	203 [171; 579]
Region											
Punjab	2.10 [1.29; 2.88]	22,246 [13,645; 30,452]	7864 [3707; 11,797]	0.74 [0.35; 1.11]	35 [20; 45]	437 [200; 494]	6361 [5510; 7221]	235 [152; 512]	189	0.91 [0.44; 1.37]	221 [143; 479]
Sindh	3.27 [2.01; 4.48]	20,941 [12,855; 28,667]	4766 [2217; 7157]	0.74 [0.35; 1.12]	23 [13; 29]	720 [329; 819]	4660 [4031; 5289]	156 [100; 368]	122	1.43 [0.68; 2.14]	127 [83; 291]
Khyber Pakhtunkhwa	2.14 [1.30; 2.94]	6669 [4053; 9151]	1990 [950; 2954]	0.64 [0.30; 0.95]	30 [17; 38]	85 [39; 97]	5406 [4675; 6127]	245 [161; 527]	200	0.90 [0.43; 1.35]	231 [150; 492]
Balochistan	3.15 [1.93; 4.31]	4805 [2941; 6579]	642 [302; 957]	0.42 [0.20; 0.63]	13 [8; 17]	115 [53; 130]	2508 [2173; 2844]	167 [110; 365]	135	1.24 [0.59; 1.85]	154 [100; 334]
Islamabad (ICT)	0.75 [0.46; 1.02]	100 [62; 137]	42 [20; 63]	0.32 [0.15; 0.47]	42 [24; 54]	765 [351; 865]	7169 [6186; 8134]	594 [388; 1315]	473	0.34 [0.16; 0.51]	583 [380; 1298]

The incremental cost of the intervention ($IntCost_{q,r}$) includes vaccine and administration. The estimated price for the vaccine is \$2.19, shared between the Government of Pakistan and Gavi. The government's fraction is anticipated to start below 25% in 2017 and gradually increase to 100% by 2026 [43]. Base case estimates are based on the full cost of \$2.19/dose, reflecting societal cost and the government's cost after 2026. Additionally, we report cost-effectiveness from the perspective of the Government of Pakistan using \$1.49 per dose cost (average cost from 2017–30, Table 1). Intervention costs assumed wastage of 10% and incremental administration costs of \$1.68 per dose based on the sum of supply chain and service delivery costs from Portnoy et al. [44]. The main outcome measure was the incremental cost-effectiveness ratio ($ICER_{q,r}$), which was estimated for each region and economic subpopulation.

$$ICER_{q,r} = \frac{IntCost_{q,r} - AvertCost_{q,r}}{VacBenefit_{q,r}} \qquad (7)$$

2.5. Sensitivity and uncertainty analysis

Individual input parameters were varied to estimate the effect of changes on estimated health and economic impacts (Table 1), using one-way and probabilistic sensitivity analysis (PSA). We used Monte Carlo simulations to vary multiple input parameters simultaneously to assess baseline predictions. Key input variables were characterized as distributions and simulated for 10,000 iterations in SimVoi [45] to produce impact and cost-effectiveness distributions by region and upper and lower 95% uncertainty limits (UL) for outputs. The effects of equitable risk and coverage were examined as hypothetical scenarios, simulated by removing risk weighted-coverage estimates and giving all subpopulations the highest regional coverage for DPT1 and DPT2 doses (97 and 96%, respectively for Islamabad).

3. Results

3.1. Distribution and co-distribution of risk factors

Our model incorporated the distribution of risk factors for diarrheal mortality and immunization to estimate the distribution of rotavirus burden, vaccination impact, and cost-effectiveness. Two main features characterized this distribution: (1) differences in risk factors and immunization across sub-populations and (2) the co-distribution or correlation among the risk factors. Children in the richest quintile were significantly less likely to be moderately or severely underweight, significantly more likely to receive ORT, and have been vaccinated with DPT1 and DPT2, compared to children in the poorest quintile (Supplement Tables 1 and 2). There were substantial regional differences in both risk and immunization coverage factors (Supplement Tables 1 and 2), with positive correlations in some community risk and coverage estimates at regional and national levels (Supplement Table 3).

3.2. Health and medical cost burden by regional and economic subpopulations

The highest estimated health burden was in Sindh (3.3 rotavirus deaths/1000 births; 95% UL: 2.0–4.5) and Balochistan (3.1 deaths/1000 births; 95% UL: 2.0–4.3, Table 2), regions with the lowest vaccination coverage, particularly for children in the poorest and poorer households (Fig. 1). Health and economic burden were inversely related in all regions except Sindh (Fig. 2). In most regions, economic burden increases with wealth, while health burden was higher among children in poorest quintiles (Fig. 2). Wide
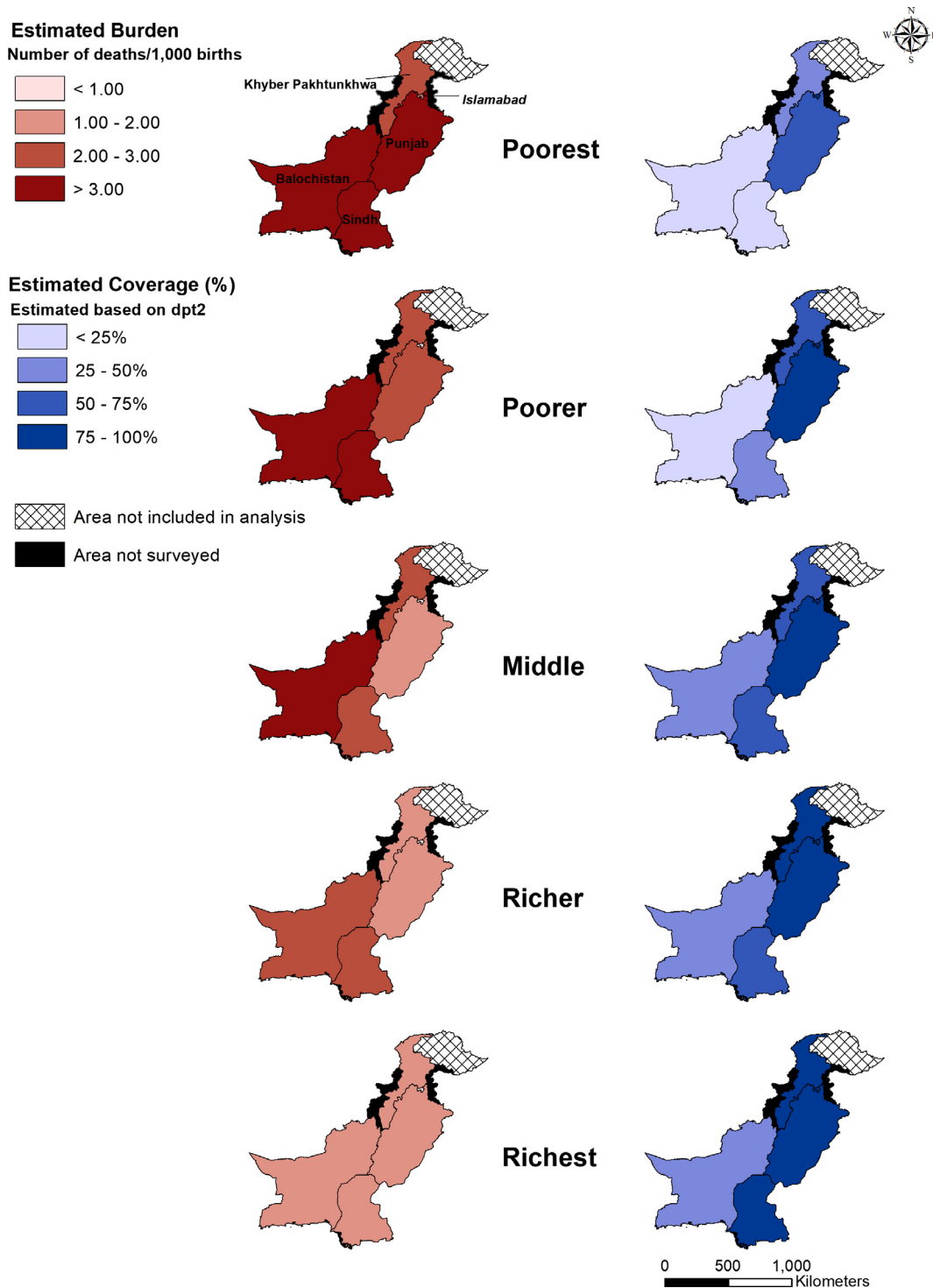
Fig. 1. Estimated rotavirus burden and vaccination coverage for each regional wealth quintile. DPT2 coverage is used as a proxy for estimating a 2-dose rotavirus vaccination schedule.

confidence intervals around average rotavirus mortality estimates indicated substantial heterogeneity nationally and within each region (Table 2, Supplement).

3.3. Impact of vaccination

Based on 2013 coverage estimates and our baseline estimates for other parameters, rotavirus vaccination introduction would prevent 3061 deaths per year, or 28% of the total burden (Table 2,

Fig. 3). Sindh and Balochistan had the lowest percent reduction with vaccination (23% and 13%, compared to 42% in Islamabad), because of lower immunization coverage rates. The greatest absolute benefits of rotavirus vaccination were in Punjab, Sindh, and KP and were generally greater for the poorest quintile (except in KP), primarily because of higher risk in these subpopulations. In contrast, percent mortality reduction was greatest in the higher wealth quintiles, where estimated coverage was the highest.
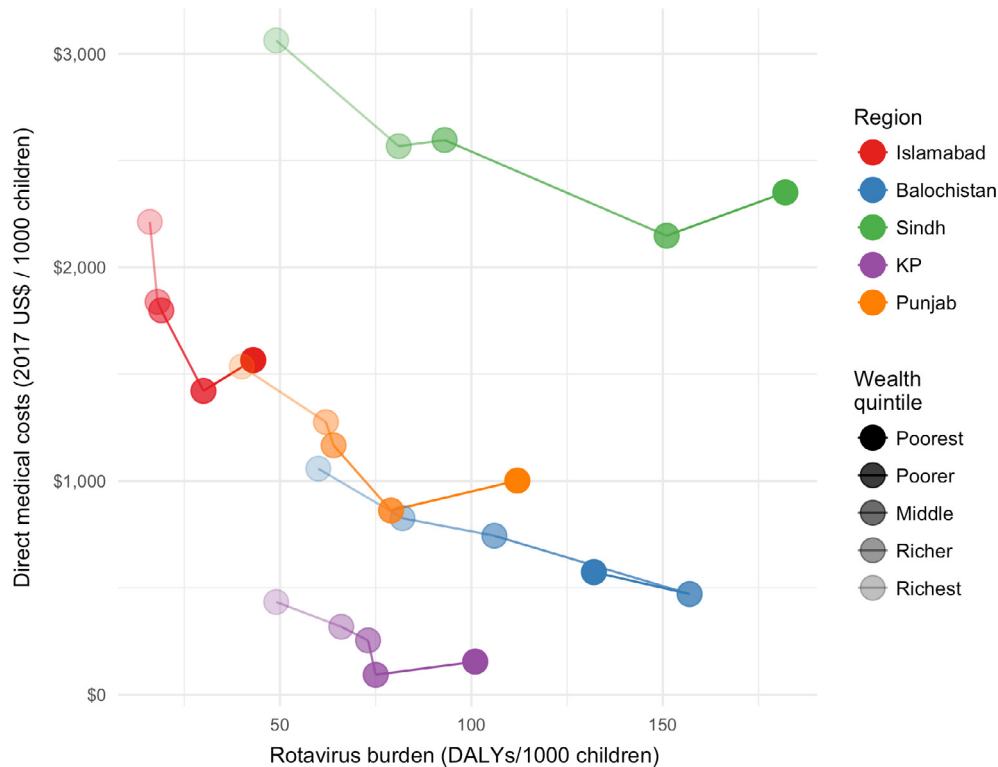
Fig. 2. Estimated direct medical costs and rotavirus mortality burden by regional quintiles in Pakistan. The y-axis shows the economic burden (direct medical costs), while the x-axis shows the health burden (DALY burden) for different region-economic sub-populations. In this figure, each line represents a region and each point a wealth quintile within it, with the darker points representing the richer quintiles. KP: Khyber Pakhtunkhwa.

3.4. Cost-effectiveness of vaccination

Sindh and Balochistan had the lowest Gavi-perspective ICERs (most cost-effective): $155 and $167/DALY, respectively, compared to $594/DALY in Islamabad (Table 2, Fig. 4a). The ICER varied within region and was lowest (most cost-effective) in the poorest quintiles in all regions due to higher disease burden (Fig. 4b). Sindh and Balochistan quintile ICERs ranged from $76/DALY to $279/DALY, compared to Islamabad where ICERs range from $354/DALY to $897/DALY (Fig. 4b). Within all regions, the two poorest wealth quintiles had higher burden and lower ICERs (more cost-effective).

In the one-way sensitivity analysis, the underlying estimate of rotavirus mortality accounted for the greatest variance (50% of overall variance) in ICER (Fig. 5). The potential impact of 'equitable' coverage would result in 4709 deaths averted per year (43%), an increase of 53% over baseline estimates assuming current coverage. Full, equitable coverage would have the greatest effect in the most vulnerable regions with a 192% increase in deaths averted in Sindh and a 295% increase in Balochistan. Within these regions, the greatest improvement would be among children in the poorest households. This scenario assuming equal coverage reduced estimated national ICERS from $279/DALY to $203/DALY (Table 2).

4. Discussion

According to our mortality and vaccination impact models, rotavirus vaccine introduction in Pakistan could result in 3061 deaths prevented per year with current routine immunization patterns. Further increases in coverage could result in an additional 1648 deaths prevented per year, if all regions could achieve the highest routine immunization rates in Islamabad. Based on our estimates, rotavirus vaccination would be highly cost-effective with an ICER of $279/DALY for the full cost of the vaccine and $224/DALY from the perspective of the government of Pakistan. This is substantially below the GNI of $1440 [46], which is often used as a threshold for cost-effectiveness in terms of $/DALY [47]. These estimates are above the base case estimates ($149/DALY, 2012 US$) from Patel et al. [38], but are well within the range of variation in their sensitivity analysis. The main difference between the two rotavirus cost-effectiveness studies is national mortality estimates are higher (3.7 deaths/1000 children) in the Patel et al. study than in this study (2.3 deaths/1000 children), reflecting use of different data sources and declining rotavirus and overall diarrheal mortality rates worldwide [48].

One of the most notable observed patterns of our results is that estimated cost-effectiveness varies substantially across regional and economic subpopulations. Estimated ICERs varied between $155/DALY and $594/DALY across the regions of Pakistan included in this model. Also, ICERs varied by more than an order of magnitude within regions (across wealth quintiles), ranging between $76/DALY and $897/DALY. While vaccination is most cost-effective in high burden areas, it is still highly cost-effective across all subpopulations (see Fig. 4).

Due to the heterogeneity in rotavirus burden, children in poor households and marginal regions are expected to benefit disproportionately. Vaccinating children in the highest risk regions would result in four-fold greater mortality reduction, compared to lower risk regions. Within all regions, the mortality reduction benefit of vaccination is 3–4 times greater for children in the poorest households compared to the richest. While vaccination has the greatest potential benefit for more vulnerable and high-risk
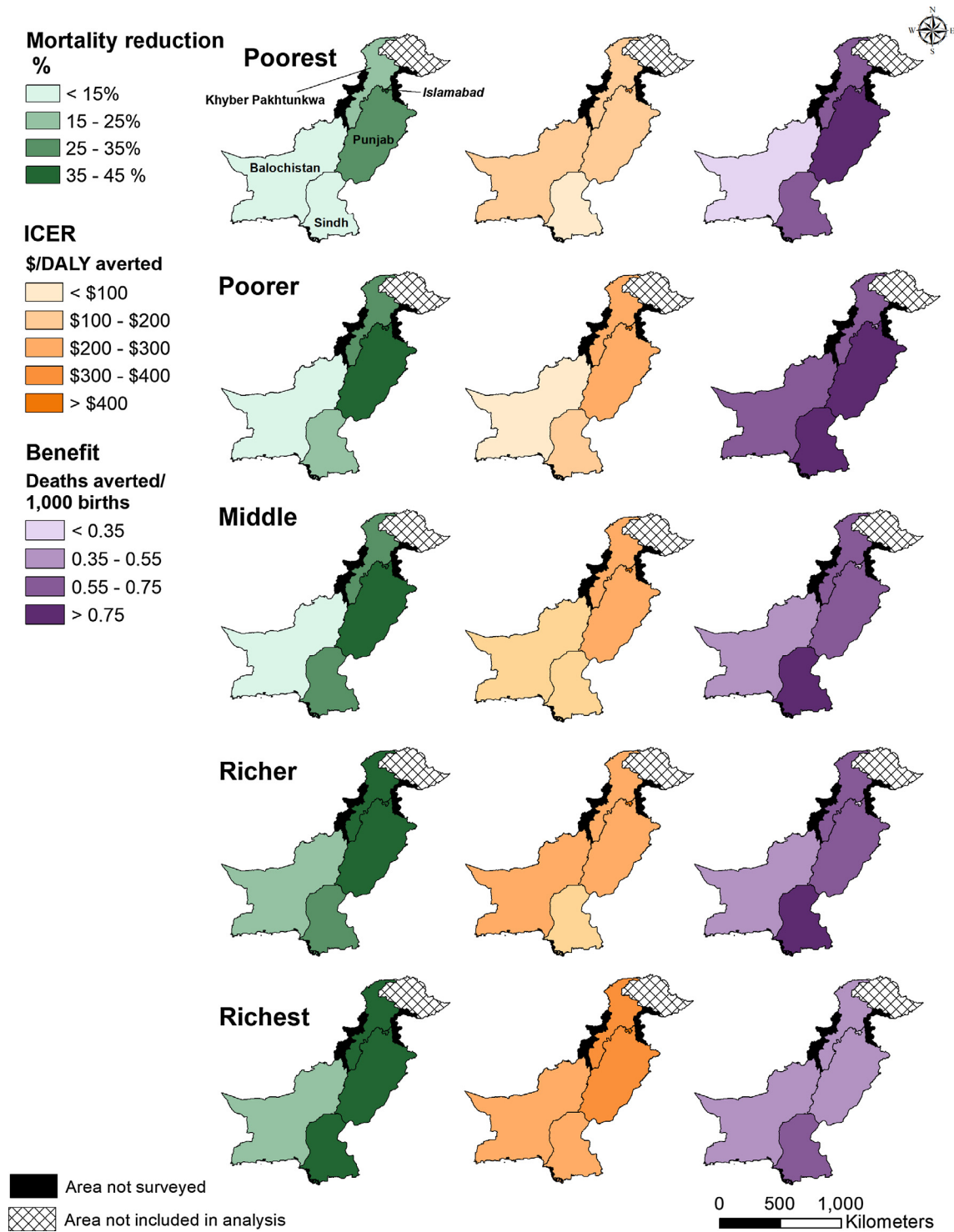
Fig. 3. Estimated impact and cost effectiveness of rotavirus vaccination by region and wealth quintile. Mortality reduction (green), cost-effectiveness ratio (orange), and benefit (purple). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

children, achieving that potential requires that vaccination reach these populations in a timely way.

The disparities in rotavirus burden and vaccination impact and cost-effectiveness are the product of underlying geographic and economic differences in diarrheal mortality risk factors, vaccination and administrative costs. While estimated rotavirus mortality in Pakistan has fluctuated over the past few decades, there is

limited data on how inequality in burden has changed and whether it is likely to change going forward. Trends in relevant risk factors over the past three PDHS surveys (1990–1, 2006–7, and 2012–13) [49] indicate that the overall rate of utilizing ORT for child diarrhea has increased slightly, and disparities between the poorest and richest wealth quintiles have declined slightly. Rates of CU5 being underweight and severely underweight have declined by 5.8% and
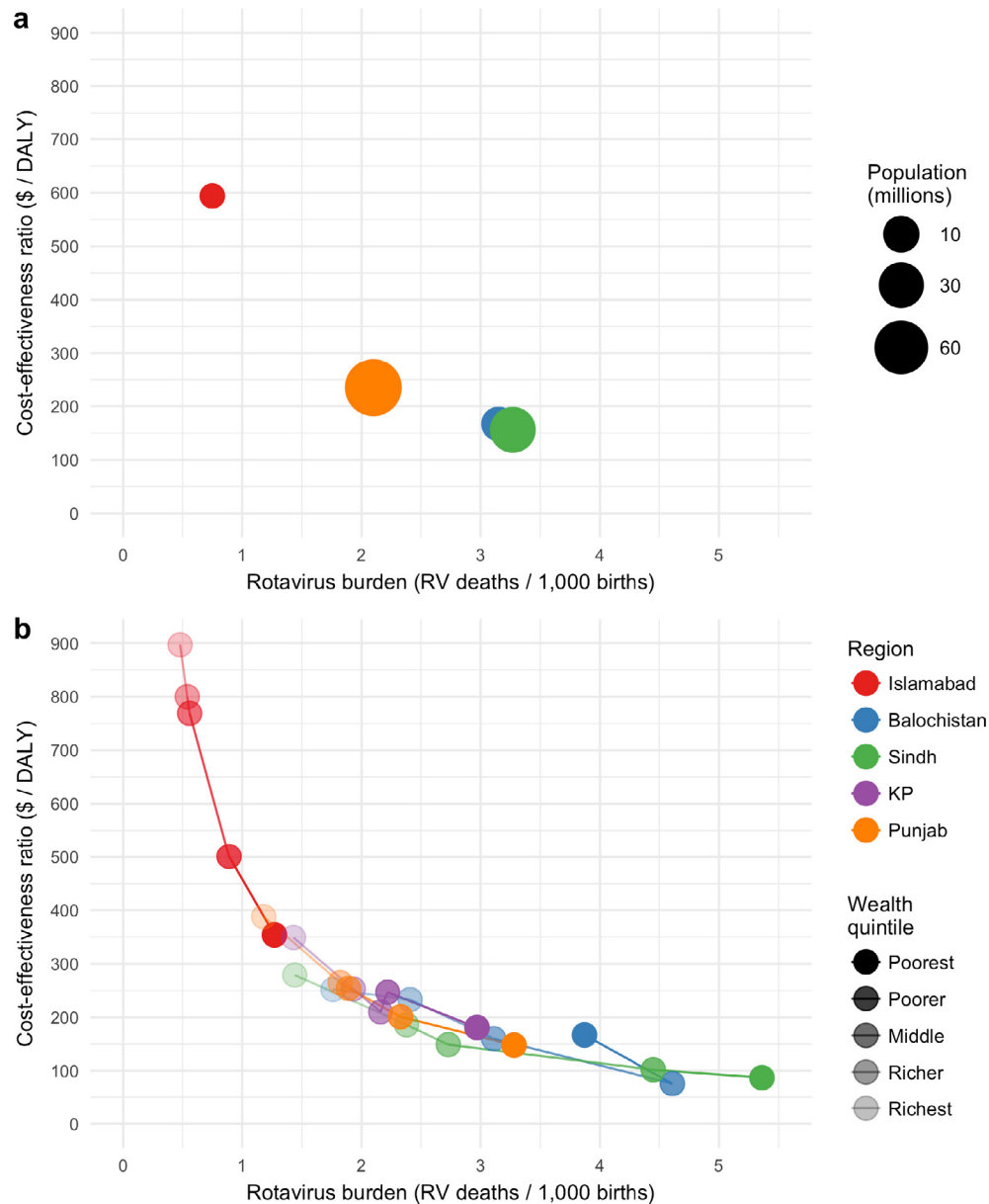
Fig. 4. Estimated incremental cost effective ratios by rotavirus mortality burden by region and population (a) and region and wealth quintile (b).

4.2%, respectively, but mostly in the four highest wealth quintiles, leading to growing inequality in undernutrition. Overall, there has been little progress in reducing inequalities in diarrheal disease mortality risk factors. Our study is limited by data availability on the variability in rotavirus vaccination efficacy and administrative costs for the most vulnerable and difficult to reach children and are assumed to be uniform across subpopulations.

The strengthening of the Expanded Programme on Immunizations (EPI) in Pakistan has resulted in important increases in vaccination coverage over time. PDHS studies suggest that coverage of DPT doses have increased by 11.7% for DPT1 and by 12.7% for DPT2 [16]. However, these improvements have been concentrated among children in the middle and higher wealth quintiles, resulting in growing disparities between the richest and poorest. Based on this analysis, the benefits and cost-effectiveness of rotavirus vaccination would be greatest if they reach economically and

geographically vulnerable children. Thus, expanding EPI coverage among the poorest and most vulnerable children would substantially increase the overall impact of rotavirus immunization.

5. Conclusion

Pakistan has a large health and economic burden from rotavirus disease and children in lower income quintiles in select regions bear an inequitable share of this disease burden. Rotavirus vaccination can avert a substantial portion of this burden and is highly cost-effective, even if support from Gavi is absent. As Pakistan expands rotavirus vaccination across the country, evidence from this study supports policy directives aimed at improving access to vaccination, particularly in low-income, high-mortality populations.
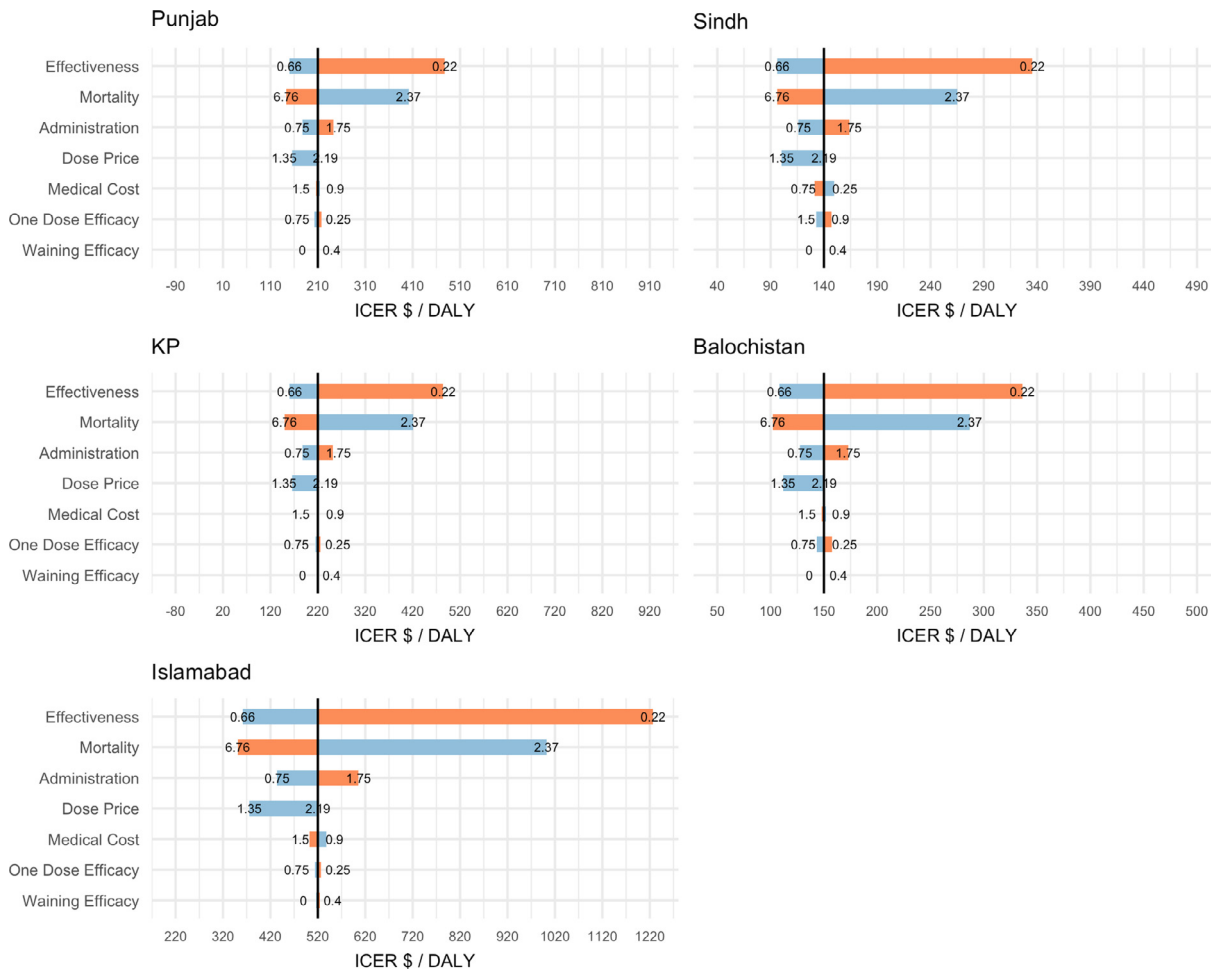
Fig. 5. Tornado diagram of the one-way sensitivity analysis of input variable variation on incremental cost-effectiveness ratio (ICER) for each region. Each input variable and tested assumption is listed on the left axes with corresponding simulated upside (orange) and downside (blue) values at the ends of each bar. The size of each horizontal bar reflects the effect on incremental cost-effectiveness ratio (ICER). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Conflict of interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2018.02.008.

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