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RESEARCH ARTICLE

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Health and economic impact of rotavirus vaccination in GAVI-eligible countries

Sun-Young Kim*^{1,2}, Steve Sweet¹, David Slichter^{1,2} and Sue J Goldie^{1,2}

Abstract

Background: Rotavirus infection is responsible for about 500,000 deaths annually, and the disease burden is disproportionately borne by children in low-income countries. Recently the World Health Organization (WHO) has released a global recommendation that all countries include infant rotavirus vaccination in their national immunization programs. Our objective was to provide information on the expected health, economic and financial consequences of rotavirus vaccines in the 72 GAVI support-eligible countries.

Methods: We synthesized population-level data from various sources (primarily from global-level databases) for the 72 countries eligible for the support by the GAVI Alliance (GAVI-eligible countries) in order to estimate the health and economic impact associated with rotavirus vaccination programs. The primary outcome measure was incremental cost (in 2005 international dollars [I\$]) per disability-adjusted life year (DALY) averted. We also projected the expected reduction in rotavirus disease burden and financial resources required associated with a variety of scale-up scenarios.

Results: Under the base-case assumptions (70% coverage), vaccinating one single birth cohort would prevent about 55% of rotavirus associated deaths in the 72 GAVI-eligible countries. Assuming I\$25 per vaccinated child (~\$5 per dose), the number of countries with the incremental cost per DALY averted less than I\$200 was 47. Using the WHO's cost-effectiveness threshold based on per capita GDP, the vaccines were considered cost-effective in 68 of the 72 countries (~94%). A 10-year routine rotavirus vaccination would prevent 0.9-2.8 million rotavirus associated deaths among children under age 5 in the poorest parts of the world, depending on vaccine scale-up scenarios. Over the same intervention period, rotavirus vaccination programs would also prevent 4.5-13.3 million estimated cases of hospitalization and 41-107 million cases of outpatient clinic visits in the same population.

Conclusions: Our findings suggest that rotavirus vaccination would be considered a worthwhile investment for improving general development as well as childhood health level in most low-income countries, with a favorable cost-effectiveness profile even under a vaccine price (\$1.5-\$5.0 per dose) higher than those of traditional childhood vaccines.

Background

While childhood diarrhea can be caused by multiple pathogens, including both bacteria and viruses, rotavirus is the most common cause of severe diarrhea leading to hospitalization or disease-specific death among children under 5 years of age [1,2]. Responsible for more than 2 million hospitalizations and 500,000 deaths annually (as of 2004), disease mortality is disproportionately borne by children in low-income countries in Africa and Asia [3]. Since almost all children are infected by age 5, and

improved hygiene, water and sanitation measures have had little impact on disease burden, vaccination is considered among the most promising of strategies to prevent mortality [2].

Rotavirus has diverse genotypes that vary geographically and over time [4-6], with clinical manifestations of infection depending heavily on the patient's age [7]. Rotavirus is also characterized by frequent reinfection, with developed natural immunity depending on the number of prior infections. In the last 5 years, two new oral, live attenuated rotavirus vaccines, Rotarix[®] (GlaxoSmith-Kline) [a two-dose monovalent live attenuated human rotavirus vaccine] and RotaTeq[®] (Merck & Co., Inc.) [a

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three-dose human-bovine reassortant pentavalent rotavirus vaccine], have been licensed and are now available in many countries [8,9]. In 2005, the World Health Organization (WHO) Strategic Advisory Group of Experts (SAGE) on Immunization, recommended the introduction of these vaccines in Europe, the United States, and Latin America, on the basis of results of phase III clinical trials [8]; both vaccines appeared to have partial efficacy of a similar magnitude as that conferred by a single natural infection. However, SAGE initially withheld a global recommendation until clinical trials could show satisfactory efficacy in Africa and Asia [8,9]. Clinical trials of Rotarix® (completed in 2008) demonstrated a reduction of rotavirus disease burden in South Africa and Malawi [10]. Based on this newer evidence, in June 2009, SAGE recommended that all countries include infant rotavirus vaccination in their national immunization programs [10].

Especially in light of the Millennium Development Goal (MDG) 4 of child mortality reduction, there has been an effort at the global level to accelerate introduction of rotavirus vaccines in developing countries. However, in addition to the uncertainties about ultimate efficacy in Africa and Asia, as well as uncertainties about the likelihood of uptake, the current vaccines are costly relative to traditional childhood vaccines. Undoubtedly, the poorest countries will require financial assistance. The GAVI Alliance has promised to provide financial support for rotavirus vaccination programs to developing countries, and the WHO and its partners have established global networks for surveillance of rotavirus, providing valuable data on the burden of severe types of acute rotavirus gastroenteritis [11]. However, given that the countries eligible for support from the GAVI Alliance (GAVI-eligible countries) face numerous challenges, not the least of which is the need to fund other children's health initiatives within constrained budgets, countries are being encouraged to consider the potential health impact, cost-effectiveness, and financial requirements carefully, before choosing to prioritize rotavirus vaccines.

The objective of this analysis is to use population-based data for 72 GAVI-eligible countries and provide information on the expected health, economic, and financial consequences of rotavirus vaccines.

Methods

Analytic overview

We synthesized population-level data on demographic structure, country- or region-specific disease burden, medical utilization patterns for treating rotavirus diseases, and costs in order to estimate the health and economic consequences associated with rotavirus vaccination programs in the 72 GAVI-eligible countries. (The data used for our study is openly available upon request.) Model-projected clinical outcomes include

intermediate health outcomes (e.g., hospitalizations), deaths averted, years of life saved (YLS), and disability-adjusted life years (DALYs) averted. The primary outcome measure for the cost-effectiveness analysis was incremental cost (expressed in 2005 international dollars [I\$] adjusted for price differences across countries using purchasing power parity estimates) per DALY averted. For the base-case we adopted a modified societal perspective and discounted future costs and disability-adjusted and unadjusted life years by 3% annually [12-15]. We have also conducted a cost-effectiveness analysis from the perspective of local government. Sensitivity analyses were conducted to explore the influence of both uncertain parameters and assumptions on results. We projected the expected reduction in rotavirus disease burden and budget impact associated with a variety of scale-up scenarios.

Model

Simulation model of the natural history of rotavirus infection

We have previously described a model of the natural history of rotavirus infection using TreeAge 2008 software (Williamstown, MA), which captures details such as the age-specific risk, probability of asymptomatic cases, rate of reinfection, correlation between strength of natural immunity and the total number of previous infections, and waning of vaccine efficacy [16]. We applied the model to Vietnam to reevaluate the cost-effectiveness of a rotavirus vaccination program [16]. We leveraged this work to develop a series of rotavirus disease models to explore uncertainties associated with analytic choices about model structure [17], and conducted corroboration exercises by comparing projected model outcomes to those obtained using the companion model described below.

Excel-based companion model

The companion rotavirus model has been developed to reflect the main features of rotavirus infection and vaccination, and to project the health and economic consequences at the population level, in settings where data are limited. The model is constructed as a static cohort simulation model and is programmed using Microsoft® Excel 2003 and Visual Basic for Applications 6.3 (Microsoft Corporation, Redmond, Washington). The model employs simplifying assumptions that rely on insights from more complex natural history models [16,17]. The upper panel in Figure 1 shows the simplified schematic of natural history represented in the Excel-based companion model. Severe cases of rotavirus gastroenteritis are considered those which are symptomatic and requiring outpatient clinic visit or hospitalization or those resulting in disease-specific deaths [18].

The Excel-based companion model is applied to birth cohorts (born in 2010) in the 72 GAVI-eligible countries.

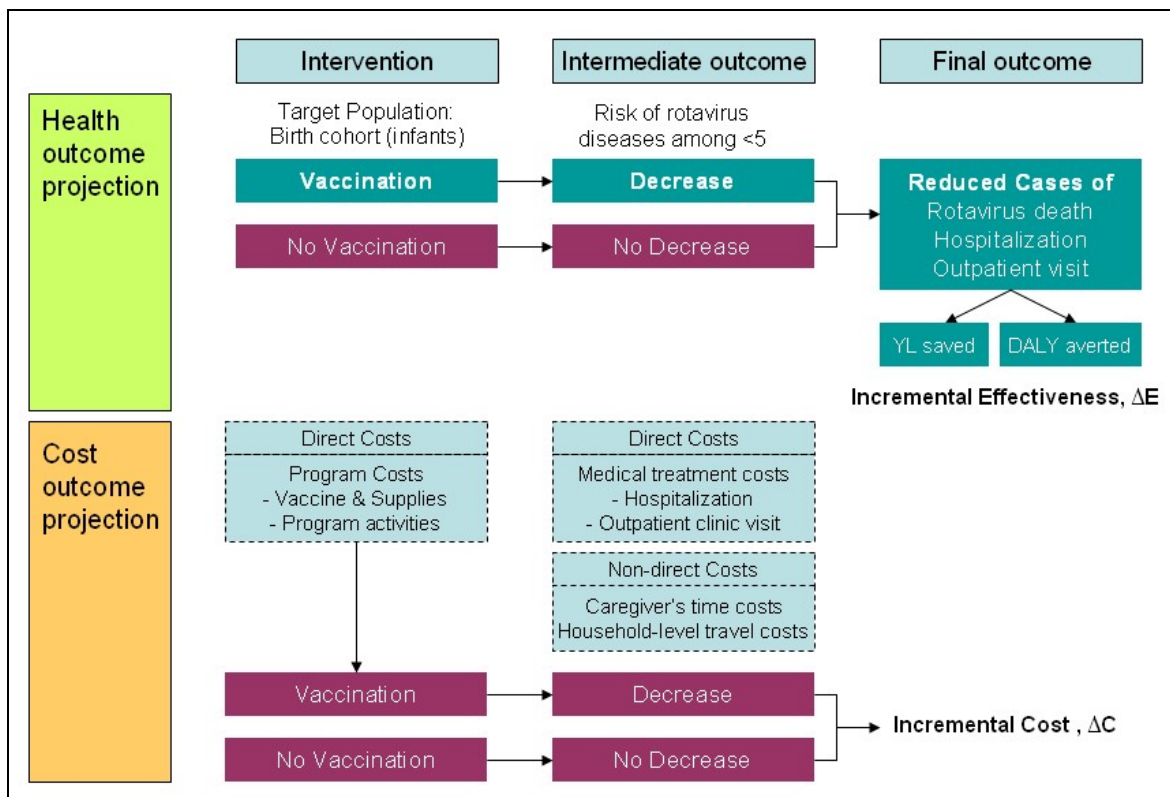
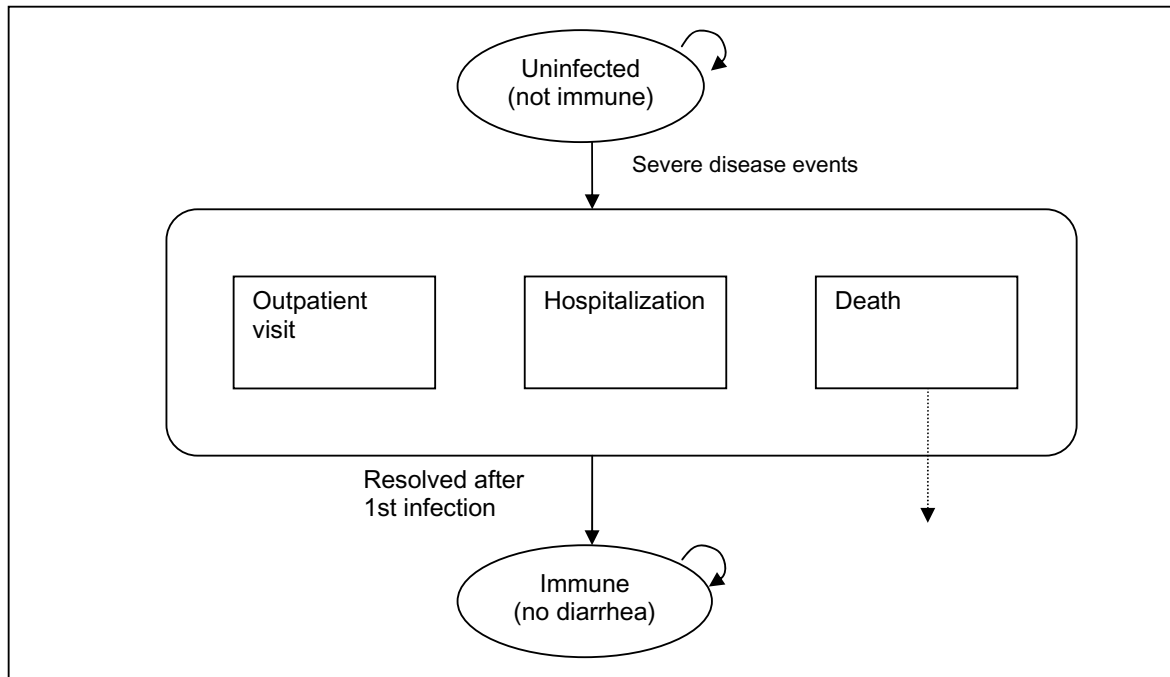


Figure 1 Schematic of the companion rotavirus model. Upper panel shows the schematic of the natural history model of rotavirus infection the companion model is based on. The model assumes one episode of rotavirus diarrhea at maximum and full protection against subsequent rotavirus diarrhea during the first 5 years of life of a vaccinated child. Lower panel presents the schematic of the companion model.

The model tracks the cohorts up to age 5, incorporating background mortality and recording population-level health and cost outcomes with and without vaccination programs. Combining country-specific or region-specific data on the incidence of rotavirus deaths, ratios of outpatient visits or hospitalizations to rotavirus deaths, and serotype distribution, the model generates estimates for the reduction in rotavirus related events requiring medical treatments (i.e., outpatient clinic visits and hospitalizations) or leading to deaths. By applying the estimates to each country's age-structured population, the model transforms them into aggregated population health outcome measures, YL and DALYs (Figure 1, **Lower Panel**). DALYs are calculated using the approach recommended by the Global Burden of Disease (GBD) study [19] but are not age-weighted (age weight modulating factor $K = 0$) [20]. We assumed that the average mean duration of a diarrheal episode was 7 days and that each episode is associated with a disability weight of 0.119 [19]. The model also tracks direct medical and non-medical costs associated with rotavirus disease events and the costs of the vaccine program from the societal perspective. The primary measure for the cost-effectiveness analysis is expressed as the incremental costs (2005 I\$) per DALY averted. The model is also used to project the financial costs and disease burden reduction at the population level for a multi-year rotavirus vaccination program, varying assumptions to simulate different demand forecasting and scale-up scenarios.

Model input and assumptions

Intervention: vaccine types and vaccination schedule

The number of doses (and schedule) recommended by the vaccine manufacturers are 2 (at 2 and 4 months) for Rotarix[®] and 3 (at 2,4, and 6 months) for Rotateq[®]. Because this analysis is intended to provide a broad policy overview of the expected health and economic outcomes of rotavirus vaccination, and not to contextualize a detailed situation of a single specific country, we chose not to distinguish the two vaccines in terms of dose and schedule or vaccine efficacy. This decision was based in large part on the WHO SAGE recommendations and in part based on published evidence: 1) a 3-dose schedule is recommended in any setting where the two vaccines, Rotarix[®] and Rotateq[®] are interchangeably used [21]; 2) efficacy data for a rotavirus vaccine obtained in one population can be extrapolated to other populations if the two populations belong to the same under 5 mortality category [10]; and 3) in a phase III Rotarix[®] trial performed in Malawi, the overall efficacy against severe rotavirus gastroenteritis of a 2-dose schedule (49.2%) showed little difference compared to the corresponding value with a 3-dose schedule (49.7%) [10]. To first generate an estimate of the potential avertable global burden with rotavirus

vaccination, we standardized an initial set of assumptions: 1) infants are given 3 doses of a rotavirus vaccine (Rotarix[®] or Rotateq[®]) at ages aligned with each countries EPI visits (or DTP schedule) (6,10, and 14 weeks or 2,4, and 6 months of age); 2) coverage is 70%, (purposefully assumed in order to illustrate differences in country-specific outcomes related to variations in epidemiology); 3) vaccine-induced immunity is durable over 5 years without waning; and 4), for both vaccines, side effects are considered negligible as long as the first and last dose of either vaccine is given at the recommended age ranges (6-15 weeks for the first dose and 8 months or 32 weeks for the last dose) [21]. We then conducted additional analyses using a range of alternative assumptions (e.g., waning of vaccine-acquired immunity).

Vaccine efficacy

We used two different approaches for estimating vaccine efficacy. For the base-case analysis, recognizing that differences in rotavirus serotype distributions would affect the overall efficacy against severe types of rotavirus, we calculated a weighted average of serotype-specific vaccine efficacy using the country- or region-specific serotype distribution data. Data for rotavirus serotype distributions were obtained from published epidemiological studies. When country-specific data were not available, region-specific estimates reported by the global networks for rotavirus surveillance were used [11] (see Additional file 1 for details).

For a secondary analysis, based on the SAGE recommendation that efficacy data of a rotavirus vaccine can be extrapolated to other populations that have the same under 5 child mortality stratum, we divided the GAVI countries into the three categories (i.e., "high" mortality for the highest quartile, "intermediate" mortality for the second highest quartile, and "low" mortality for the lowest two quartiles [10]). We then extrapolated the pooled efficacy for a 2- or 3-dose schedule obtained from Malawi (49.5%) [10] to GAVI-eligible countries that belong to the "high" child mortality stratum and the corresponding data from South Africa (76.9%) [10] to the countries that fall on "intermediate" strata. Currently, there are no corresponding efficacy data obtained in low income countries with "low" under 5 mortality. Rather than using the data from industrialized countries with "low" under 5 mortality, we conservatively chose to use the data from South Africa for the low-child mortality GAVI-eligible countries. Under 5 mortality data to stratify countries for efficacy data extrapolation were obtained from the WHO World Health Statistics database [22] (Table 1).

Demographic data and assumptions

For country-specific age-structure that incorporates background mortality, we used the estimates of population size (1-year interval) from UN World Population Prospects 2006 Revision [23]. Age-specific life expect-

Table 1: Country-specific profiles of the 72 GAVI-eligible countries

Country ^a	GNI per capita (2008 US\$)	GAVI grouping for co-financing ^b	DTP3 coverage (2008)	Under 5 child mortality (per 1,000 live births) (2006)	Under 5 rotavirus mortality (per 100000 children <5) (2004)	Percentage of death due to diarrhea among children under 5 (2000)
AFR D						
Angola	3,450	4	81%	260	389	19.1
Benin	690	1	93%	148	182	17.1
Burkina Faso	480	1	99%	204	256	18.8
Cameroon	1,150	3	84%	149	179	17.3
Chad	530	1	43%	209	266	18.1
Comoros	750	1	81%	68	64	13.6
Ghana	670	2	87%	120	92	12.2
Guinea	390	1	70%	161	188	16.5
Guinea-Bissau	250	1	79%	200	283	18.6
Liberia	170	4	92%	235	331	17.3
Madagascar	410	1	88%	115	141	16.9
Mali	580	1	99%	217	307	18.3
Mauritania	840	1	74%	125	153	16.2
Niger	330	1	89%	253	392	19.8
Nigeria	1,160	2	57%	191	228	15.7
Sao Thome	1,020	1	99%	96	129	16.0
Senegal	970	1	88%	116	158	17.1
Sierra Leone	320	4	87%	269	439	19.7
The Gambia	390	1	96%	114	107	12.2
Togo	400	1	89%	107	134	13.8
AFR E						
Burundi	140	4	92%	181	255	18.2
Central African Republic	410	4	51%	174	210	14.7
Congo	1,970	4	89%	126	86	11.2
Cote d'Ivoire	980	4	74%	127	223	14.8
Democratic Republic of the Congo	150	4	83%	205	281	18.1
Eritrea	300	4	85%	74	84	15.6
Ethiopia	280	1	81%	123	213	17.3
Kenya	770	2	85%	121	135	16.5
Lesotho	1,080	1	91%	132	25	3.9
Malawi	290	1	91%	120	225	18.1
Mozambique	370	1	80%	138	183	16.5
Rwanda	410	1	97%	160	272	18.5
Tanzania	430	1	84%	118	147	16.8
Uganda	420	1	79%	134	165	17.2
Zambia	950	1	95%	182	227	17.5
Zimbabwe	^c	2	75%	85	106	12.1
AMR A, B & D						
Cuba	^c	2	99%	7	1	1.3
Guyana	1,420	3	93%	62	119	21.4
Honduras	1,800	3	93%	27	43	12.2
Bolivia	1,460	3	83%	61	66	14.3

Table 1: Country-specific profiles of the 72 GAVI-eligible countries (Continued)

Haiti	660	4	53%	80	133	16.5
Nicaragua	1,080	2	96%	26	30	12.2
EMR D						
Afghanistan	^c	4	85%	257	338	18.9
Djibouti	1,130	3	89%	130	145	16.6
Pakistan	980	2	73%	97	95	14.0
Somalia	^c	4	31%	145	315	18.7
Sudan	1,130	4	93%	89	79	12.9
Yemen	950	1	87%	100	108	16.1
EUR B & C						
Armenia	3,350	3	89%	24	29	10.5
Azerbaijan	3,830	3	95%	89	125	15.3
Georgia	2,470	3	92%	32	42	11.5
Kyrgyzstan	740	2	95%	41	86	14.1
Tajikistan	600	2	86%	68	177	16.4
Uzbekistan	910	2	98%	44	88	14.8
Moldova	1,470	2	95%	19	5	2.0
Ukraine	3,210	3	90%	24	2	1.2
SEAR B & D						
Indonesia	2,010	3	77%	34	60	18.3
Korea, Democratic Republic	^c	2	92%	55	56	18.9
Sri Lanka	1,790	3	98%	13	16	13.5
Timor Leste	2,460	4	79%	55	115	21.9
Bangladesh	520	1	87%	69	89	20.0
Bhutan	1,900	1	96%	70	98	20.9
India	1,070	2	84%	76	102	20.3
Myanmar	^c	1	85%	104	128	21.1
Nepal	400	1	82%	59	91	20.5
WPR B						
Cambodia	600	1	91%	82	226	16.6
Kiribati	2,000	3	82%	64	127	21.9
Lao People Democratic Republic	750	1	61%	75	122	15.6
Mongolia	1,680	2	96%	42	67	14.5
Papua New Guinea	1,010	2	52%	73	128	15.3
Solomon Islands	1,180	1	78%	72	45	8.8
Viet Nam	890	2	93%	17	21	10.4

a The six WHO geographical regions are the African Region (AFR), Eastern Mediterranean Region (EMR), Region of the Americas (AMR), European Region (EUR), South-East Asian Region (SEAR), and Western Pacific Region (WPR). Categories for mortality rates include very low child, very low adult mortality (A), low child, low adult mortality (B), low child, high adult mortality (C), high child, high adult mortality (D), and high child and very high adult mortality (E). Combining the two dimensions, we modeled 36 countries from AFR (with 20 in AFR D and 16 in AFR E); 6 countries from EMR D; 6 countries from AMR A, B & D; 8 countries from EUR B & C; 9 countries from SEAR B & D; and 7 countries from WPR B.

b The GAVI Alliance new vaccine co-financing policy (which came into effect in 2008) requires GAVI-eligible countries to share new vaccine costs at one of four levels depending on the country's ability to pay: (1) Poorest group countries will pay \$0.20/dose of the first vaccine and \$0.15/dose for the 2nd and 3rd vaccines; (2) Intermediate group countries will pay \$0.30/dose of the first vaccine and \$0.15/dose for the 2nd and 3rd vaccines; (3) Least Poor group countries will pay \$0.20/dose of the first vaccine and \$0.15/dose for the 2nd and 3rd vaccines for the first year, but will increase their copayment by 15% annually; and (4) Fragile group countries will pay \$0.10/dose of the first vaccine and \$0.15/dose for the 2nd and 3rd vaccines.

c Data are not available.

tancy data (grouped in five-year intervals) for calculating years of life lost as a component of DALYs were obtained from WHO life tables (for year 2006) [24]. To facilitate comparison of the results across regions, for the present analysis, the 72 GAVI-eligible countries were clustered into 11 groups according to the WHO classification system, which is based on geographical location and mortality rates (see footnotes to Table 1).

Incidence of rotavirus disease events

We estimated age-specific incidence rates of rotavirus-associated deaths by applying regional estimates of age distribution (across ages 0, 1, 2, 3, and 4) of severe rotavirus gastroenteritis cases obtained from published literature [16,25-28] to the WHO estimates of the country-specific cumulative number of rotavirus deaths among children under 5 years of age [29] (Table 1). Incidence rates of outpatient visits or hospitalization vary widely depending on the health care infrastructure and resources available in a country. Estimates of country-specific ratios of cumulative incidence of outpatient visits or hospitalizations to deaths were obtained from published literature; when country-specific data were not available, regional estimates or neighboring countries' values were used. The age-specific incidence rates for non-fatal outcomes were then estimated by adjusting cumulative incidence of each outcome by the same age distribution data mentioned above.

Costs

Costs included both direct medical costs (vaccination program costs plus medical treatment costs) and indirect costs (travel costs and caregivers' time costs). Since the price of a rotavirus vaccine and program costs to deliver the vaccine in local settings are not known, we use a composite cost approach to estimate the vaccination program costs among the direct, medical costs. In doing so, we distinguish cost items that are tradable (e.g., vaccine wastage, insurance and security fees associated with freight into the country) from those that are typically non-tradable (e.g., administration, immunization support and monitoring/programmatic expenses). We conduct analyses assuming a 3-dose vaccination schedule with total cost per vaccinated child of I\$10 and of I\$25, implying vaccine prices per dose of approximately US\$1.50 and US\$5.00 respectively. For a composite cost of I\$25 per vaccinated child, we assume the following breakdown of the total costs: rotavirus vaccine purchase of US\$15.00 (3 doses at US\$5.00 each); vaccine wastage of approximately US\$2.65 (~15% of vaccine price); freight and insurance costs of approximately US\$0.90 (~6% of vaccine price); administrative costs of I\$1.50; immunization support (including cold chain, training, and operational costs) of I\$2.95; and other programmatic costs (including surveillance and monitoring and social mobilization) of I\$2.00. The lower cost of I\$10 was derived by assuming 3 doses

of vaccine at US\$1.50 each, wastage of approximately US\$0.79, freight and insurance costs of approximately US\$0.27, administrative costs of I\$0.50, immunization support of I\$2.00, and programmatic costs of I\$1.94. For both composite cost estimates, we assumed that the costs reflect any initial start-up cost and that the non-tradable components (such as administration, immunization support and other programmatic costs) would reflect incremental costs associated with introducing rotavirus vaccines into a national immunization programs to varying extents, depending on countries' health system infrastructure.

Costs for hospitalization were based on country-specific data. When data were not available, we based estimates on WHO-CHOICE data for the cost of a bed-day at a secondary hospital, conservatively assuming one pre-hospitalization consultation in an outpatient setting, one-time hospitalization, and an average length of stay of 3 days for hospitalization (see also Additional file 1). Similarly, costs for outpatient visits were based on country-specific data when available, and, when data were not available, were based on the use of WHO-CHOICE data for a 20-minute visit at health center (80% coverage) assuming one visit per episode. We calculated caregiver's time for hospitalization or outpatient visit by multiplying an average length of stay for hospitalization (3 days \times 8 hours/day) or an average length of an outpatient visit (6 hours) by an estimated country-specific average hourly wage. The average hourly wage data for each country were estimated by analyzing the data from the Labor Statistics database [30] and the World Development Indicators [31], taking into account unemployment and underemployment rate and distribution of the main industries in a country (Additional file 1). We obtained estimates of average transport costs for a visit to medical facilities from published studies for some countries and extrapolated the data to countries in the same region for which country-specific estimates were not available (Additional file 1).

Cost-effectiveness analysis

For the base-case, we estimated the cost-effectiveness of a rotavirus program in the 72 GAVI-eligible countries from the societal perspective, following a single birth cohort over a 5-year time horizon. The primary outcome measure of the analysis was incremental cost-effectiveness ratio (expressed in 2005 I\$ per DALY averted). The incremental cost is the sum of vaccination program costs, averted medical treatment costs for children, and averted caregivers' time and travel costs. We have also evaluated the cost-effectiveness of rotavirus vaccination from the local government perspective, including direct medical costs only and adjusting vaccine costs using the GAVI's co-financing scheme for new vaccines [32] (see footnotes

to Table 1 for details). The government savings from the averted medical treatment costs were calculated by adjusting the total averted medical costs for the public sector's percentages of total health expenditure [31].

Sensitivity analysis

In order to explore uncertainties surrounding model projected outcomes, we performed univariate sensitivity analyses, varying key parameter values and assumptions one at a time. For example, in a sensitivity analysis, we assumed that vaccine efficacy against severe rotavirus diseases would decline over a 5-year time horizon by ~14% annually, based on 2-year efficacy data obtained from a published study [33]. We have also conducted multivariate sensitivity analyses by developing multiple scenarios based on different combinations of analytic choices (e.g., discount rate or perspective), efficacy levels, vaccination program costs, etc.

Budget impact analysis and scale-up scenarios

When considering whether to introduce a new vaccine into a national immunization program, local policy makers need information on total cost as well as value for money, in order to assess the affordability and sustainability of a vaccination program. To provide policymakers with more practical budgetary information, we conducted a budget impact analysis over a 10-year time horizon (2010-2019) from the perspective of budget holders (i.e., local governments) [34,35] by extending the base-case analysis using the same Excel-based model. We first developed alternative roll-out scenarios (i.e., vaccination introduced at different coverage levels), in which the year of rotavirus vaccine introduction, maximum achievable coverage rate, and years to full coverage were varied across countries. The financial forecasts are based on the program cost per child of I\$25 (i.e., US\$5 per vaccine dose). We calculated the vaccine costs to local governments according to the GAVI's co-financing scheme [32] (Table 1), but used the same composite approach as the base-case cost-effectiveness analysis in estimating the incremental costs of delivering rotavirus vaccines. The financial forecasts were expressed in US\$ because budgets are typically expressed in nominal rather than real terms. Note that the financial requirements are not discounted, based on the published guidelines that discounting is not necessary for budget impact analysis [34,35].

For the base-case roll-out scenario, building upon the two previous approaches—an explicit 2-Phase scenario envisioned by Artherly et al. [36] and Wolfson et al.'s approach [37], we categorized the 72 GAVI-eligible countries into 10 groups according to each country's national income level (2008) (Table 1), the most recent year's DPT3 (the third dose of Diphtheria-Pertussis-Tetanus vaccine) coverage (Table 1), past history of new vaccine (i.e.,

Hib or HepB vaccines) introduction, and Artherly and colleagues' demand forecasting results [36]. Table 2 presents the details of the 10 categories and rotavirus vaccine demand forecasting for 10 consecutive cohorts being introduced between 2010-2019 for each country. Following the approach used by Wolfson et al. [37], we used DTP3 coverage from 2008 (the most recent year available) as a proxy for a full coverage. We also used the past trends in the coverage of Hib, HepB, and DTP3 to forecast years of first introduction and years to full coverage. We then assumed that 1) countries in Category 1 roll out in Year 1 (2010), and countries in Category 2 roll out in 2011, etc., with countries in Category 10 rolling out in Year 10 (2019). (Note that, because Nicaragua has already introduced Rotarix®, we use 2006 as their start date.); 2) it takes 2 or 3 years after implementation to reach full coverage for Category 1, 4 years for Categories 2 and 3, 5 years for Categories 4-6, 6 years for Categories 7-8, and 7 years for Categories 9-10; and 3) once full coverage is achieved, the coverage level would be maintained (Table 2). We also evaluated alternative, more optimistic roll-out scenarios by using Wolfson et al.'s original assumptions adjusted with the most recent year's data for GNI per capita and DTP3 coverage [37] and by assuming a flat coverage of 70% over a 10-year period.

Results

Model validation

To ensure that the companion population-based model produced results consistent with our state-transition model when both were subject to our simplifying assumptions, we compared projected health outcomes and cost-effectiveness from the two different models for Vietnam. While the absolute averted deaths reflects both epidemiological differences in the incidence and proportion of vaccine-targeted serotypes, the cost-effectiveness ratios estimated using the two models differ by less than 5% (data not shown). Our previous work [17], which explored model uncertainty by comparing results from five different models of the natural history of rotavirus infection, also reaffirmed that our companion model yielded results consistent with those from more complex natural history models. According to the previous analysis [17], within the category of static, deterministic, aggregate-level models, different choices in model structure lead to relatively modest differences in the estimated cost-effectiveness of rotavirus vaccination while intermediate "non-severe" epidemiologic outcomes vary more substantially depending on choices of model structure.

Health outcomes

Under the base-case assumptions (70% coverage, a limit of one rotavirus disease event per child over the first 5 years of life, and vaccine efficacy against severe rotavirus

Table 2: Implied coverage rates for a base-case scale-up scenario (%) (Continued)

Nicaragua	1 ^b	96.0	96.0	96.0	96.0	96.0	96.0	96.0	96.0	96.0	96.0
EMR D											
Afghanistan	10										31.0
Djibouti	2		46.0	56.8	67.5	78.3	89.0	89.0	89.0	89.0	89.0
Pakistan	4				63.0	65.0	67.0	69.0	71.0	73.0	73.0
Somalia	9									33.0	32.7
Sudan	3			22.0	39.8	57.5	75.3	93.0	93.0	93.0	93.0
Yemen	6						9.0	24.6	40.2	55.8	71.4
EUR B & C											
Armenia	1	55.0	66.3	77.7	89.0	89.0	89.0	89.0	89.0	89.0	89.0
Azerbaijan	1	95.0	95.0	95.0	95.0	95.0	95.0	95.0	95.0	95.0	95.0
Georgia	1	55.0	67.3	79.7	92.0	92.0	92.0	92.0	92.0	92.0	92.0
Kyrgyzstan	1	10.0	38.3	66.7	95.0	95.0	95.0	95.0	95.0	95.0	95.0
Tajikistan	1	39.0	54.7	70.3	86.0	86.0	86.0	86.0	86.0	86.0	86.0
Uzbekistan	1	5.0	36.0	67.0	98.0	98.0	98.0	98.0	98.0	98.0	98.0
Moldova	1	81.0	85.7	90.3	95.0	95.0	95.0	95.0	95.0	95.0	95.0
Ukraine	1	4.0	32.7	61.3	90.0	90.0	90.0	90.0	90.0	90.0	90.0
SEAR B & D											
Indonesia	4				42.0	49.0	56.0	63.0	70.0	77.0	77.0
Korea, Democratic Republic	10										27.0
Sri Lanka	3			62.0	71.0	80.0	89.0	98.0	98.0	98.0	98.0
Timor Leste	4				57.0	61.4	65.8	70.2	74.6	79.0	79.0
Bangladesh	7							5.0	18.7	32.3	46.0
Bhutan	3			90.0	91.5	93.0	94.5	96.0	96.0	96.0	96.0
India	3			6.0	25.5	45.0	64.5	84.0	84.0	84.0	84.0
Myanmar	7							8.0	20.8	33.7	46.5
Nepal	7							2.0	15.3	28.7	42.0
WPR B											
Cambodia	5					50.0	58.2	66.4	74.6	82.8	91.0
Kiribati	2		36.0	47.5	59.0	70.5	82.0	82.0	82.0	82.0	82.0
Lao People Democratic Republic	8								50.0	51.8	53.7
Mongolia	2		95.0	95.3	95.5	95.8	96.0	96.0	96.0	96.0	96.0
Papua New Guinea	4				60.0	58.4	56.8	55.2	53.6	52.0	52.0
Solomon Islands	2		53.0	59.3	65.5	71.8	78.0	78.0	78.0	78.0	78.0
Viet Nam	5					78.0	81.0	84.0	87.0	90.0	93.0

a The profile of each category is as follows:

Category 1: 13 countries classified by Atherly et al.'s demand forecasting study [36] as "Phase 1" countries that are likely to introduce rotavirus vaccines earlier than other countries.

Category 2: Lower middle per capita income (\$976-3,705) and introduction of both Hib and HepB vaccines.

Category 3: Lower middle per capita income (\$976-3,705), either Hib or HepB vaccine introduction, and high (>80%) to very high (>90%) DTP3 coverage.

Category 4: Lower middle per capita income (\$976-3,705), either Hib or HepB vaccine introduction, and low (<70%) to moderate (>70%) DTP3 coverage.

Category 5: Low income (<\$975), Hib or HepB vaccine introduction, and very high (>90%) DTP3 coverage.

Category 6: Low income (<\$975), both Hib and HepB vaccine introduction, and high (>80%) DTP3 coverage.

Category 7: Low income (<\$975), either Hib or HepB vaccine introduction, and high (>80%) DTP3 coverage.

Category 8: Low income (<\$975), either Hib or HepB vaccine introduction, and low (<70%) to moderate (>70%) DTP3 coverage.

Category 9: Low income (<\$975), neither Hib nor HepB vaccine introduction.

Category 10: 8 countries judged by Atherly et al. [36] to be countries that are not likely to introduce rotavirus vaccines.

b Introduced rotavirus vaccine in 2006.

cases adjusted for country-specific serotype distribution), vaccinating one single birth cohort would prevent approximately 52% (range: 50%-59%) of severe rotavirus disease events across the 72 GAVI-eligible countries compared to no vaccination (Table 3). However, the distribution of the absolute numbers of the reduced rotavirus disease burden would vary across regions or countries according to the varying levels of risk of rotavirus death. The number of rotavirus deaths averted per 1,000 vaccinated children varied from near 0 (Cuba) to 16 (Sierra Leone) (Table 3). The upper panel of Figure 2 shows that more than a half of the absolute global reduction (in terms of DALYs) would occur in the African region, and that the South-East Asian Region is another region that would benefit greatly from rotavirus vaccine introduction. The lower panel of Figure 2 indicates that the highest reduction in burden would be achieved in countries with a high disease burden (≥ 200 rotavirus deaths per 100,000 children under 5 years of age) but a similar reduction would be achieved in countries with a medium burden (100-200 rotavirus deaths per 100,000 children under 5 years of age) because reduction in disease burden also depends heavily on population size and country-specific vaccine efficacy adjusted for local rotavirus serotype distributions.

Cost-effectiveness

Table 4 shows the incremental cost-effectiveness ratios of a rotavirus vaccination program in each of the 72 countries for the two different estimated total costs per vaccinated child of I\$10 and I\$25, which correspond to the per dose vaccine costs of US\$1.5 and US\$5. Assuming I\$25 per vaccinated child for the base-case, the number of countries with the incremental cost per DALY averted less than I\$100 was 23. Among the rest of the countries, the corresponding ratios of 24 countries fell between I\$100-I\$200. It should be noted that the incremental cost per DALY averted was relatively high in four countries (Cuba, I\$28,440; Moldova, I\$4,500; Sri Lanka, I\$1,300; and Ukraine, I\$12,160), mainly due to their relatively low rotavirus mortality (Cuba, 1; Moldova, 5; Sri Lanka, 16; and Ukraine, 2 per 100,000 children under age 5). Assuming I\$10 per vaccinated child, rotavirus infant vaccination would be cost-saving in 10 countries, and, in another 55 countries, the incremental cost per DALY averted would be less than I\$200. However, in the four countries with relatively low rotavirus disease burden, the ratios would still be relatively high, with I\$11,330, I\$1,760, I\$490, and I\$4,820, respectively, for Cuba, Moldova, Sri Lanka, and Ukraine. Table 4 also presents the cost-effectiveness results from the local government perspective, in which the per-child vaccination program costs accrued to local governments range between I\$10.3-I\$10.6 (depending on the level of national income and the history of other new

vaccine introduction) when assuming US\$5 per vaccine dose in the market. The results suggest that, under this alternative government perspective, rotavirus vaccination would be considered more cost-effective than for the base-case societal perspective, presumably due to the financial support for vaccine purchase from GAVI.

While there is no consensus on a threshold cost-effectiveness ratio under which an intervention is cost-effective, a useful proxy suggested by WHO to compare different public health interventions is per capita GDP [38]. In this context, to facilitate comparison of the cost-effectiveness of rotavirus vaccines in different settings, we compared the base-case results with each country's per capita GDP and found that a rotavirus vaccination program would be cost-effective in all GAVI countries except the four with relatively low rotavirus death rates (Table 4).

Sensitivity analyses

Results were most sensitive to vaccination cost per child, rotavirus-associated mortality, ratios of hospitalizations and outpatient visits to deaths, vaccine efficacy against severe gastroenteritis, and the discount rate. For example, at a total cost per vaccinated child of I\$5, rotavirus vaccination was shown to be cost-saving in 54 countries and for the rest of the countries (except for Cuba, Moldova, Sri Lanka, and Ukraine) the incremental cost-effectiveness ratios ranged between I\$1-I\$170 per DALY averted. With a total cost per vaccinated child of I\$50, rotavirus vaccines were not cost-saving in any GAVI-eligible countries. Results were moderately sensitive to hospitalization, outpatient visit costs, and level of vaccine immunity waning. When we decreased age-specific vaccine efficacy by ~14% annually over a 5-year time horizon in India, for instance, the incremental cost per DALY averted (at I\$25 per child) increased from I\$200 to I\$220. The results were robust to duration of the disease, disability weight for diarrhea, transportation cost per visit, length of stay for hospitalization, and time per outpatient visit.

When we used standard age weighting ($K = 1$) [19] instead of uniform age weighting ($K = 0$), outcomes looked more favorable. For example, using $K = 1$, the total numbers of DALYs averted (discounted at 3%) among the 72 GAVI-eligible countries increased to ~8.1 million (compared to ~7.1 million with $K = 0$), and the incremental costs per DALY averted decreased by approximately 9-13% for each of the GAVI-eligible countries.

We conducted analyses using alternative vaccine efficacy data by following the WHO SAGE recommendation for efficacy data extrapolation across countries. The average rotavirus death reduction for the GAVI-eligible countries was reduced to ~41% (compared to ~52%), since the average vaccine efficacy against severe rotavirus diseases was lower using this approach than calculating based on

Table 3: Health outcomes of rotavirus vaccination in the GAVI-eligible countries

Country	Base-case vaccine efficacy (adjusted for serotype distribution)			Vaccine efficacy based on SAGE recommendation		
	Reduction in risk of severe rotavirus disease events	Rotavirus deaths averted (per 1000 vaccinated children)	DALYs averted	Reduction in risk of severe rotavirus disease events	Rotavirus deaths averted (per 1000 vaccinated children)	DALYs averted
AFR D						
Angola	55%	14.2	176,385	35%	9.0	111,341
Benin	55%	6.7	42,644	35%	4.2	26,918
Burkina Faso	50%	8.6	92,836	35%	5.9	63,999
Cameroon	54%	6.6	67,042	35%	4.2	42,761
Chad	55%	9.8	76,358	35%	6.2	48,200
Comoros	55%	2.4	1,245	54%	2.3	1,221
Ghana	59%	3.7	44,965	35%	2.2	26,291
Guinea	55%	6.9	43,736	35%	4.3	27,608
Guinea-Bissau	50%	9.5	13,602	35%	6.5	9,366
Liberia	55%	12.1	38,173	35%	7.6	24,096
Madagascar	55%	5.2	68,520	35%	3.3	43,252
Mali	55%	11.1	110,369	35%	7.0	69,669
Mauritania	55%	5.7	10,359	35%	3.6	6,539
Niger	55%	14.4	160,612	35%	9.1	101,384
Nigeria	51%	7.7	733,421	35%	5.3	498,170
Sao Thome	55%	4.7	430	35%	3.0	272
Senegal	55%	5.8	45,473	35%	3.7	28,704
Sierra Leone	55%	15.9	62,305	35%	10.1	39,329
The Gambia	55%	4.0	4,250	35%	2.5	2,682
Togo	55%	5.0	21,192	35%	3.1	13,377
AFR E						
Burundi	55%	9.3	67,442	35%	5.8	42,572
Central African Republic	55%	7.7	19,559	35%	4.8	12,346
Congo	55%	3.2	7,180	35%	2.0	4,532
Cote d'Ivoire	51%	7.6	85,210	35%	5.2	57,935
Democratic Republic of the Congo	55%	10.3	541,455	35%	6.5	341,786
Eritrea	55%	3.1	11,263	54%	3.0	11,045
Ethiopia	55%	7.8	443,905	35%	4.9	280,209
Kenya	55%	5.0	132,053	35%	3.1	83,357
Lesotho	55%	0.9	838	35%	0.6	529
Malawi	57%	8.6	81,905	35%	5.2	50,027
Mozambique	55%	6.8	90,101	35%	4.3	56,875
Rwanda	55%	9.9	75,890	35%	6.2	47,905
Tanzania	57%	5.5	146,305	35%	3.4	89,138
Uganda	55%	6.0	153,907	35%	3.8	97,151
Zambia	51%	7.8	56,160	35%	5.3	37,952
Zimbabwe	52%	3.6	21,407	35%	2.4	14,392

AMR A, B & D

Table 3: Health outcomes of rotavirus vaccination in the GAVI-eligible countries (Continued)

Cuba	57%	0.0	63	54%	0.0	60
Guyana	57%	4.8	969	54%	4.6	923
Honduras	57%	1.7	6,710	54%	1.6	6,386
Bolivia	57%	2.6	12,692	54%	2.5	12,080
Haiti	57%	5.2	26,275	35%	3.2	16,098
Nicaragua	57%	1.2	3,384	54%	1.1	3,195
EMR D						
Afghanistan	53%	12.5	254,469	35%	8.2	166,606
Djibouti	53%	5.4	2,234	35%	3.5	1,463
Pakistan	53%	3.5	315,915	35%	2.3	206,836
Somalia	55%	12.1	78,642	35%	7.7	49,641
Sudan	53%	2.9	65,913	35%	1.9	43,155
Yemen	53%	4.0	67,530	35%	2.6	44,213
EUR B & C						
Armenia	59%	1.1	907	54%	1.0	834
Azerbaijan	59%	4.7	14,086	35%	2.8	8,329
Georgia	59%	1.7	1,471	54%	1.6	1,352
Kyrgyzstan	59%	3.3	7,922	54%	3.1	7,277
Tajikistan	59%	7.1	24,217	54%	6.5	22,246
Uzbekistan	59%	3.6	41,188	54%	3.3	37,836
Moldova	59%	0.2	159	54%	0.2	146
Ukraine	59%	0.1	590	54%	0.1	542
SEAR B & D						
Indonesia	57%	2.3	187,993	54%	2.2	176,588
Korea, Democratic Republic	57%	2.1	12,982	54%	2.0	12,194
Sri Lanka	57%	0.6	3,424	54%	0.6	3,216
Timor Leste	57%	4.3	4,470	54%	4.1	4,199
Bangladesh	55%	3.4	231,585	54%	3.3	225,739
Bhutan	57%	3.8	858	54%	3.6	806
India	53%	3.6	1,777,110	54%	3.7	1,802,809
Myanmar	57%	4.9	79,028	35%	3.0	47,784
Nepal	58%	3.5	52,750	54%	3.2	48,998
WPR B						
Cambodia	57%	8.6	63,250	35%	5.2	38,244
Kiribati	57%	4.9	118	54%	4.6	111
Lao People Democratic Republic	57%	4.6	14,067	54%	4.3	13,213
Mongolia	57%	2.6	2,316	54%	2.5	2,176
Papua New Guinea	57%	5.0	16,493	54%	4.7	15,492
Solomon Islands	57%	1.7	493	54%	1.6	463
Viet Nam	58%	0.8	26,089	54%	0.8	24,032

I\$ = International dollars; DALY = Disability-adjusted life year; ICER = Incremental cost-effectiveness ratio.

AFR = African Region; EMR = Eastern Mediterranean Region; EUR = European Region; AMR = Region of the Americas; WPR = Western Pacific Region; SEAR = South-East Asian Region.

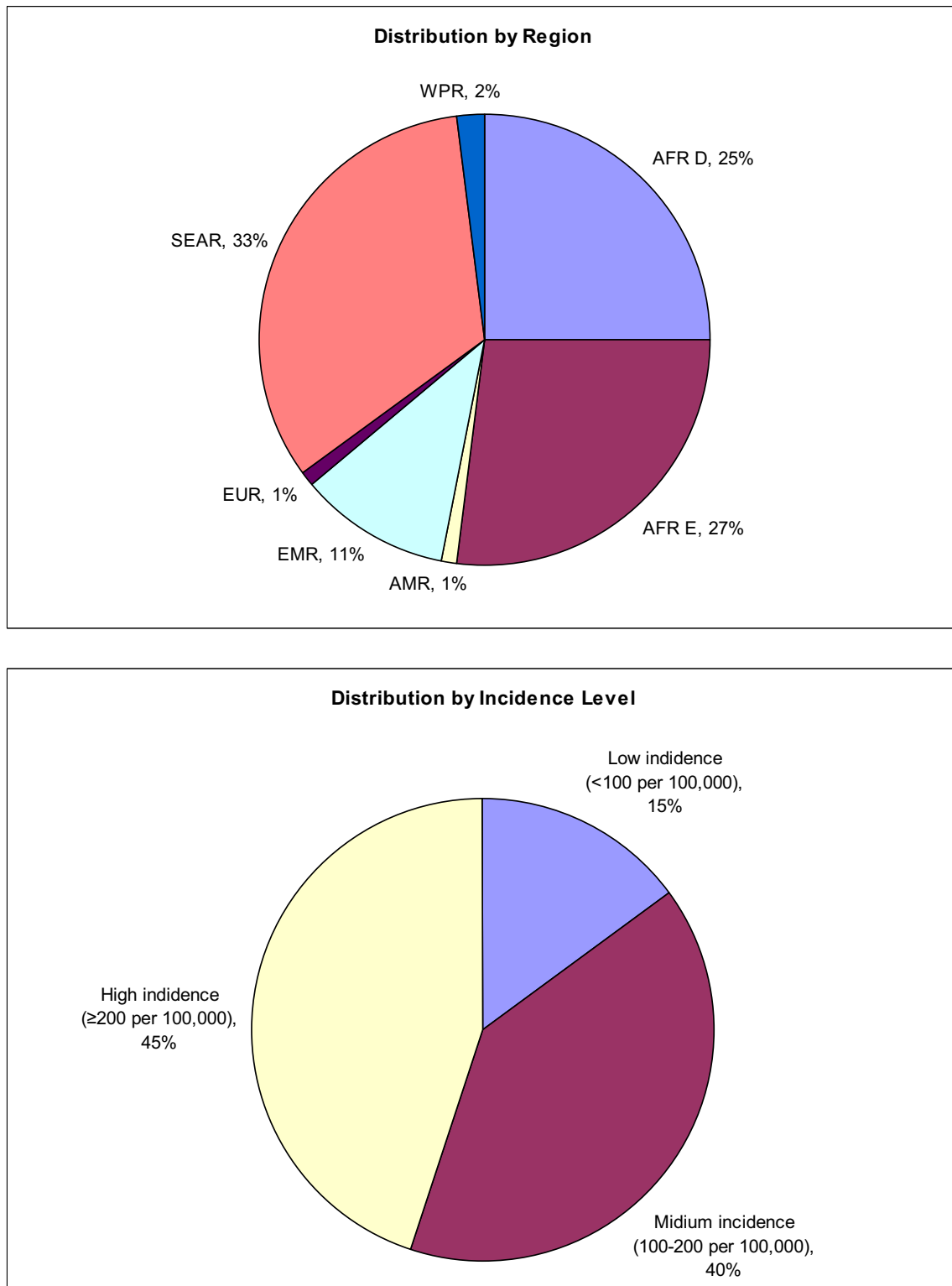


Figure 2 Distribution of averted rotavirus disease burden (DALYs) in the GAVI-eligible countries. Upper panel shows the distribution of averted DALYs associated with rotavirus infection by region. Lower panel shows the corresponding distribution by the level of rotavirus mortality burden (among children under age 5).

Table 4: Cost-effectiveness of rotavirus vaccination in the GAVI-eligible countries

Country	Base-case vaccine efficacy (adjusted for serotype distribution)			Vaccine efficacy based on SAGE recommendation		
	ICER ^a (I\$/DALY averted) I\$10 per vaccinated child	ICER ^a (I\$/DALY averted) I\$25 per vaccinated child	ICER ^b (I\$/DALY averted) based on GAVI's co-financing scheme	ICER ^a (I\$/DALY averted) I\$10 per vaccinated child	ICER ^a (I\$/DALY averted) I\$25 per vaccinated child	ICER ^b (I\$/DALY averted) based on GAVI's co-financing scheme
AFR D						
Angola	saving	26	4	0.2	68	22
Benin	25	108	52	57	190	87
Burkina Faso	22	90	37	42	141	59
Cameroon	22	108	57	54	190	93
Chad	saving	54	33	17	113	59
Comoros	119	341	150	122	348	153
Ghana	71	221	100	142	398	176
Guinea	18	99	54	49	178	88
Guinea-Bissau	7	68	37	26	113	57
Liberia	17	67	32	37	114	53
Madagascar	20	124	65	60	225	108
Mali	5	58	29	26	109	51
Mauritania	21	116	52	58	209	92
Niger	saving	36	23	10	78	42
Nigeria	27	102	48	51	162	74
Sao Thome	40	152	65	83	262	112
Senegal	32	125	56	68	215	95
Sierra Leone	2	41	21	17	79	37
The Gambia	59	196	87	112	328	145
Togo	46	155	75	88	262	121
AFR E						
Burundi	22	84	44	46	145	70
Central African Republic	20	96	46	50	171	78
Congo	74	250	111	143	422	185
Cote d'Ivoire	21	95	47	44	153	72
Democratic Republic of the Congo	19	76	39	41	131	62
Eritrea	95	266	117	97	272	120
Ethiopia	28	98	45	55	166	74
Kenya	37	150	68	81	260	115
Lesotho	397	1,061	459	655	1,707	737
Malawi	26	93	40	55	165	71
Mozambique	31	115	48	64	198	83
Rwanda	1	58	30	23	114	54
Tanzania	42	147	66	87	258	114
Uganda	31	127	62	68	220	102

Table 4: Cost-effectiveness of rotavirus vaccination in the GAVI-eligible countries (Continued)

Zambia	23	103	45	49	166	72
Zimbabwe	78	251	110	134	391	170
AMR A, B & D						
Cuba	11,332	28,443	12,240	11,909	29,888	12,862
Guyana	4	113	40	7	122	44
Honduras	85	386	190	95	411	201
Bolivia	47	246	120	53	262	128
Haiti	4	105	56	46	212	102
Nicaragua	217	646	289	234	688	307
EMR D						
Afghanistan	saving	47	29	15	90	48
Djibouti	saving	90	54	25	179	92
Pakistan	42	192	102	95	325	159
Somalia	saving	39	32	11	83	51
Sudan	84	266	121	148	426	190
Yemen	26	160	82	73	276	132
EUR B & C						
Armenia	227	685	312	254	753	341
Azerbaijan	saving	95	68	35	223	123
Georgia	131	429	206	148	473	225
Kyrgyzstan	59	215	99	68	239	109
Tajikistan	6	80	48	10	91	53
Uzbekistan	saving	122	58	saving	144	67
Moldova	1,763	4,497	1,949	1,925	4,900	2,122
Ukraine	4,816	12,161	5,243	5,249	13,245	5,710
SEAR B & D						
Indonesia	80	302	136	90	326	146
Korea, Democratic Republic	118	363	154	129	390	165
Sri Lanka	487	1,303	565	522	1,391	603
Timor Leste	41	161	67	46	174	73
Bangladesh	50	209	104	52	216	106
Bhutan	38	175	75	44	190	81
India	54	201	97	53	198	96
Myanmar	28	137	74	75	256	126
Nepal	62	215	102	70	235	110
WPR B						
Cambodia	saving	44	34	10	111	63
Kiribati	4	111	50	9	122	54
Lao People Democratic Republic	15	132	77	20	144	83
Mongolia	77	274	114	85	296	123
Papua New Guinea	saving	84	36	saving	95	41

Table 4: Cost-effectiveness of rotavirus vaccination in the GAVI-eligible countries (Continued)

Solomon Islands	143	444	186	156	476	200
Viet Nam	193	799	390	228	885	427

I\$ = International dollars; DALY = Disability-adjusted life year; ICER = Incremental cost-effectiveness ratio.

AFR = African Region; EMR = Eastern Mediterranean Region; EUR = European Region; AMR = Region of the Americas; WPR = Western Pacific Region; SEAR = South-East Asian Region.

a ICERs are for a strategy of vaccinating 70% of a single birth cohort born in 2010 assuming a vaccination program cost of I\$10 and I\$25 per vaccinated child compared to no vaccination.

b ICERs are for a strategy of vaccinating 70% of a single birth cohort born in 2010, but vaccination program costs vary across countries according to the GAVI's co-financing scheme [32].

country- or region-specific serotype distribution and serotype-specific vaccine efficacy. Accordingly, rotavirus vaccination appeared less cost-effective; for instance, assuming this alternate efficacy and I\$25 per vaccinated child, only seven countries had an incremental cost per DALY averted under I\$100 (Table 4).

Budget impact: Forecasting disease burden reduction and financial costs

Table 5 summarizes the impact of alternative scale-up scenarios (combined with different vaccine efficacy estimates) on the overall disease burden reduction aggregated across the GAVI countries over a 10-year period. The first four rows in Table 5 present the results based on the base-case rollout scenarios. The results from the first scenario (assuming the base-case rollout scenario, vaccine efficacy based on the SAGE approach, and vaccine immunity waning) show that a 10-year effort for rotavirus vaccine scale-up would prevent about 41 million cases of outpatient visits, 4.5 million hospitalizations, and 0.9 million deaths caused by rotavirus in the GAVI countries. Without assuming immunity waning, the second scenario projects higher levels (~10%) of reduction in disease burden. The other alternative scenarios combined with different assumptions show very similar patterns. Similarly, Table 6 shows the aggregate financial requirements in the GAVI countries using the same set of scale-up scenarios. Figure 3 presents the incremental budget impact for each year of the 10-year time horizon, using Djibouti as an example. In our base-case rollout scenario, the country is assumed to provide rotavirus vaccines starting in 2011 (Table 2), achieve full coverage (89%) in 2015, and maintain full coverage for the rest of the time horizon. For each year, the left-hand bars in the graph indicate the financial costs of sustaining a rotavirus program without considering the savings to the government from averted treatment costs, while the right-hand bars indicate the financial costs when including such savings. (See Additional file 1 for country-specific results not considering the savings to the government.)

Discussion

While child mortality is reported to have decreased in general since 1990, mortality among young children remains high in many developing countries. The most recent World Health Statistics show that diarrhea makes up the second or third cause of childhood deaths in most low-income countries [22]; in 68 of the 72 GAVI-countries, diarrhea accounts for more than 10% of deaths among young children. Since rotavirus is the most common cause of severe gastroenteritis among young children, any interventions to control rotavirus infection have the potential to greatly improve childhood mortality, contributing to achieving one of the MDG targets.

Our findings show that routine infant vaccination using either of the two new recent vaccines would prevent 0.9-2.8 million deaths associated with rotavirus infection among children under age 5 in the poorest parts of the world over the next decade (2010-2019), depending on vaccine scale-up scenarios. Rotavirus vaccination programs would also prevent 4.5-13.3 million estimated cases of hospitalization and 41-107 million cases of outpatient clinic visits in the same population over the same intervention period.

Our results also show that rotavirus vaccine programs would be considered a cost-effective public health intervention in most GAVI countries; using the WHO's cost-effectiveness threshold based on per capita GDP, the vaccines were considered cost-effective in 68 of the 72 countries (~94%). It should be noted that a rotavirus vaccination program might not prove cost-effective in countries with a relatively low rotavirus mortality rate like Cuba, Ukraine, and Moldova. Although the likelihood that a country will introduce a new vaccine or scale-up rate is not always proportionate to the level of disease burden, these results may affect policy makers' decisions whether or not to introduce a vaccine. For example, although Cuba is classified into a high demand region in a previous study [36] and in the present study, Cuba's rotavirus associated mortality rate is less than 1 per 100,000 children under age 5 and estimated incremental cost-effectiveness is about I\$30,000 per DALY averted (at the

Table 5: Health impact of alternative scale-up scenarios in the GAVI-eligible countries

No	Scale-up scenarios	No. of children vaccinated (in million)	No. of outpatient visits averted (r = 0%) (in million)	No. of hospitalization averted (r = 0%) (in million)	No. of deaths averted (r = 0%) (in million)	YL saved (r = 3%) (in million)	DALYs averted (r = 3%) (in million)
1	Base-case rollout scenario (Table 2) Vaccine efficacy based on the SAGE approach Vaccine immunity waning (14% annually)	281.8	40.7	4.5	0.9	20.3	20.4
2	Base-case rollout scenario (Table 2) Vaccine efficacy based on the SAGE approach No vaccine immunity waning	281.8	44.1	4.9	1.0	22.0	22.1
3	Base-case rollout scenario (Table 2) Vaccine efficacy adjusted for serotype distribution Vaccine immunity waning (14% annually)	281.8	47.8	5.6	1.2	25.3	25.4
4 ^a	Base-case rollout scenario (Table 2) Vaccine efficacy adjusted for serotype distribution No vaccine immunity waning	281.8	51.7	6.0	1.3	27.3	27.4
5	(Modified) Wolfson et al. scenario [37] Vaccine efficacy based on the SAGE approach No vaccine immunity waning	410.5	64.2	7.7	1.6	35.6	35.7
6	(Modified) Wolfson et al. scenario [37] Vaccine efficacy adjusted for serotype distribution No vaccine immunity waning	410.5	81.4	10.4	2.2	48.1	48.3
7	A flat coverage of 70% Vaccine efficacy based on the SAGE approach No vaccine immunity waning	537.0	85.9	10.1	2.1	48.9	49.1

Table 5: Health impact of alternative scale-up scenarios in the GAVI-eligible countries (Continued)

8	A flat coverage of 70% Vaccine efficacy adjusted for serotype distribution						
	No vaccine immunity waning	537.0	106.6	13.3	2.8	64.5	64.7

r = discount rate; YL = years of life; DALYs = disability-adjusted life-years; I\$ = international dollars; SAGE = Strategic Advisory Group of Experts on Immunization.

a Base-case analysis.

Table 6: Budget impact of alternative scale-up scenarios in the GAVI-eligible countries

No	Scale-up scenarios	No. of children vaccinated (in million)	Financial costs ^a			
			Global society perspective (Total vaccination program costs) (US\$, million)	GAVI Alliance perspective (Vaccine cost support) (US\$, million)	Local government perspective (not including medical cost savings) ^b (US\$, million)	Local government perspective (including medical cost savings) ^b (US\$, million)
1	Base-case rollout scenario (Table 2) Vaccine efficacy based on the SAGE approach Vaccine immunity waning (14% annually)	281.8	5,879	4,079	1,800	1,714
2	Base-case rollout scenario (Table 2) Vaccine efficacy based on the SAGE approach No vaccine immunity waning	281.8	5,879	4,079	1,800	1,707
3	Base-case rollout scenario (Table 2) Vaccine efficacy adjusted for serotype distribution Vaccine immunity waning (14% annually)	281.8	5,879	4,079	1,800	1,695
4 ^c	Base-case rollout scenario (Table 2) Vaccine efficacy adjusted for serotype distribution No vaccine immunity waning	281.8	5,879	4,079	1,800	1,686
5	(Modified) Wolfson et al. scenario [30] Vaccine efficacy based on the SAGE approach No vaccine immunity waning	410.5	8,573	5,943	2,630	2,472

Table 6: Budget impact of alternative scale-up scenarios in the GAVI-eligible countries (Continued)

6	(Modified) Wolfson et al. scenario [30] Vaccine efficacy adjusted for serotype distribution					
	No vaccine immunity waning	410.5	8,573	5,943	2,630	2,414
7	A flat coverage of 70% Vaccine efficacy based on the SAGE approach					
	No vaccine immunity waning	537.0	11,222	7,785	3,437	3,236
8	A flat coverage of 70% Vaccine efficacy adjusted for serotype distribution					
	No vaccine immunity waning	537.0	11,222	7,785	3,437	3,170

r = discount rate; YL = years of life; DALYs = disability-adjusted life-years; I\$ = international dollars; SAGE = Strategic Advisory Group of Experts on Immunization.

a All 10-year forecasts are based on the composite program cost of I\$25 (corresponding to US\$5 per vaccine dose) per vaccinated child and are not discounted.

b The vaccine costs to local governments are based on the GAVI's co-financing scheme [32].

c Base-case analysis.

composite vaccination cost of I\$25 per vaccinated child). It is conceivable that policy makers might want to consider using resources to introduce other childhood vaccines or to extend coverage of existing health interventions that target a higher burden of disease.

In the present analysis, the most influential factor in the cost-effectiveness results was per child vaccination costs, which includes rotavirus vaccine costs, vaccine wastage, and any activities to support the delivery of the vaccines. Since the data on country-specific incremental costs for introducing a new childhood vaccine into a national immunization program are rarely available for low-income countries, we chose to use a composite cost approach, assuming a total program cost of I\$10 or I\$25 per vaccinated child. Accordingly, our base-case cost-effectiveness results use standardized vaccination program costs across the 72 GAVI countries, so the main differences in the incremental cost-effectiveness ratios may be attributable to the differences in disease burden (i.e., rotavirus associated mortality rates, ratios of rotavirus associated hospitalizations or outpatient visits to rotavirus deaths) and vaccine efficacy adjusted for serotype distributions. Note that, although the discount rate was still relatively influential, it was not as important as it is with vaccines where benefits are realized in the distant future (e.g., HPV or HBV vaccines). The results were robust to country-specific hourly wage rates or transportation costs per medical visit, which were used in calculating direct non-medical costs such as caregivers' time costs or travel costs. The results were not sensitive to assumptions

about medical utilization such as average length of hospitalization or average time spent per outpatient clinic visit.

Note that our base-case estimates of the main health outcome (i.e. DALYs averted) are based on uniform age weights ($K = 0$), primarily for normative reasons, while a majority of previous similar studies use the standard age weights ($K = 1$) used by the WHO GBD study [19]. Uniform age weighting leads to relatively lower years of life lost (YLL) compared with those associated with standard age weighting ($K = 1$) over the age range of age 0-4 years [20]. Accordingly, when assuming similar model structure and parameter values, our results are more conservative since our base-case analysis ($K = 0$) yields a lower number of DALYs averted than other similar studies that evaluate the impact of rotavirus vaccination in terms of DALYs incorporating non-uniform age weights ($K = 1$) (as also shown in the sensitivity analysis results).

Although the WHO SAGE recommended global use of rotavirus vaccines based on the evidence from recent clinical trials, there is a high level of uncertainty about short-term and longer-term vaccine efficacy in local settings given the variability of rotavirus serotype distributions across regions and over time. Our analysis shows the implication of following SAGE's recommendation to transfer vaccine efficacy by using data from other countries with comparable levels of childhood mortality. In a majority of the GAVI countries, the extended vaccine efficacy following the SAGE approach was lower than the weighted average of serotype-specific vaccine efficacy used in our base-case analysis. Correspondingly, the

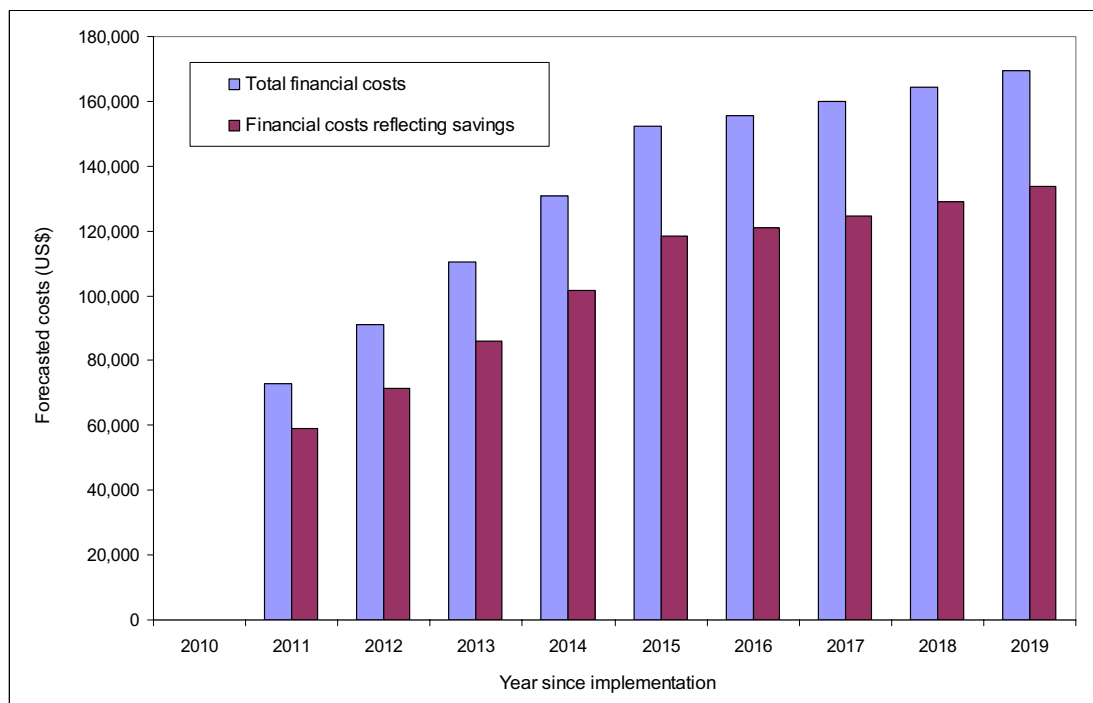


Figure 3 Budget impact of rotavirus vaccination in Djibouti. This figure shows the budget impact of a rotavirus program in Djibouti for each year of a 10-year time horizon. For each year, the difference between the bars indicates the savings to the government from averted treatment costs.

results of a secondary analysis using the SAGE approach showed the estimated avertable burden to be about 30% (0-70%) lower.

Recently an increasing number of published studies have evaluated the health and economic consequences of rotavirus vaccines in different settings, using various modeling approaches [16,25,26,36,39-59]. Ten studies [16,25,36,39-44,52] have assessed cost-effectiveness of rotavirus vaccination in low-income countries. When subject to the same currency type, inflation and vaccine price, our results were comparable to those from the studies performed in low-income country settings. For example, when we roughly adjusted Rose et al.'s results for India that are obtained using an individual-level Markov model [39] for currency type and inflation, the adjusted incremental cost-effectiveness ratio of ~\$140 per DALY averted was comparable to our result for India, \$200 per DALY averted (at \$25 per vaccinated child). When we assumed similar program costs, the discrepancy in the two studies' results was further reduced.

The cost-effectiveness profiles of rotavirus vaccines from the present study are also very similar to those for HPV vaccines reported in a previous study [60], which was performed using a similar approach in the 72 GAVI-eligible countries. That study reported that at a cost per

vaccinated girl of \$10 (\$2 per dose), for 49 of 72 countries, the cost per DALY averted was less than \$100 (or the program was cost-saving), and for an additional 12 countries, less than \$200. At higher costs per vaccinated girl (e.g. \$25), for 33 of 72 countries, the cost per DALY averted was less than \$300, and for an additional 23 countries, less than \$500 [60]. However, provided vaccine prices are similar, the financial resources required are very different, in large part due to differences in the size of the target populations (i.e., infants of both genders versus adolescent girls). Interestingly, although not immediately intuitive, the avertable mortality burden from the two vaccines is also similar. For example, while annual deaths among the 72 GAVI countries are estimated to be ~466,000 from rotavirus [29] and ~161,000 from cervical cancer [61], if we restrict the comparison to female gender, the annual deaths are ~230,000 versus ~161,000. Further, these estimates represent deaths based on a snapshot of a population structure for a particular calendar year, and do not reflect a future population dynamics. Consider the present day (2010) cohort of newborn infants and the present day cohort of 9-year old girls (2010) in the GAVI-eligible countries. Modeled projections show approximately 508,000 of the infants will die from rotavirus and 580,000 of the 9-year old girls will

eventually die from cervical cancer. Clearly both vaccines are priorities.

Although a rotavirus program proves cost-effective over a wide range of parameter values and alternative assumptions, countries need information on affordability of the vaccines as well. That is, in most low-income countries with severe resource constraints, multiple public health priorities compete for a limited shared budget; policy makers need to know the financial costs required to implement any program as well as its value for money. In the present study, in addition to the secondary cost-effectiveness analysis from the local government perspective, we performed a budget impact analysis based on simplifying assumptions, taking into account the 'new vaccine co-financing policy' recently announced by the GAVI Alliance, in order to project financial requirements and potential savings from averted medical costs for each year of the 10-year period. Our findings suggest that, with GAVI's support, the costs to each GAVI country would be reduced to approximately I\$10-I\$11 when assuming a composite program cost of I\$25, but that covering this would still be a substantial burden to the lowest-income GAVI countries. This type of analysis may be useful to policy makers seeking to address the question of affordability of new vaccines by comparing the budget impact forecast with their own projected total immunization budget. Assessment of affordability is not complicated when there is a single earmarked budget for a new vaccine of interest. However, if there are multiple other immunization (or public health) programs competing for a shared budget, choosing an optimal set of immunization programs under a budget constraint can be challenging. Recently there have been a number of studies aiming to help policy makers with resource allocation, taking into account multiple criteria such as ethical or political considerations in addition to technical efficiency [62-65].

Note that the results of our financial forecasting and overall disease burden reduction are, of course, sensitive to the forecasted level of demand for rotavirus vaccine. We base our base-case scale-up scenario on local experience with other childhood vaccines and national income levels. However, there are reasons why this forecast may be over- or under-estimated. For instance, there may be discrepancies between reported and actual uptake rates in local settings simply due to the challenges of collecting health information across entire populations. Further, while we assumed that all children covered would receive a full 3 doses of vaccine, in practice dose completion rates may vary, affecting the total cost and altering cost-effectiveness (due to both changes in cost and changes in impact if vaccine efficacy with fewer than 3 doses is lower than that under a full 3-dose course). Thus, to come up with more reliable forecasts for financial requirements associated with new vaccine introduction, more research

is needed to improve the quality of coverage data and to conceptualize an approach to forecasting future uptake rate more realistically. Also, some operational research is needed to identify factors that might affect the sustainability of scale-up scenarios.

Our study has several limitations. First, we synthesized available data using an Excel-based model that relies on simplifying assumptions; this was a purposeful tradeoff in that, unlike our past detailed models of a single country [16], here we sought to provide a broad perspective on avertable burden and cost-effectiveness of a global investment to vaccinate children against rotavirus. As such, this simple model cannot capture indirect effects that might result from a large-scale routine immunization program. If a rotavirus program can provide such benefits among non-vaccinated subpopulations, as suggested in recent published studies that used a dynamic mathematical model to estimate the cost-effectiveness of rotavirus vaccines in the United States [58,66], we may be underestimating benefits. Second, unlike our previously published model applied to a single country [16], this static model applied to 72 countries is implicitly based on a decision-tree structure, and thus has a limited capacity to explore uncertainty surrounding natural history of rotavirus infection and potential serotype replacement that might occur in the long term after vaccine introduction [17,67]. Third, our analysis assumes composite costs rather than estimating individual country-specific vaccine delivery costs. Accordingly, our results should be carefully interpreted by donors or global policy makers interested in the relative cost-effectiveness of the rotavirus vaccines conditional on alternative strategies to achieve coverage. We emphasize the need for future research to estimate the incremental costs of delivering new rotavirus vaccines in local settings. Lastly, while we tried to estimate country-specific data for the ratios of hospitalizations and outpatient visits to deaths and for serotype distributions of rotavirus, country-specific data were often not available, leaving us to use data from neighboring countries or regional average.

Conclusion

The limitations of our study suggest that our findings should be considered for only what they are intended-broad estimate of the potential impact and value of rotavirus vaccination. Our main findings suggest that rotavirus vaccine introduction would be considered a worthwhile investment for improving general development as well as public health level in most low-income countries, with a favorable cost-effectiveness profile even under a vaccine price (\$1.5-\$5.0 per dose) higher than those of traditional childhood vaccines. In addition, our study provides information on an approximate future stream of financial costs that need to be included in

health budgets. Further, as more evidence on vaccine efficacy and safety, particularly associated with vaccination schedule in local settings [68], and more country-specific data (e.g., data from the cMYP immunization financing database) become available, our analysis can serve as baseline for any future refinement of country-specific results.

Additional material

Additional file 1 Supplementary information on model inputs and results. The document provides detailed information on some of the key model inputs and results, including vaccine efficacy adjusted for serotype distributions, length of stay for rotavirus associated hospitalizations, hourly wage, transportation costs, and country-specific budget impact analysis results.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

SK and SG conceptualized and designed the study. SK and DS acquired data and performed analyses. SK, SS, DS, and SG interpreted the data and results. SK drafted the manuscript. SG provided administrative and technical support, and DS and SS provided technical expertise in managing data quality. All authors contributed to the revision of the manuscript and approved the final version.

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