Projected Health And Economic Impact Of Rotavirus Vaccination In GAVI-Eligible Countries: 2011–2030

By: Richard D. Rheingans, Deborah E. Atherly, Kristen D.C. Lewis, Jacqueline Tate & Umesh D. Parashar

Abstract
Rotavirus is the leading cause of diarrheal disease in children under 5 years of age. It is responsible for more than 450,000 deaths each year, with more than 90% of these deaths occurring in low-resource countries eligible for support by the GAVI Alliance. Significant efforts made by the Alliance and its partners are providing countries with the opportunity to introduce rotavirus vaccines into their national immunization programs, to help prevent childhood illness and death. We projected the cost-effectiveness and health impact of rotavirus vaccines in GAVI-eligible countries, to assist decision makers in prioritizing resources to achieve the greatest health benefits for their populations. A decision-analytic model was used to project the health outcomes and direct costs of a birth cohort in the target population, with and without a rotavirus vaccine. Current data on disease burden, vaccine efficacy, immunization rates, and costs were used in the model. Vaccination in GAVI-eligible countries would prevent 2.46 million childhood deaths and 83 million disability-adjusted life years (DALYs) from 2011 to 2030, with annual reductions of 180,000 childhood deaths at peak vaccine uptake. The cost per DALY averted is $42 for all GAVI countries combined, over the entire period. Rotavirus vaccination would be considered very cost-effective for the entire cohort of GAVI countries, and in each country individually, as cost-effectiveness ratios are less than the gross domestic product (GDP) per capita. Vaccination is most cost-effective and has the greatest impact in regions with high rotavirus mortality. Rotavirus vaccination in GAVI-eligible countries is very cost-effective and is projected to substantially reduce childhood mortality in this population.

1. Introduction

Diarrhea is the second-leading cause of childhood mortality worldwide, and is responsible for approximately 1.34 million deaths each year in children under 5 years of age [1]. Rotavirus is the primary cause of diarrheal disease in this population, accounting for 30–40% of diarrheal deaths [2]. Although the illness affects children in every country, over 90% of the deaths occur in the developing world. The introduction of effective rotavirus vaccines creates the possibility of significantly reducing diarrheal mortality and hospitalizations. Growing evidence from middle and upper income countries where rotavirus vaccination has been introduced, suggests that the vaccine is associated with reduced hospitalizations and even death among children less than 5 years of age. According to recent reports from Europe, Australia and the United States, reductions of 70–95% of hospitalizations for rotavirus-specific diarrhea and 35–48% for all-cause diarrhea have occurred after the vaccine was introduced into routine immunization programs [3–8]. These reductions in diarrheal hospitalizations have also been observed in lower-middle income countries in Latin America [9,10]. For the first time, real reductions in diarrheal deaths have also been recorded. In Mexico, researchers observed a 35% reduction in childhood diarrheal deaths after vaccine introduction, and in Brazil similar trends were seen [11–13].

In low-income countries that bear the vast majority of rotavirus mortality, there is less direct evidence of the effectiveness of
vaccination at scale, in part because many of these countries are only now making decisions regarding national universal vacci-
nation programs. Nicaragua introduced the vaccine into the
routine immunization schedule in 2006 – the first GAVI-eligible
country to do so. A 46% reduction against all rotavirus hospital-
izations was noted, as well as a 58% reduction in the number of
cases of severe rotavirus disease requiring intravenous (IV) fluids
[14].

To make the decision to introduce new and relatively expensive
vaccines, policy makers will benefit from reliable estimates
of the costs and outcomes that might be attained through routine
immunization. The best available estimates are typically based on a
combination of regularly updated information on epidemiological
burden, vaccine efficacy, immunization delivery, effectiveness, vac-
cine demand, price, and economic burden. This includes a growing
number of national level studies [15–18] as well as global analyses
[19,20].

Improved estimates are essential for deciding whether to intro-
duce rotavirus vaccination but also how to do so. All such ex ante
analyses have uncertainties associated with them, which can be
reduced as new information becomes available. Since the publica-
tion of our earlier analysis of expected impacts in GAVI-eligible
countries, additional data have emerged on the vaccine efficacy
in Africa and Asia [21–23], immunization delivery [24], epidemi-
ological burden of disease [1,2], and vaccine market dynamics such
as pricing and demand. Much of this new information will have
a substantial influence on the cost-effectiveness and impact
of rotavirus vaccines, thus highlighting the importance of an updated
analysis.

2. Methods

2.1. Model

We used an Excel-based model to estimate the economic and
health impact of rotavirus vaccination in GAVI-eligible countries
from 2011 to 2030 [25]. Principal model inputs and their values are
listed in Table 1. Annual birth cohorts were followed for a five-year
period and the health outcomes and associated healthcare costs
of rotavirus both with and without vaccination, were estimated for
this population. GAVI-eligible countries were modeled individually
and results were grouped by World Health Organization (WHO)
region (see Table 2).

We conducted the analysis from a healthcare system perspec-
tive, focusing on costs and benefits to donors and governments.
We included direct medical costs from outpatient visits and
hospitalizations including the cost of diagnostic tests, medica-
tion, supplies, facilities, and personnel, as well as the cost of
vaccination. Costs of informal medical treatment, as well as indi-
rect medical and non-medical costs are not included in the
model.

We estimated health burden in terms of disability-adjusted life
years (DALYS) and deaths. DALYS quantify the years of life lost due
to premature death and the years lived with disability [26]. We cal-
culated DALYS due to rotavirus mortality based on the standardized
life expectancy at age one [27]. DALYS from rotavirus cases result-
ing in outpatient or hospital visits were calculated based on default
disability weights [26], an estimated illness duration of six days,
and were age-weighted [28,29].

Estimates of DALYS averted by universal rotavirus vaccination
were used to calculate the incremental cost-effectiveness ratio
(US$/DALY averted). Estimates are expressed in 2010 US dollars,
and all future costs and DALYS were discounted at a rate of 3%
annually.

2.2. Healthcare costs of rotavirus

Country-specific estimates of hospital and outpatient costs were
derived from WHO-CHOICE data [30], which standardizes costs
for healthcare visits according to the geographical region and
mortality stratum. We multiplied the per diem costs with an
average length of hospital stay of four days [19] and diagnos-
tic and medication costs were estimated as a proportion of the
per visit and per diem costs [31,32]. Cost estimates were con-
verted from Year 2005 international dollars to 2010 US dollars
using the Consumer Price Index [33] and official exchange rates
[34].

<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model parameters: values for base case scenario and ranges.</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Base-case value</th>
<th>Range</th>
<th>Source</th>
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</thead>
<tbody>
<tr>
<td><strong>Health</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>5-year risk of rotavirus mortality</td>
<td>Country-specific</td>
<td>±25%</td>
<td>[55]</td>
</tr>
<tr>
<td>5-year risk of rotavirus hospitalization</td>
<td>0.016</td>
<td>0.012–0.02</td>
<td>[37]</td>
</tr>
<tr>
<td>5-year risk of rotavirus outpatient visit</td>
<td>0.020</td>
<td>0.152–0.252</td>
<td>[37]</td>
</tr>
<tr>
<td>Average hospital length of stay</td>
<td>4 days</td>
<td>3–5</td>
<td>[19]</td>
</tr>
<tr>
<td>Years of life lost (YLL) per death-discounted, age weighted</td>
<td>34</td>
<td>NA</td>
<td>[56]</td>
</tr>
<tr>
<td>Years of life lived with disability (YLD) per event-discounted, age-weighted</td>
<td>0.00037</td>
<td>NA</td>
<td>[56]</td>
</tr>
<tr>
<td><strong>Vaccine efficacy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Against severe rotavirus gastroenteritis</td>
<td>57% (high)</td>
<td>41–69% (high)</td>
<td>[21–23,57–59]</td>
</tr>
<tr>
<td>resulting in hospitalization or death (by childhood mortality strata)</td>
<td>72% (mid)</td>
<td>55–85% (mid)</td>
<td>[21–23,57–59]</td>
</tr>
<tr>
<td>85% (low)</td>
<td>70–94% (low)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(by childhood mortality strata)</td>
<td>70% (mid)</td>
<td>56–80% (mid)</td>
<td>[21–23,57–59]</td>
</tr>
<tr>
<td>78% (low)</td>
<td>58–89% (low)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Against severe all-cause gastroenteritis (high childhood mortality setting)</td>
<td>24.8%</td>
<td>12.6–35.3%</td>
<td>[21–23]</td>
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<tr>
<td><strong>Efficacy of one dose</strong></td>
<td>50% of full course efficacy</td>
<td>Assumption</td>
<td></td>
</tr>
<tr>
<td>Relative coverage</td>
<td>90%</td>
<td>60–100%</td>
<td>Assumption</td>
</tr>
<tr>
<td><strong>Costs</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization unit cost</td>
<td>$17–232</td>
<td>±25%</td>
<td>WHO-CHOICE website</td>
</tr>
<tr>
<td>Outpatient unit cost</td>
<td>$1–13</td>
<td>±25%</td>
<td>WHO-CHOICE website</td>
</tr>
<tr>
<td>Vaccine program cost per dose</td>
<td>$0.25–1.25</td>
<td>±25%</td>
<td>[35]</td>
</tr>
</tbody>
</table>
2.3. Vaccination program costs

Vaccination program costs include those costs associated with storing, delivering and administering the vaccine once it arrives in the country. The vaccine program costs were estimated using the WHO Global Immunization Vision and Strategy (GIVS) costing tool [35]. A program cost per dose was estimated for each of the countries, and a regional, weighted average was calculated and used in the analysis.

2.4. Health care utilization and mortality associated with rotavirus

We used updated country estimates of childhood deaths due to diarrhea and rotavirus-specific illness, to revise the baseline disease burden figures for our analysis [1,36]. We estimated rotavirus-associated outpatient visits and hospitalizations by multiplying the total diarrhea-related outpatient visits and hospitalizations by the estimated proportion attributable to rotavirus [37]. Rotavirus medical visits and deaths were distributed into the following age categories: 0–2 months, 3–5 months, 6–8 months, 9–11 months, 12–23 months, 24–35 months, 36–47 months, and 48–59 months [19].

2.5. Vaccine efficacy

Recent clinical trials of rotavirus vaccine in sub-Saharan Africa and Southeast Asia found lower levels of vaccine efficacy than observed in trials in Latin America that were used in the original model [21–23]. As noted by the WHO Strategic Advisory Group of Experts (SAGE), this finding is not unexpected [38] and is consistent with results from studies of other live, oral vaccines such as polio, typhoid and cholera that suggest lower efficacy or immunogenicity in developing country populations compared to industrialized countries [39–41].

Efficacy estimates against severe rotavirus diarrhea, any rotavirus diarrhea, and all-cause severe gastroenteritis for countries in the African and Asian regions were calculated and applied by child mortality strata (see Table 1). Pooled random effects mean estimates from the trials conducted in the high mortality countries of Ghana, Kenya, Bangladesh, South Africa, Malawi and Mali were applied to countries with under-5 mortality rates >30/1000. Estimates from the study in Vietnam were applied to countries with child mortality rates ≤30/1000. Previous estimates from trials in Latin America were still used for Latin American and Caribbean countries. Estimates of efficacy against severe rotavirus gastroenteritis are used as a proxy for efficacy against mortality and hospitalization, and efficacy against any rotavirus gastroenteritis corresponds to efficacy against outpatient visits.

2.6. Forecasted demand and price over time

Atherly et al. [19] demonstrated that estimates of the impact and cost-effectiveness of vaccination over time depend heavily on assumptions about which countries introduce vaccine, the timing of their introduction and how price changes over time as a result of market factors such as increased demand and the entry of new manufacturers. Many countries have expressed interest in rotavirus vaccines, leading several to apply for vaccine support from GAVI [42]. Recent estimates have projected a total of over 40 country introductions of rotavirus vaccine by 2015; this figure is in addition to the five countries that introduced vaccine prior to 2012 [43,44]. Thus, for this analysis we have assumed that a total of 47 countries will adopt by 2015, based on current GAVI predictions. We estimated that 17 of the remaining 25 countries would introduce vaccines, leading several to apply for vaccine support from GAVI manufacturers. Many countries have expressed interest in rotavirus vaccines, leading several to apply for vaccine support from GAVI manufacturers. Many countries have expressed interest in rotavirus vaccines, leading several to apply for vaccine support from GAVI manufacturers. Many countries have expressed interest in rotavirus vaccines, leading several to apply for vaccine support from GAVI manufacturers. Many countries have expressed interest in rotavirus vaccines, leading several to apply for vaccine support from GAVI manufacturers.
2.7. Vaccine coverage and delivery

We estimated vaccine coverage using UNICEF/WHO best estimates for DPT1 and DTP2 for each country. Then, updated estimates on the timing of routine vaccinations from Clark et al. were incorporated [24]. We also assumed that the coverage rate for children at the highest risk of rotavirus mortality was 90% of the vaccination rate for other children, since children who die of diarrhea may have had less access to vaccination and other health care resources [48].

2.8. Sensitivity analyses

One-way sensitivity analysis was conducted to assess the impact of specific variables on the number of deaths averted and cost-effectiveness of vaccination. Variables included rotavirus mortality incidence, vaccine efficacy, relative coverage (the adjustment made for inequitable vaccine access in those children most likely to die), vaccination program costs, and timing of vaccine dosing.

A probabilistic uncertainty analysis was done to assess the combined effect of multiple variables on vaccination impact (deaths averted) and cost-effectiveness ($/DALY averted) in the base-case analysis. A Monte Carlo simulation was performed using distributions for the key input variables, including rotavirus mortality, vaccine efficacy, vaccination systems costs, and relative coverage. Multiple iterations (10,000) randomly drew values from the input variable distributions and generated a distribution of output values and corresponding uncertainty limits (5th and 95th percentiles of the output distributions).

2.9. Scenario analyses

2.9.1. Efficacy against severe all-cause gastroenteritis

Pooled data from the trials in Africa and Asia were used to estimate the deaths averted and cost-effectiveness of vaccine against severe, all-cause gastroenteritis. Since data from the Latin American and Caribbean (AMR) and European (EUR) regions were not available, we used the base case estimates for rota-specific efficacy and impact in these regions, to allow us to report total GAVI estimates.

2.9.2. Indirect benefits

For some vaccines, indirect protection through herd immunity is an important determinant of impact as it benefits populations who may not be reached with routine vaccination [49]. There is some evidence from large scale introduction studies of rotavirus vaccines that are consistent with indirect protection. For example, data from the United States, El Salvador and Australia indicate declines in rotavirus disease among older, unvaccinated children [45,50,51]. Currently, there is insufficient evidence to firmly establish such an effect so we have not incorporated it into our base case estimates of effectiveness. However, a scenario on indirect effects has been included as a part of our sensitivity analysis. This indirect effects scenario assumed that for each outcome, non-vaccinated children would receive a level of protection proportional to the efficacy in vaccinated children and the level of coverage. Specifically, we assumed that unvaccinated children would receive half of the level of protection as vaccinated children, times the proportion of children vaccinated. So at 50% coverage and 60% efficacy in vaccinated children, unvaccinated would receive 15% protection, while at 95% coverage, unvaccinated children would receive 28.5% protection. These simplified assumptions are intended to provide a preliminary estimate of the potential impact.

2.9.3. Constant vaccine price over time

Vaccine price is an important determinant of both cost-effectiveness and affordability. The base case represents a price trajectory over time, but it is also important to understand the relative cost-effectiveness of vaccine at various set prices. We ran scenarios to determine the cost-effectiveness of vaccination at prices of $7.00, $5.00, $2.50 and $1.50 per dose, assuming these prices remain constant through 2030.

3. Results

3.1. Base case: vaccine impact

Between 2011 and 2030, rotavirus vaccination for 72 GAVI-eligible countries is projected to avert the deaths of more than 2.4 million children, and prevent more than 83 million disability-adjusted life years (DALYs) (Table 3). Ranges for these figures, calculated from probabilistic sensitivity analysis are 1.8–3 million deaths and 54–95 million DALYs averted. More than 95% of the averted burden would occur in the African (AFR), Eastern Mediterranean (EMR) and Southeast Asian (SEAR) regions combined. For every 1000 children vaccinated, 89 health care visits, $1000 in medical expenses and 93 DALYs would be avoided. The health benefits per 1000 children vaccinated vary widely, and are highest in the GAVI-eligible countries of the Eastern Mediterranean (142 DALYs averted) and African (118 DALYs averted) regions and lowest in the Western Pacific region (13 DALYs averted). The EMR and AFR regions include several high rotavirus mortality countries, while seventy percent of the GAVI-eligible population in the WPR region

<table>
<thead>
<tr>
<th>WHO region</th>
<th>AMR</th>
<th>EUR</th>
<th>AFR</th>
<th>EMR</th>
<th>SEAR</th>
<th>WPR</th>
<th>All GAVI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of deaths averted</td>
<td>39,140</td>
<td>24,270</td>
<td>1,352,870</td>
<td>549,830</td>
<td>482,300</td>
<td>10,100</td>
<td>2,458,510 (1,800,000–3,000,000)</td>
</tr>
<tr>
<td>Total DALYs averted</td>
<td>1,335,000</td>
<td>829,800</td>
<td>46,132,900</td>
<td>18,725,200</td>
<td>16,448,400</td>
<td>347,400</td>
<td>83,818,700 (54,000,000–95,000,000)</td>
</tr>
<tr>
<td>Impact per 1000 children vaccinated</td>
<td>78 (58–84)</td>
<td>37 (20–45)</td>
<td>118 (71–137)</td>
<td>142 (89–173)</td>
<td>52 (34–65)</td>
<td>13 (6–15)</td>
<td>93 (56–108)</td>
</tr>
<tr>
<td>Health care visits averted</td>
<td>145</td>
<td>125</td>
<td>85</td>
<td>85</td>
<td>87</td>
<td>114</td>
<td>89</td>
</tr>
<tr>
<td>Medical costs averted</td>
<td>$2260</td>
<td>$2130</td>
<td>$600</td>
<td>$960</td>
<td>$1360</td>
<td>$885</td>
<td>$1000</td>
</tr>
<tr>
<td>Cost per DALY averted 2010 (US$)</td>
<td>$63 ($44–90)</td>
<td>$116 ($62–173)</td>
<td>$38 ($26–55)</td>
<td>$30 ($18–40)</td>
<td>$60 ($45–90)</td>
<td>$231 ($170–440)</td>
<td>$42 ($31–64)</td>
</tr>
</tbody>
</table>
is represented by Vietnam, a country with good rotavirus surveillance data and a very low rotavirus mortality rate.

Annual deaths averted rise sharply between 2011 and 2019 as countries are introducing vaccine into their national immunization systems (Fig. 1). Once full introduction and target vaccine coverage is reached in all 72 countries, rotavirus vaccine is expected to prevent approximately 180,000 of the 429,000 estimated rotavirus deaths each year in these countries, reaching a cumulative 2.46 million deaths averted by 2030.

3.2. Base case: cost-effectiveness

Under the base case scenario, the cost-effectiveness of rotavirus vaccination is $42/per DAILY averted. Cost-effectiveness ratios were highest in the Western Pacific region ($231) and lowest in the Eastern Mediterranean ($30). The World Health Report suggests that an intervention averting one DAILY at a cost that is less than the GDP per capita, is very cost-effective. Those averting each DAILY at a cost between one and three times the GDP per capita are cost effective [52]. Based on this threshold, rotavirus vaccination under the base-case scenario, is very cost-effective in every region. The lowest GDP per capita in each region (representing the poorest country) is higher than the CE ratio for that region, and is higher than the upper value of the confidence range as well, suggesting that vaccination is very cost-effective in all 72 countries. The cost-effectiveness decreases over time as the number of infants vaccinated increases (Fig. 2). The higher ratios in the first two years are primarily driven by a higher vaccine price and the presence of vaccination programs in relatively lower burden countries of Latin America. As time progresses, the price drops dramatically and higher-burden countries begin to introduce the vaccine, leading to lower, more favorable cost-effectiveness ratios.

3.3. Scenario analysis

Under an alternative scenario including all-cause diarrhea mortality, rotavirus vaccination is projected to avert more than 2.9 million deaths associated with all causes of diarrhea, with 60% of the impact occurring in the African region (Table 4). The cost-effectiveness is $39 per DAILY averted for all regions combined, with a high of $254 in the Western Pacific region and low of $30 in the African and Eastern Mediterranean regions, meeting the threshold for a very-cost-effective intervention at the global and regional levels. Under a scenario that assumes indirect benefits of vaccination, rotavirus vaccine is once again, very cost-effective and could avert the deaths of an estimated 3 million children in GAVI-eligible countries.

Vaccination remains very cost-effective for all GAVI countries combined, under all price scenarios. At $7.00 per dose, the cost per DAILY averted is $176, and at a low of $1.50 per dose, the incremental CE ratio is $37. Regionally, vaccination is very-cost-effective in all regions at all price levels, with the exception of the Western Pacific region, where it is between one and three times GDP at prices of $7.00 and $5.00 per dose.

3.4. One-way sensitivity analysis

Only small changes in the cost-effectiveness of vaccination occurred when values for key variables were changed (Table 5). The CE ratio increases to a high of $62 when relative coverage decreases to 60% and the ratio declines to a low of $32 when rotavirus mortality estimates are increased by 25%. Variations in estimates of vaccine efficacy, baseline rotavirus mortality and relative coverage have a substantial impact on projected deaths averted, whereas changes in the timing of vaccination have a more modest effect.

Table 4
Scenario analyses: vaccination impact and cost-effectiveness on all-cause diarrheal mortality, and with indirect effects; and cost-effectiveness at different vaccine prices, by WHO region and all GAVI countries.

<table>
<thead>
<tr>
<th>Region</th>
<th>AMR</th>
<th>EUR</th>
<th>AFR</th>
<th>EMR</th>
<th>SEAR</th>
<th>WPR</th>
<th>All GAVI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case scenario</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Deaths averted</td>
<td>39,140</td>
<td>24,275</td>
<td>1,352,870</td>
<td>549,830</td>
<td>482,300</td>
<td>10,100</td>
<td>2,458,510</td>
</tr>
<tr>
<td>Cost/DAILY averted</td>
<td>$63</td>
<td>$116</td>
<td>$38</td>
<td>$30</td>
<td>$60</td>
<td>$231</td>
<td>$42</td>
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<tr>
<td>Scenario 1. All-cause diarrheal mortality</td>
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<tr>
<td>Deaths averted</td>
<td>39,140</td>
<td>24,275</td>
<td>1,786,000</td>
<td>590,300</td>
<td>505,540</td>
<td>10,300</td>
<td>2,955,555</td>
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<tr>
<td>Cost/DAILY averted</td>
<td>$63</td>
<td>$116</td>
<td>$30</td>
<td>$30</td>
<td>$66</td>
<td>$254</td>
<td>$39</td>
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<td>Scenario 2. Indirect effects</td>
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<tr>
<td>Deaths averted</td>
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<td>32,090</td>
<td>1,703,880</td>
<td>668,500</td>
<td>588,800</td>
<td>11,880</td>
<td>3,052,175</td>
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<td>Cost/DAILY averted</td>
<td>$50</td>
<td>$78</td>
<td>$30</td>
<td>$25</td>
<td>$46</td>
<td>$190</td>
<td>$33</td>
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<tr>
<td>Scenario 3. Constant vaccine price over time: cost/DAILY averted</td>
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<tr>
<td>$7.00</td>
<td>197</td>
<td>318</td>
<td>138</td>
<td>100</td>
<td>264</td>
<td>1152</td>
<td>176</td>
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<tr>
<td>$5.00</td>
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<td>100</td>
<td>71</td>
<td>185</td>
<td>815</td>
<td>125</td>
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<tr>
<td>$2.50</td>
<td>61</td>
<td>111</td>
<td>53</td>
<td>36</td>
<td>87</td>
<td>394</td>
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<td>$1.50</td>
<td>31</td>
<td>65</td>
<td>34</td>
<td>22</td>
<td>48</td>
<td>225</td>
<td>37</td>
</tr>
</tbody>
</table>

Table 5
One-way sensitivity analysis showing the influence of selected variables on the cost-effectiveness and impact of vaccination.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Deaths averted</th>
<th>Cost/DAILY averted (US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case</td>
<td>2,458,510</td>
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<tr>
<td>RV mortality</td>
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<tr>
<td>Base</td>
<td>2,458,510</td>
<td>42</td>
</tr>
<tr>
<td>25%</td>
<td>3,073,000</td>
<td>32</td>
</tr>
<tr>
<td>−25%</td>
<td>1,844,000</td>
<td>54</td>
</tr>
<tr>
<td>Vaccine efficacy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base</td>
<td>2,458,510</td>
<td>42</td>
</tr>
<tr>
<td>High</td>
<td>2,802,000</td>
<td>36</td>
</tr>
<tr>
<td>Low</td>
<td>1,936,210</td>
<td>56</td>
</tr>
<tr>
<td>Relative coverage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100%</td>
<td>2,729,000</td>
<td>37</td>
</tr>
<tr>
<td>Base – 90%</td>
<td>2,458,510</td>
<td>42</td>
</tr>
<tr>
<td>60%</td>
<td>1,647,000</td>
<td>62</td>
</tr>
<tr>
<td>Timing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base – current</td>
<td>2,458,510</td>
<td>42</td>
</tr>
<tr>
<td>On-time</td>
<td>2,058,000</td>
<td>39</td>
</tr>
<tr>
<td>Vaccination system cost</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base – GIVS</td>
<td>2,458,510</td>
<td>42</td>
</tr>
<tr>
<td>50%</td>
<td>N/A</td>
<td>48</td>
</tr>
<tr>
<td>−50%</td>
<td>N/A</td>
<td>36</td>
</tr>
</tbody>
</table>
4. Discussion

This analysis focuses specifically on estimating the health impact and cost-effectiveness of rotavirus vaccination in GAVI-eligible countries, utilizing recent developments in the field. We have incorporated the reported vaccine efficacy data from low-resource settings in Africa and Asia, utilizing pooled estimates based on Under5 mortality strata [53]. We have used the recently updated WHO estimates for rotavirus mortality, which are slightly lower than previously reported [36]. In addition, this analysis captures evolutions in market dynamics such as the increased demand for vaccine in high-burden countries and reductions in vaccine prices. There has been a surge in country applications from GAVI-eligible countries for rotavirus vaccines, and the first in Africa – North Sudan – initiated rotavirus immunization in the national childhood immunization schedule in July 2011 [42].

The 72 countries included in this analysis carry nearly 95% of the burden of rotavirus mortality, accounting for approximately 429,000 annual deaths in young children under five. The introduction of rotavirus vaccines in these GAVI-eligible countries will have significant public health impact in terms of deaths and hospitalizations averted, and would be considered a very cost-effective intervention. Rotavirus immunization could avert the deaths of 2.46 million children in these countries between 2011 and 2030. Cost-effectiveness improves rapidly in the early years, when vaccine price reductions are anticipated and high-mortality countries begin to introduce vaccine.

Rotavirus vaccines have demonstrated modest vaccine efficacy in resource-poor settings with the highest rates of Under5 mortality and rotavirus-associated mortality [21–23]. Annual reduction of 180,000 childhood deaths could be expected in these countries, representing a 42% reduction in total rotavirus mortality. Lower vaccine efficacy in high-burden countries is the primary factor limiting overall impact. However, 98% of the estimated rotavirus deaths averted among these countries occur in those with the highest rates of childhood death and lowest vaccine efficacy. For instance, the 10 countries with the highest rates of rotavirus mortality per capita (>300/100,000) are in Africa and the Middle East. These would experience the greatest benefit from the introduction of rotavirus vaccines. So despite lower efficacy, the public health impact will be enormous in those countries with the greatest burden.

Regional variations in the cost-effectiveness and public health impact of rotavirus vaccination were observed in this analysis. These regional differences in cost-effectiveness and health outcomes are more influenced by underlying disease burden than by vaccine efficacy. For example, despite lower estimated vaccine efficacy in the African and Eastern Mediterranean populations, the vaccine has the greatest public health impact – measured by DALYs averted per 1000 children vaccinated – and is the most cost-effective in these regions that carry the highest rotavirus mortality.
rates. In contrast, countries included in the Western Pacific region have the lowest average mortality rate, and although higher vaccine efficacy estimates were applied to this population, the health impact is smaller and the cost-effectiveness ratio is higher compared to other regions.

Of global health importance is the overall impact of rotavirus vaccines on all-cause severe diarrheal morbidity and mortality. Applying the figure of 24.8% vaccine efficacy against all-cause severe gastroenteritis deaths (pooled estimate as described above), yields estimates of the impact of vaccine that are 20% higher than the base case results of 2.46 million rotavirus deaths averted. The difference may be explained, in part, by undetected rotavirus in the populations from which these all-cause diarrhea efficacy results were derived, due to late presentation in the course of the diarrheal episode and/or limited diagnostic sensitivity of the ELISA system used. The variance may also be due to an overestimate of vaccine efficacy against all-cause severe gastroenteritis in the clinical trials. For example, if all-cause efficacy was measured only through the rotavirus season and then annualized, the estimate would be falsely high.

Results from the scenario that modeled the indirect effects of vaccination suggest that the impact may be greater than estimated in the base case. The 25% increase in deaths averted is dependent upon the simplifying assumptions used in modeling this scenario. It is not surprising that impact expands, since more children are benefiting from vaccination compared to the base case. In addition to improving overall impact, indirect protection may also increase equity by providing protection to higher risk children who would not otherwise be vaccinated. However this would likely depend on proximity and other population dynamics between vaccinated and unvaccinated children, and needs to be examined in the field.

This study has some limitations. We used DPT vaccine coverage as a proxy for rotavirus vaccines; however, we did not include the potential impact on coverage by the age restrictions placed on the timing of administration of rotavirus vaccines [54]. The restrictions may decrease overall coverage, and therefore impact, compared to that achieved with DPT, but these data will only be available after countries have introduced. We did lower DPT coverage rates in our base case analysis though, to account for the assumption that there may be inequity in vaccine coverage, especially for those most likely to die from rotavirus, thus resulting in a more conservative estimate. As more data become available, these coverage assumptions will become more refined and accurate. In addition, although we have used available data and historical trends to project country introductions, it is very difficult to accurately predict adoption patterns, particularly more than a few years in the future. We have illustrated a snapshot of one potential demand scenario that attempts to capture the impact of rotavirus vaccines in all GAVI-eligible countries. However, changes in the timing and inclusion of country introductions will occur as time goes on, so updated analyses will be required to reflect the impact of these changes.

This analysis strongly supports the WHO recommendation for the introduction of the live, oral rotavirus vaccines in countries with high Under5 mortality, high diarrheal incidence and limited health resources. Rotavirus immunization is very cost effective and has significant public health impact in the GAVI-eligible countries which carry the greatest burden of rotavirus morbidity and mortality. Rotavirus vaccines are utilized in several middle- and high-income countries where there has been a dramatic decline in rotavirus associated hospitalizations and savings to the medical health system. As the GAVI Alliance is bridging the funding gap for new vaccines, and many countries are applying for financial support, the major impact of rotavirus vaccines on child mortality and health in the hardest hit populations may soon be realized.

Disclosures
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Conflict of interest
The authors have no conflicts to declare.

Disclaimer
The findings and conclusions of this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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[38] Conclusions and recommendations from the Immunization Strategic Advisory Group. WHO Epidemiol Rec 2006;81(January (1)):1–11.


