Effects Of Geographic And Economic Heterogeneity On Rotavirus Diarrhea Burden And Vaccination Impact And Cost-Effectiveness In The Lao People's Democratic Republic

By: **Richard Rheingans**, John D. Anderson IV, Karoun H. Bagamian, and Clinton J. Pecenka

Abstract

Rotavirus enteritis is responsible for nearly 200,000 child deaths worldwide in 2015. Globally, many low- and middle-income countries have introduced rotavirus vaccine, resulting in documented reductions in hospitalizations and child mortality. We examined the potential impact and cost-effectiveness of introducing rotavirus vaccination in Lao People's Democratic Republic using an Excel-based spreadsheet model. We estimated mortality risk factors, patterns of care seeking, and vaccination access to predict outcomes for regional, provincial, and socioeconomic subpopulations for one birth cohort through their first five years of life and life course in Disability-Adjusted Life Years estimates. Socioeconomic status was defined by categorizing households into regional wealth quintiles based on a national asset index. We modeled a two-dose ROTARIX vaccine under current Gavi pricing and efficacy estimates from Bangladesh and Vietnam. DPT1 and DPT2 coverages were used to estimate rotavirus vaccination coverage. Probabilistic sensitivity analysis was used to assess the impact of uncertainty on model parameters on predicted incremental cost-effectiveness ratios (ICERs), including scenarios of increases in vaccination coverage. Rotavirus vaccination would prevent 143 child deaths/year, or 28% of annual rotavirus burden. The estimated national level ICER for rotavirus vaccination was $140/DALY, with regional socioeconomic subpopulation estimates ranging from $72/DALY for the poorest in the Central region to $353/DALY for the richest in the North region, indicating high cost-effectiveness. Within regions, ICERs are most favorable for children in the poorer and poorest quintiles. However, the full benefits of rotavirus vaccination will only be realized by reducing disparities in vaccination coverage, access to treatment, and environmental health. Improving vaccination coverage to equitable levels alone would prevent 87 additional child deaths per year.

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Effects of geographic and economic heterogeneity on rotavirus diarrhea burden and vaccination impact and cost-effectiveness in the Lao People's Democratic Republic

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A B S T R A C T

Rotavirus enteritis is responsible for nearly 200,000 child deaths worldwide in 2015. Globally, many low- and middle-income countries have introduced rotavirus vaccine, resulting in documented reductions in hospitalizations and child mortality. We examined the potential impact and cost-effectiveness of introducing rotavirus vaccination in Lao People's Democratic Republic using an Excel-based spreadsheet model. We estimated mortality risk factors, patterns of care seeking, and vaccination access to predict outcomes for regional, provincial, and socioeconomic subpopulations for one birth cohort through their first five years of life and life course in Disability-Adjusted Life Years estimates. Socioeconomic status was defined by categorizing households into regional wealth quintiles based on a national asset index. We modeled a two-dose ROTARIX vaccine under current Gavi pricing and efficacy estimates from Bangladesh and Vietnam. DPT1 and DPT2 coverages were used to estimate rotavirus vaccination coverage. Probabilistic sensitivity analysis was used to assess the impact of uncertainty on model parameters on predicted incremental cost-effectiveness ratios (ICERs), including scenarios of increases in vaccination coverage. Rotavirus vaccination would prevent 143 child deaths/year, or 28% of annual rotavirus burden. The estimated national level ICER for rotavirus vaccination was $140/DALY, with regional socioeconomic subpopulation estimates ranging from $72/DALY for the poorest in the Central region to $353/DALY for the richest in the North region, indicating high cost-effectiveness. Within regions, ICERs are most favorable for children in the poorer and poorest quintiles. However, the full benefits of rotavirus vaccination will only be realized by reducing disparities in vaccination coverage, access to treatment, and environmental health. Improving vaccination coverage to equitable levels alone would prevent 87 additional child deaths per year.

1. Introduction

Over the past two decades, child mortality due to diarrhea in Lao Peoples Democratic Republic (Lao PDR) has declined significantly from 501 deaths in 1995 to 97 deaths/100,000 children in 2015 [1]. The decline is likely due to a combination of factors including improved environmental conditions, treatment, and underlying nutritional status. For example, estimated household access to improved drinking water has increased from 40% to 76% coverage and improved sanitation from 21% to 74% coverage between 1995 and 2015 [2]. Reported use of oral rehydration therapy (ORT) has also gone from 31.6% in 1996 [3] to 57.4% in 2012 [4]. Underweight among children under five years of age (U5), a key risk factor for diarrheal mortality [5], has declined nationally from 37.1% in 2006 [6] to 26.6% in 2012 [4]. However, these improvements are distributed unequally, leaving some geographic and economic sub-populations with high risk of diarrheal mortality [4].

Nevertheless, diarrheal disease remains a key cause of child mortality, with rotavirus as the most important diarrheal pathogen with estimates ranging from 528,000 in 2013 [7] to nearly 200,000 child deaths worldwide in 2015 [8]. Globally, 92 countries have introduced rotavirus vaccine, resulting in documented reductions in hospitalizations and child mortality [9–14]. This raises the question of how effective and cost-effective rotavirus

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vaccination would be in Lao PDR. A recent systematic review suggests high rotavirus vaccine efficacy in East and Southeast Asia but cited a lack of estimates on vaccine effectiveness in this region from selected studies before 2011 [15]. A subsequent, multi-country study using 2006 data [6], suggested rotavirus vaccination would be impactful and cost-effective in Lao PDR [16] Recent trial studies in neighboring Vietnam concluded that pentavalent rotavirus vaccines were efficacious against severe rotavirus gastroenteritis [17].

In this study, we examine the potential impact and cost-effectiveness of rotavirus vaccination in geographic and economic subpopulations within Lao PDR. In other studies, geographic and economic factors have been shown to influence the potential risk factors for rotavirus mortality, economic burden of disease, and benefits of vaccination [18–20]. We use household survey data on diarrheal mortality risk factors, patterns of care seeking, and access to vaccination to predict impact and cost-effectiveness across regional, provincial, and economic sub-populations. We examine potential factors that may influence vaccination patterns and affect the potential for high and equitable coverage of rotavirus vaccination. This information provides important insights into what subpopulations vaccination might have the greatest impact on and be most cost-effective for; and how improvements in routine vaccination may further increase the benefits of rotavirus vaccine introduction.

2. Methods

2.1. Overview

We used a spreadsheet-based model developed in Microsoft Excel [21] to predict health and economic outcomes of rotavirus vaccination for an annual birth cohort of children through their first five years of life [18–20]. We estimated outcomes for subpopulations of children by geography and socioeconomic status (SES), accounting for heterogeneity in diarrheal disease burden and access to healthcare across each region. Child-level data from the 2012 Lao Social Indicator Survey (LSIS) [4] was used to populate cohort models from three geographic regions within Lao PDR, representing all 17 provinces. Nationally and within each region, data were aggregated into wealth quintiles based on an asset index [22] and served as the modeling unit of analysis. Future outcomes were discounted at 3% and costs were estimated in 2017 inflation-adjusted US dollars using changes in consumer price indices [23].

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

INPUT	VALUE	RANGE	REFERENCE
Rotavirus mortality	Deaths		
Annual national rotavirus mortality rate among children <5 (deaths/1000 live births)	0.70	0.51–0.86; Triangular	Mean [7,29]
Risk factors for mortality			[4]
Oral rehydration treatment	93% effective	–	[32]
Undernourished	Relative risk	1–12.5	[5]
RV vaccine – efficacy			
Full course (2 doses): years 1–2	48.3%	24.2–72.4%; Triangular	[17]
Single dose reduced efficacy	50%	25–75%; Triangular	Assumption
Reduced efficacy in years 3–5	20%	0–40%; Triangular	Assumption
Vaccination			
Dose 1–2 coverage	Varies by region-wealth quintile		[4]
Vaccination timing			
Medical costs (2017 US$)			
Mean medical cost per child (5-year risk)	$2.49	±25%; Triangular	[16]
Healthcare utilization by sub-group			All under 5 children [4]
Medications (mean)			
All seeking care	$1.73		[41]
Informal care (mean)			
All seeking care	$0.58		[41]
Hospitalization cost (mean)			4 day stay [40]
Rate	0.02		[16]
Cost per episode			[40]
Private	$54.33		
Public	$42.15		
Outpatient cost (mean)			
Rate	0.20		[16]
Cost per episode	$2.52		[40]
Urban			
Private	$3.97		
Public	$2.81		
Rural			
Private	$2.80		
Public	$1.98		
Cough cases that receive formal care	57.4%		Under 5 children, [4]
Children that received packaged ORS	42.7%		Under 5 children, [4]
Vaccine costs			
Vaccine price			
Full Gavi price (US$/dose)	$2.02		[63]
Lao PDR price (US$/dose)	$1.23		[47]
Administration (US$)	$1.64	±25%; Triangular	[45]

All statistical analyses and predicted values accounted for complex LSIS design in Stata 14 [24]. Maps and figures were created using *ggmap* [25] and *ggplot2* [26] in R [27].

2.2. Burden of rotavirus mortality

Overall base case rotavirus mortality rates for children U5 were based on a combined mean rate from IHME Global Burden of Disease (GBD) [28,29] and Maternal Child Epidemiology Estimation (MCEE) [7] estimates for Lao PDR (Table 1), cumulated over the first five years of life. However, substantial heterogeneity in rotavirus mortality risk exists among economic and geographic populations due to differential nutritional status and access to basic care for diarrheal disease [30]. Thus, we developed an evidence-based individual risk index [19,20] to estimate the relative distribution of mortality within these region-wealth quintile populations (Eqs. (1) and (2) in [20]). Regional populations of children in Lao PDR were estimated by combining overall 2015 subnational population estimates from the World Bank [31] with GBD U5 population estimates for 2015 [29]. The distribution of U5 children in each region is assumed to be the same as the distribution of the overall subnational population.

We used 2012 LSIS data on 12 to 24-month-old children (1 YROs) to calculate individual risk index values and aggregate means for each subpopulation. The literature suggests a child's nutritional status (as measured by weight-for-age) and the likelihood of receiving ORT if he/she experiences a diarrheal event are quantitatively linked to diarrheal mortality [5,32]. Data on ORT were only available for children who experienced an episode of diarrhea in the previous two weeks, so we estimated individual propensity for receiving ORT with a logistic regression model and extrapolated to all 1 YROs based on age, wealth quintile, gender and region [19,20]. We also used a multivariate linear regression model to show differences between regions, wealth quintiles and urban/rural setting in key risk factors and coverage (Supplemental material).

Mortality risk was converted into disability-adjusted life years (DALYs) using age weighting and discounting [33]. We did not estimate DALYs associated with acute case morbidity since over 98% of DALYs associated with rotavirus diarrhea in low-income settings are associated with mortality [34,35]. We estimated timing of deaths by distributing overall subpopulation estimates of rotavirus mortality over the first 12 months of life and annually for years 2–4 using monthly and annual estimates of rotavirus gastroenteritis events from Sanderson et al. [36] (Eq. (4) in [20]).

2.3. Vaccination coverage and effectiveness

We estimated vaccination effectiveness and benefits by combining information on coverage and efficacy of each dose by time period with expected burden over time and an adjustment that accounts for correlations between risk and DPT2 coverage (Eqs. (4) and (5) in [20]). Vaccination efficacy was based on a two-dose vaccine assuming Lao PDR introduction with ROTARIX® (ROTARIX is a registered trademark of GlaxoSmithKline Biologicals SA, used under license by GlaxoSmithKline Inc.) with delivery alongside DPT1 and DPT2. Dose coverage and timing were estimated for each region-wealth quintile subpopulation of 1 YROs [4] (Eq. (4) in [20]). Vaccine efficacy estimates were based on combined trial evidence from Bangladesh and Vietnam [17]. We assumed incomplete immunization (receiving only one dose) would have a reduced efficacy of 50% compared to a full course, conservatively assumed an annual 20% reduction in efficacy in years 3 through 5 [37] (Table 1). Efficacy against rotavirus mortality is assumed comparable to efficacy against severe illness, an assumption common in the absence of complete data. Lastly, we assumed vaccine efficacy does not vary across subpopulations in baseline estimates, despite evidence of variability based on income [37], region [38], and nutritional status [39]. However, we explore a scenario where vaccine efficacy is assumed to be the low estimate (24.2%) for the poorest two quintiles in sensitivity analysis.

2.4. Economic outcomes

Patterns of healthcare utilization for diarrheal treatment vary geographically and by socio-economic status, thus, direct medical costs for rotavirus treatment are also expected to vary. However, limited data was available on the extent of variability, so we combined published estimates of overall diarrhea five-year risk direct medical costs per child [16] with an estimate of relative cost per child in each subpopulation (Table 1). The 2012 LSIS did not include data on medical facility utilization after an episode of self-reported diarrhea. Instead, we used utilization after symptoms of respiratory illness for all U5 children, combined with inpatient and urban/rural outpatient WHO-CHOICE facility cost estimates, [40] and published medicine costs [41] as ORT costs.

We extrapolated predicted values from a linear regression of treatment costs as the dependent variable and age (years), regional wealth quintile, region and urban/rural setting as predictors, since only a subset of children displayed symptoms prior to LSIS. We estimated costs of seeking informal care (traditional healer or pharmacy) by averaging published estimates [41] and extrapolated medical facility costs to the rest of the surveyed children based on regression results. The medical costs per episode are largely consistent, if not conservative, relative to other estimates from the region [41–44].

Likelihood of receiving packaged ORT was calculated by replicating the analysis used to calculate ORT propensity ($PrORS_i$) in Rheingans et al. [20], except with logistic regression including all children in LSIS. Predicted propensity was multiplied by predicted medicine costs after diarrheal episodes [41]. Both facility and ORT costs were normalized by the mean value across children, summed for each child and aggregated to 1 YRO subpopulation relative medical costs.

Averted (or prevented) costs were estimated for each subpopulation based on vaccine coverage and efficacy (Eq. (6) in [20]). Baseline vaccine and administrative costs were estimated assuming Gavi, the Vaccine Alliance (Gavi) prices for ROTARIX of $2.02, with wastage of 10% and an incremental administration cost of $1.64 per dose based on estimated program dose delivery and supply costs for Lower Middle Income Countries [45]. Administration costs are on the lower end of a broad range of relatively recent costing studies [46]. We explored a scenario in which administrative costs would be the higher ($2.05) for the poorest two quintiles, simulating potentially higher costs of reaching subpopulations with lower vaccine access in the sensitivity analysis.

We also included estimates of costs from the Lao PDR perspective with Gavi co-financing (Table 1), based on co-financing shares for other vaccines, Lao PDR's current Gavi status [47–49]. The main outcome measure was the incremental cost-effectiveness ratio (ICER), which was estimated for each region and economic subpopulation (Eq. (7) in [20]).

2.5. Temporal, geographic, and socio-economic patterns of vaccination

We conducted a series of ancillary analyses to assess the prospects and barriers for achieving full and equitable coverage of rotavirus vaccination. First, we examined temporal patterns of DPT2 immunization by geographic and economic subpopulations. We used data from 2000 to 2006 [6,50] to estimate patterns of coverage among 1 YROs by region and wealth quintile. Second, we conducted multivariate regressions to assess the contribution of

geographic and socio-economic factors on DPT2, among 1 YROs for 2012 [4] (Supplemental materials).

2.6. Sensitivity and uncertainty analysis

A series of one-way probabilistic sensitivity analyses (PSA) assessed the impact of uncertainty in individual input on predicted ICERs (see Table 1 input value ranges). Key input variables were characterized as distributions in a Monte Carlo simulation procedure of 10,000 iteration to develop a distribution of estimated impact and cost-effectiveness by region in SimVoi [51]. In addition to the two aforementioned scenarios, we examined a scenario of the impact of incremental 10% reductions in vaccine under-coverage from current estimates to full coverage in each region. PSA was used to estimate upper and lower 95% uncertainty limits for all key outputs.

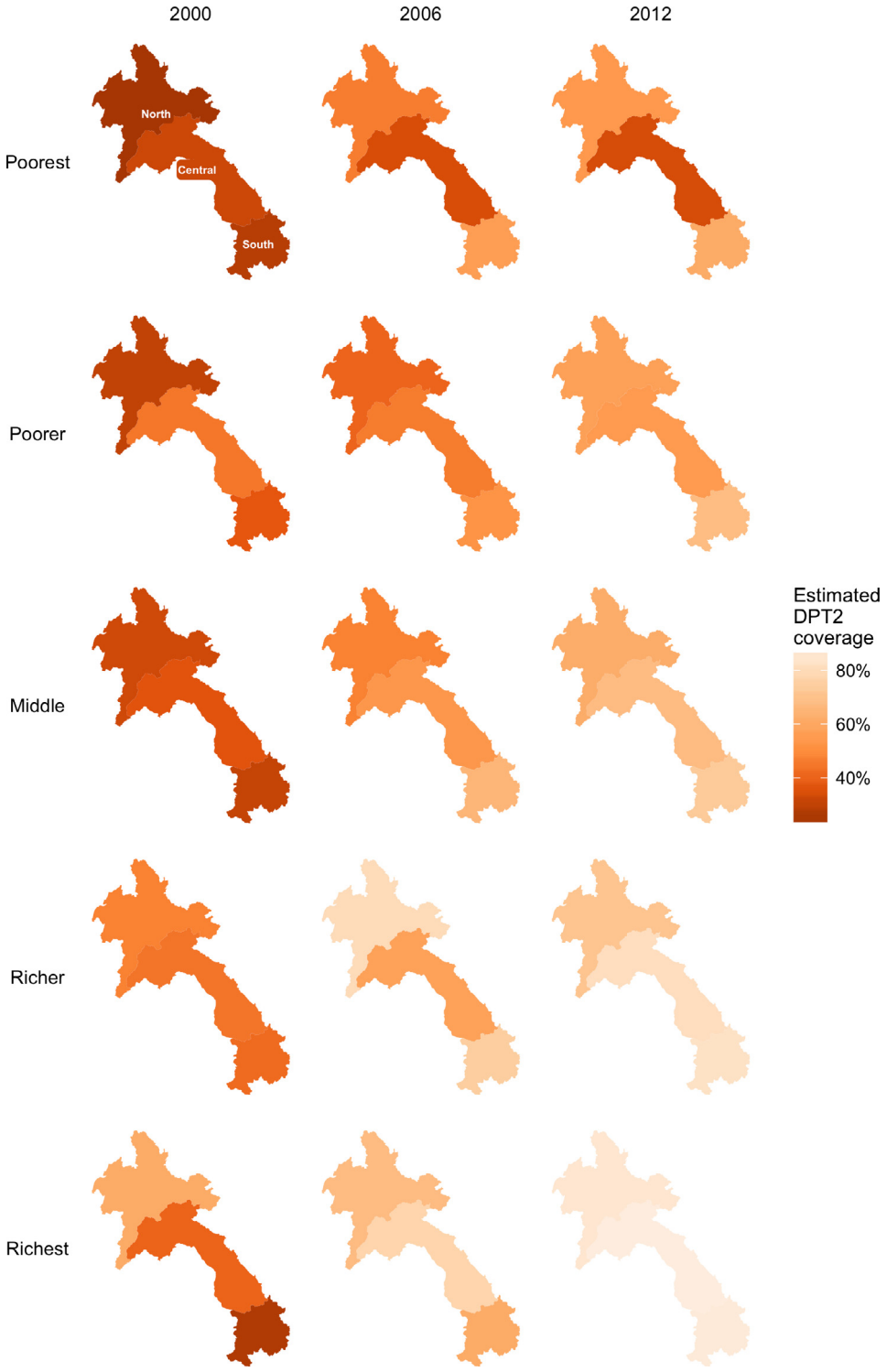

Fig. 1. Estimated vaccination coverage for each regional wealth quintile. DPT2 coverage was used as a proxy for estimating a two-dose rotavirus vaccination schedule.

3. Results

3.1. Distribution and co-distribution of risk factors

The spreadsheet model used (1) the distribution of risk factors for diarrheal mortality and immunization across sub-populations (regional and economic) and (2) the co-distribution or correlation among the risk factors to estimate the distribution of rotavirus burden, vaccination impact, and cost-effectiveness. Logistic regression analysis of associations between underlying factors on risk and benefit variables showed the richest households had significantly better access to timely vaccination and ORT and were less likely to be underweight than children in the poorest households (Supp. Table 1). There were also substantial geographic differences, with children in the North region more likely to be vaccinated and not underweight than children in the Central and South regions. We found correlations between cluster level means of (1) region and economic determinants and (2) risk factors and immunization at national and regional levels (Supplemental materials).

3.2. Health and medical cost burden

Rotavirus disease burden was estimated for each regional-economic subgroup based on the overall burden envelope and risk index derived from individual risk factors. The highest estimated annual health burden was in the South region (0.69 RV deaths/1000 births), followed closely by the Central region (0.65 deaths/1000 births) and the North region (0.61 deaths/1000 births, Table 2). All three regions have relatively low vaccination coverage (DPT 2 range: 34–89%), especially for children in the poorest and poorer households (Fig. 1, Supplemental Table 1). Estimates reflect regional average mortality for children in each subpopulation (Supplemental Table 2), however, there is substantial heterogeneity within each wealth quintile group as well (Supplemental Fig. 1b). There is a higher mode for the poorer and poorest wealth quintiles and long right tails with high risk children and substantial overlaps in the region and wealth distributions, but the key difference is the higher fraction of high risk children in the poorer and poorest quintiles (Supplemental Fig. 1).

The South region had the highest estimated rotavirus health burden while the North region had the highest estimated household economic burden (Table 2). The inverse relationship between health and economic burden is evident in Fig. 2 which shows the economic burden and DALY burden for different region-economic subpopulations. In all three regions, estimated mean direct medical costs increase with wealth, while health burden is higher among children in poorest quintiles.

3.3. Vaccination and risk

The risk distribution of vaccinated and unvaccinated children (DPT1 and DPT2) indicates that unvaccinated children were more likely to be at high risk (Supplemental Fig. 2). While the vaccination status of high-risk children is of primary concern, we also examined community immunization coverage by risk level, to assess the potential for herd immunity. Children in the highest risk quintile (red curve) were the most likely to have low community coverage, while the 20% of children with the lowest risk are most likely to have high community coverage (Supplement Fig. 3).

3.4. Impact of vaccination

Estimates of vaccination impact (as percent and absolute DALY reduction) are based on the risk index, access to and timeliness of vaccination in each sub-group. Rotavirus vaccination introduction

Table 2
Estimated national and regional burden, impact and cost-effectiveness of rotavirus vaccine introduction on the first five years of life for a modeled cohort of children in Lao PDR. Average Lao PDR incremental cost effectiveness ratio (ICER) estimates are based on proposed subsidies for the first five years of vaccine introduction. The last two columns show estimates of impact based on assumptions of equal risk for children across quintile groups.

	Annual burden (RV deaths/1000 births)	RV deaths/year	RV deaths averted/year	Annual benefit (RV deaths averted/1000 births)	% Reduction	Direct medical costs ($/1000 births)	Costs averted ($/1000 births)	Vaccination costs ($/1000 births)	ICER ($/DALY averted)	Average Lao PDR Perspective ICER ($/DALY averted)
NATIONAL	0.65 [0.54; 0.82]	541 [453; 681]	143 [87; 220]	0.18 [0.11; 0.28]	28 [17; 38]	3617 [3356; 3674]	945 [563; 1410]	5207 [4754; 5661]	140 [81; 253]	103
REGION										
North	0.61 [0.51; 0.77]	160 [134; 201]	42 [25; 64]	0.16 [0.10; 0.24]	26 [16; 36]	2509 [2447; 2682]	653 [390; 977]	4938 [4507; 5366]	158 [95; 275]	119
Central	0.65 [0.54; 0.82]	268 [224; 337]	66 [39; 100]	0.16 [0.10; 0.24]	24 [15; 34]	6488 [6368; 6954]	1587 [948; 2370]	4927 [4500; 5356]	124 [64; 245]	84
South	0.69 [0.58; 0.87]	114 [95; 143]	36 [22; 56]	0.22 [0.13; 0.34]	32 [20; 45]	1852 [1800; 1978]	594 [351; 883]	5757 [5256; 6261]	138 [84; 239]	105

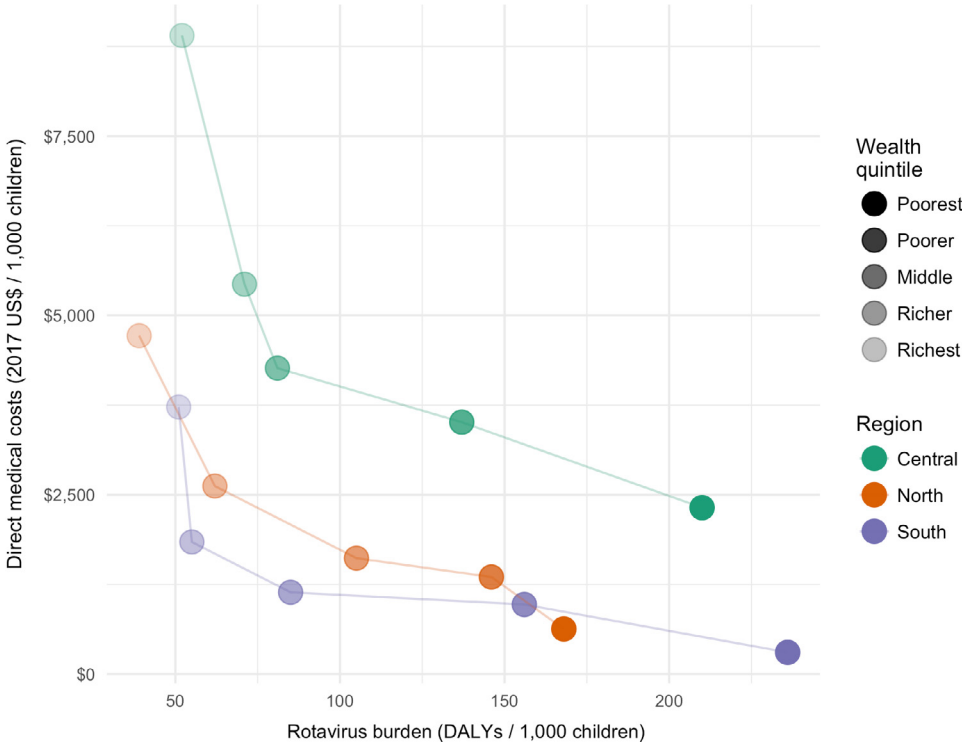

Fig. 2. Estimated direct medical costs and rotavirus mortality burden by regional quintiles in Lao PDR.

would prevent 143 deaths/year, or 28% of the total burden. Regionally, rotavirus vaccination will reduce disease burden by 24% (Central), 26% (North) and 32% (South) (Table 2), with the greatest estimated reductions in children living in the richer and richest households (Fig. 3c) but the greatest benefit is in the poorer and poorest quintiles of all regions (Fig. 3b).

3.5. Cost-effectiveness of vaccination

The incremental cost-effectiveness ratio ($/DALY) is lowest (most cost-effective) for the Central region ($124/DALY) compared to the North region ($158/DALY, Table 2). The ICER varies within region and is lowest (most cost-effective) in the poorer and poorest quintiles (Fig. 3d) in all regions due to the higher burden of disease (Figs. 3a and 4). In the Central region, ICERs ranged from $78/DALY (poorest) to $144/DALY (richer), compared to the North region where ICERs range from $98/DALY to $353/DALY (Fig. 3d).

3.6. Uncertainty and sensitivity analysis

The main results of the one-way PSA demonstrated vaccine effectiveness accounted for much of the overall variance in the ICER, the most of all variables (Supplemental Fig. 4). A scenario assuming lower efficacy for the poorest two quintiles resulted in ICERs that were 60–70% higher. A second scenario assuming higher administrative costs to reach children in the poorest two quintiles did not significantly increase ICER estimates.

We examined the potential effect of 'full and equitable' coverage on impact and cost-effectiveness by considering scenarios where the proportion not vaccinated (under-coverage) was reduced in 10% increments (Supplemental Fig. 5). Universal vaccination coverage in all regions and quintiles would result in 230 deaths prevented per year (43% reduction), 1.6 times higher than baseline estimates. Universal coverage would have the greatest effects on impact in the South region where full coverage resulted in 1.7 times more deaths averted (Supplemental Fig. 5a), with the most improvement in cost-effectiveness in the Central region (Supplemental Fig. 5b). Higher administrative costs

4. Discussion

Rotavirus gastroenteritis remains an important cause of child mortality and health economic burden in Lao PDR [8,16]. Results from this study suggest rotavirus vaccine introduction would be an effective and cost-effective way of improving child health. The national level ICER, was $140/DALY which is highly cost-effective based on suggested 2016 GNI ($2 \times \$2150$) and GDP ($3 \times \$2353$) per capita thresholds (current US$) [52,53]. Results from sensitivity analyses showed even lower ICERs at low-end cost estimates ($1.23/dose), showing that rotavirus vaccination in Lao PDR could be even more cost-effective as lower cost vaccines currently used nationally (e.g. ROTAVAC, Bharat Biotech International) become WHO prequalified.

These conclusions are important, though consideration of cost-effectiveness of rotavirus vaccination introduction must be additionally weighed in the context of budget restrictions and these results suggesting health and economic burden of childhood rotavirus enteritis varies significantly across subpopulations [54,55]. Within the three major regions, rotavirus burden estimates were approximately 4 to 5 times greater among children in the poorest 20% of households, compared to the richest 20% (Fig. 3a). Similarly, we found significant differences among provinces based on economic, geographic, and maternal education (Supplemental Table 4). ICERs lower (more cost-effective) than the national ICER were found in poorest and poorer regional wealth subpopulations (see Fig. 4).

While wealthier subpopulations had lower estimated rotavirus health burden, they tended to have higher economic burden. Higher access to diarrheal treatment corresponds to reduced mortality, but higher economic burden. As a result, rotavirus

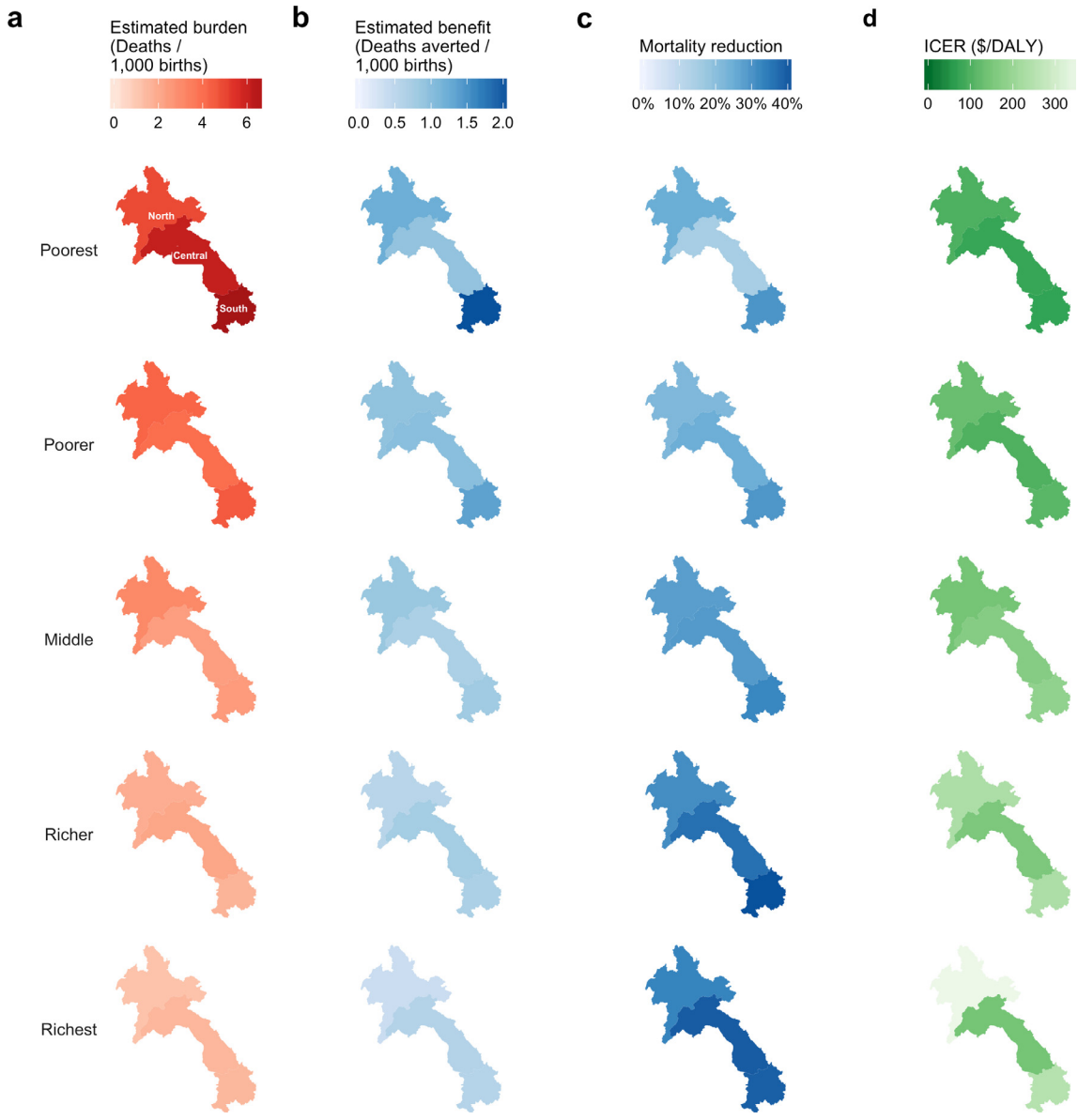

Fig. 3. Estimated burden (a), benefit (b), mortality reduction (c) and cost effectiveness (d) of rotavirus vaccination by region and wealth quintile cumulated over the first five years of life.

vaccination could provide important health and economic benefits, but the mix of economic and health benefits would differ across subpopulations. Given higher burden of disease, rotavirus vaccination has greater potential for health gains and greater cost-effectiveness among marginalized subpopulations. However, gains are dependent upon sustained immunization coverage and equity improvements.

Over the past decade routine immunization has increased across the three major Lao PDR regions (Fig. 1). Several studies documented effective strategies for improvements in coverage and equity. A village health worker mobile phone notification intervention demonstrated potential for increasing Hepatitis B vaccination levels [56], while another study found multi-lingual community-based workshops were effective at increasing childhood immunization [57]. These results suggest a need to explore strategies that overcome both household- and community-level constraints.

There is a small body of literature on the determinants of non-vaccination in Lao PDR [58–60]. One study examined the effects of household and supply-side factors affecting non-vaccination for measles among 9 to 23 month olds [60]. At the household level, distance to facilities, income, media access, and paternal literacy were important predictors. On the supply-side, vaccination supply, cold chain, health care worker training, and management all affected vaccination. Studies of a recent Diphtheria outbreak also investigated causes of non-vaccination and found ethnicity, distance to facilities, and lack of information were important factors [61,62].

Supplemental Fig. 6 suggests a general correlation between routine immunization coverage and risk factors for rotavirus mortality at the provincial level. Correlations could be driven by factors including economic level, mobility, education, and access to health services which influence immunization and other health seeking behaviors (Supplemental Materials). Several provinces outperform

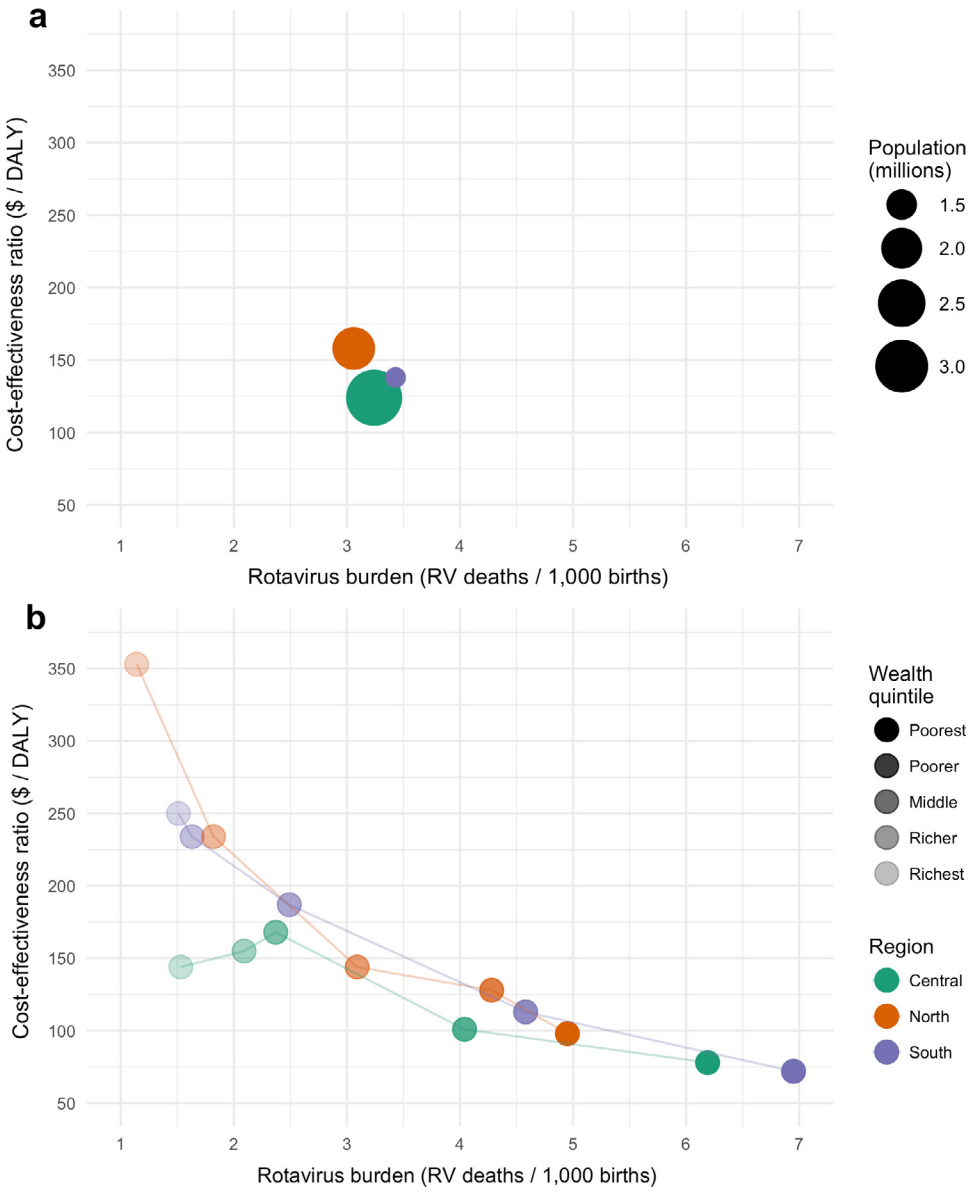

Fig. 4. Estimated incremental cost-effectiveness ratios by rotavirus mortality burden by region and population (a) and wealth quintile (b) cumulated over the first 5 years of life.

what might be expected given their economic, geographic, and educational conditions (e.g. Louang-Namtha, Oudomxai, Xaignabouli, Khammouan, Salavan, and Champasak), while others underperform (Supplemental Fig. 6).

5. Conclusions

Successful rotavirus immunization introduction requires concerted and innovative efforts ensuring that children in marginalized households and communities fully benefit to realize full health, economic and equity gains. This requires overcoming economic, geographic, cultural, and organizational barriers to access to vaccination and determinants of child rotavirus enteritis risk. Doing so could increase the potential health benefits by 160% and ensure that rotavirus vaccination promotes health equity.

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.2018.02.009.

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