Rotavirus Vaccination: Cost-Effectiveness and Impact on Child Mortality in Developing Countries

By:Richard D. Rheingans, Deborah Atherly, Robert Dreibelbis, Umesh D. Parashar, Carol Levin & John Wecker

Abstract

Background. Rotavirus is the leading cause of severe gastroenteritis in children !5 years of age and is responsible for 1500,000 deaths annually; 85% of this burden is in low-income countries eligible for financial support from the GAVI Alliance. We projected the uptake, health impact, and cost-effectiveness of introducing rotavirus vaccination in GAVI-eligible countries to help policy makers in prioritizing resources to gain the greatest health improvements for their constituencies.

Methods. A demand forecast model was used to predict adoption of rotavirus vaccine in the poorest countries in the world. We then modeled health outcomes and direct costs of a hypothetical birth cohort in the target population for scenarios with and without a rotavirus vaccine with use of data on health outcomes of rotavirus infection, vaccine effectiveness, and immunization rates.

Results. Vaccination would prevent 2.4 million rotavirus deaths and 182 million disability-adjusted life-years (DALYs) in 64 of the 72 GAVI-eligible countries introducing vaccine from 2007 through 2025. The cost per DALY averted decreases over time, from a high of US$450 per DALY averted in the first year to a sustained low of $30 per DALY during 2017–2025, with a cumulative figure of $43 per DALY averted during 2008–2025. By applyingthe baseline scenario with an initial vaccine price of $7 per dose for a 2-dose vaccine, with a gradual decrease beginning in 2012 and stabilizing at $1.25 per dose by 2017, vaccination was very cost-effective in all GAVI-eligible countries with use of each country's gross domestic product per DALY averted as a threshold.

Conclusions. Introduction of rotavirus vaccines into the world's poorest countries is very cost-effective and is projected to substantially reduce childhood mortality

Richard D. Rheingans, Deborah Atherly, Robert Dreibelbis, Umesh D. Parashar, Carol Levin & John Wecker (2009) "Rotavirus Vaccination: Cost-Effectiveness and Impact on Child Mortality in Developing Countries" *Journal of Infectious Diseases* issue 200 pp. S28-S38 Version of Record Available From www.oxfordjournals.org

The developing world carries the greatest burden of rotavirus infection, the leading cause of severe gastroenteritis in children <5 years of age. Of the 500,000 annual deaths caused by rotavirus, >90% occur in developing countries [1]. During the past 3 years, 2 new rotavirus vaccines have been licensed and introduced in the public sectors of several high- and middle-income countries in the Americas and Europe. Although the introduction of these vaccines in the developing world could substantially reduce global rotavirus morbidity and mortality, a 10–20 year delay [2] between introduction of new vaccines in the industrialized world and availability in the developing world is common [3, 4]. There has been a significant increase in support from the global community to improve vaccine access and to accelerate introduction of new vaccines in low-income countries, including the formation of the GAVI Alliance (formerly known as the Global Alliance for Vaccines and Immunization), which supports vaccine introduction programs in countries with a gross national income per capita of US$1000 or less. In 2006, the same year during which rotavirus vaccine was first introduced in affluent countries, it was also introduced in the first GAVI-eligible country, Nicaragua, through a donation program by the manufacturer. Several additional low-income countries were poised to introduce vaccine in 2008 with support from the GAVI Alliance.

Early introduction of new vaccines in low-income countries is unprecedented, and it is important to understand the potential health and economic impacts. The cost-effectiveness and impact of rotavirus vaccination has been assessed for many countries representing a wide range of income levels, vaccine prices, and treatment costs [5–13]. However, no evaluations have modeled the cost-effectiveness and impact of accelerated introduction of rotavirus vaccines in high-burden countries over time, nor have existing analyses investigated the dynamic interplay between vaccine demand, impact, and cost-effectiveness for a variety of pricing scenarios.

We conducted a global cost-effectiveness and impact analysis of universal rotavirus vaccination programs for the world's poorest countries for the period 2007–2025. We estimated the costs and benefits of introducing rotavirus vaccine in countries eligible for GAVI Alliance support and estimated the projected impact and cost-effectiveness for multiple vaccine price and demand scenarios.

METHODS

We used a Microsoft Excel–based model to estimate the economic and health burden of rotavirus and the cost-effectiveness of vaccination in GAVI-eligible countries [14]. Principal model inputs are described in Table 1. Countries were modeled individually, and results were grouped by World Health Organization (WHO) region (Table 2). The model estimated health outcomes and health care costs associated with rotavirus for a series of annual birth cohorts [40], each followed up for a 5-year period. In addition, the model estimated the health care costs averted and the reduction in disease burden after vaccine introduction.

We conducted the analysis from a health care system perspective, focusing on direct medical costs from outpatient visits and hospitalizations, including the cost of diagnostic tests, medication, supplies, facilities, and personnel. Nonmedical costs to households and productivity losses to caregivers are included in the model, but results are not shown. Costs of informal medical treatment are not included in the model. No economic costs were included for cases that resulted in death or for patients who did not seek formal medical attention.

We estimated health burden in terms of disability-adjusted life-years (DALYs), which quantify the years lost because of mortality and the years lived with disability [41]. Estimates of DALYs averted by universal rotavirus vaccination were used to calculate the incremental cost-effectiveness ratio (ICER; US$ per DALY averted). Estimates are expressed in 2007 US dollars, and all future costs and DALY estimates were discounted at a rate of 3% annually.

Rotavirus-Associated Outpatient Visits, Hospitalizations, and Mortality

We estimated rotavirus-associated outpatient visit and hospitalization rates based on the approach described by Parashar et al [15]. We estimated rotavirus-associated outpatient visits and hospitalizations by multiplying the total number of diarrhea-related outpatient visits and hospitalizations by the estimated proportion attributable to rotavirus [15].

Estimates of rotavirus-associated mortality rates for each country were taken from the WHO [1]. On the basis of existing literature, 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 [16, 17, 42–68].

We calculated DALYs attributable to rotavirus mortality based on the standardized life expectancy at 1 year of age [69]. DALYs from cases of rotavirus disease resulting in outpatient or hospital visits were calculated on the basis of default disability weights [36] and an estimated illness duration of 6 days [70]. DALY estimates included age weights and an annual discount rate of 3% [71].

Health Care Costs of Rotavirus

Direct medical costs include the cost of an outpatient visit or hospital stay plus costs of diagnostic tests and medications. Estimates of country-specific hospital costs were derived from the WHO Choosing Interventions that are Cost Effective project [72], which standardized costs for outpatient visits and per diem hospitalizations according to geographical region and mortality stratum. We calculated mean outpatient and hospital unit costs for each region by taking a population-weighted mean of country-specific cost estimates. We estimated the mean length of hospital stay as 4 days [6, 16–35], and diagnostic and medication costs were estimated as a proportion of the per visit and per diem costs [73, 74]. Cost estimates were converted from year 2000 international dollars to 2007 US dollars with use of the Consumer Price Index [75], purchasing power parity, and official exchange rates [76].

Vaccination Cost

Costs of vaccination include administration costs, price per dose, and expected losses from waste. The cost of vaccine programs and administration was estimated using the WHO Global Immunization Vision and Strategy costing tool [77]. Cost per dose was calculated for each of the countries, and a regional, weighted mean was calculated and used in the analysis. Because of uncertainty of vaccine price over time, we calculated cost-effectiveness with use of fixed prices of $1.25 per dose and $7 per dose and with use of price trajectories that project price changes over time.

Table 2. Seventy-Two GAVI-Eligible Countries Categorized by Analysis Group and World Health Organization Region

Countries where efficacy and safety of rotavirus vaccine among these or similar populations have been confirmed in clinical trials at the time of the analysis (projected adoption, 2008–2011)
Region of the Americas
Bolivia
Cuba
Guyana
Haiti[a]
Honduras
Nicaragua
European Region
Armenia
Azerbaijan
Georgia
Kyrgyzstan
Moldova
Tajikistan
Ukraine
Uzbekistan
Countries likely to await results of ongoing rotavirus vaccine clinical trials before introduction (projected adoption 2011–2018)
African region
Angola[a]
Benin
Burkina Faso
Burundi[a]
Cameroon
Central African Republic[a]
Chad
Comoros
Congo[a]
Congo DR[a]
Côte d'Ivoire
Eritrea
Ethiopia
The Gambia
Ghana
Guinea
Guinea-Bissau
Kenya
Lesotho
Liberia
Madagascar
Malawi
Mali
Mauritania
Mozambique
Niger
Nigeria
Rwanda
São Tomé & Principe
Senegal
Sierra Leone
Tanzania
Togo
Uganda
Zambia
Zimbabwe
Eastern Mediterranean region
Afghanistan[a]
Djibouti
Pakistan
Somalia
Sudan
Yemen
Southeast Asian region
Bangladesh
Bhutan
DPR Korea[a]
India
Indonesia
Myanmar
Nepal
Sri Lanka
Timor-Leste
Western Pacific region
Cambodia
Kiribati
Lao PDR
Mongolia
Papua New Guinea
Solomon Islands
Vietnam

[a] Countries not included in the current analysis because of projected adoption dates after 2025.

Vaccine Effectiveness

We modeled the effectiveness of a live attenuated monovalent human rotavirus vaccine administered orally with 2 doses of diphtheria, tetanus, and pertussis (DTP) vaccine at ~2 and ~4 months of age, respectively. The effectiveness of vaccination within a given birth cohort was estimated by combining information on vaccine efficacy, expected coverage of 1 and 2 doses, and the relative coverage of children at the highest risk of mortality. Efficacy against severe rotavirus disease resulting in hospitalizations or mortality was 85% [37]. Efficacy against outpatient visits was estimated at 78% on the basis of the mean efficacy against severe rotavirus gastroenteritis (85%) [37] and any [38] rotavirus gastroenteritis (70%). One dose was assumed to be 50% as efficacious as a full course.

Vaccine Coverage

We used coverage rates for the third dose of DTP from WHO Immunization Coverage Estimates and Trajectories [77] to estimate coverage of rotavirus vaccine over time in each country. We combined country-specific population coverage estimates for the first and second doses of DTP with age-specific timing estimated by region from 17 demographic and health surveys from 2001 or later [78]. The model assumed a relative vaccine coverage rate among children at the highest risk of rotavirus mortality as 90% of the vaccination coverage of other children, because it is possible that children who die of diarrhea may have had less access to care, including routine vaccination.

Table 1. Variables Used in the Cost-Effectiveness and Impact Analyses

Variable	Reference(s)	Baseline estimate (range)	Distribution for uncertainty analysis
Health			
5-Year risk of hospitalization for rotavirus	[15]	0.016 (0.012–0.020)	Triangular
5-Year risk of outpatient visit for rotavirus	[15]	0.202 (0.152–0.252)	Triangular
Duration of hospital stay, days	[6, 16–35]	4.0 (3.0–5.0)	Triangular
YLL per death (discounted and weighted)	[36]	34.0	NA
YLD per event (discounted and weighted)	[36]	0.00037	NA
5-Year risk of mortality for rotavirus	…	Country-specific	Triangular (±25%)
Vaccine efficacy			
Severe rotavirus gastroenteritis resulting in hospitalization or death	[37]	0.85 (0.70–0.94)	Log normal
Moderate rotavirus gastroenteritis resulting in outpatient visit	[37, 38]	0.78 (0.58–0.89)	Log normal
Effectiveness reduction with 1 dose	Authors' assumption	0.5	NA
Effectiveness reduction in subsequent seasons for mild cases	[39]	0.04	NA
Health care cost, by region, 2007 US$			Triagular (±25%)
Region of the Americas			
Hospitalization	…	122.41	…
Outpatient visit	…	8.03	…
Vaccine program and administration	…	0.64	…
European region			
Hospitalization	…	11.15	…
Outpatient visit	…	7.20	…
Vaccine program and administration	…	1.16	…
African region			
Hospitalization	…	47.39	…
Outpatient visit	…	3.05	…
Vaccine program and administration	…	0.53	…
Eastern Mediterranean region			
Hospitalization	…	73.06	…
Outpatient visit	…	5.36	…
Vaccine program and administration	…	0.69	…
Southeast Asian region			
Hospitalization	…	32.94	…
Outpatient visit	…	1.72	…
Vaccine program and administration	…	0.46	…
Western Pacific region			
Hospitalization	…	60.35	…
Outpatient visit	…	3.39	…
Vaccine program and administration	…	0.24	…

NOTE. NA, not applicable; YLD, years lived with disability; YLL, years of life lost.

Vaccination Demand Forecast and Vaccine Introduction

To estimate the total number of children vaccinated each year from 2007 through 2025, we conducted a demand forecast analysis for GAVI-eligible countries with use of Cennium Forecaster for Birth Cohort Vaccines in Developing Countries (Applied Strategies Consulting), a decision-support software.

Model inputs. Model inputs included country-level population and birth cohort data, vaccine coverage rates, funding options, vaccine dosing schedule, vaccine price, and expected year of introduction [2]. The demand forecast model incorporated population and birth cohort estimates for each country through 2025, to capture demographic trends [69].

Price-demand scenarios. Three price-demand scenarios were developed for the analysis: baseline, accelerated, and delayed. Changes in the mean price of a single dose of a 2-dose vaccine for each scenario are shown in Figure 1. For all 3 price-demand scenarios, an initial price of US$7 per dose for a 2-dose vaccine was assumed on the basis of existing multinational supplier prices for lower-middle–income countries in Latin America [79] and an eventual price stabilization at $1.25 per dose after developing country manufacturers enter the market and increase supply with lower-cost products. This long-run price was estimated on the basis of a cost-of-goods analysis conducted in 2005 and assumes that most supply would be produced by manufacturers in developing countries, either with their own products or with transferred technology from multinational suppliers by 2017.

For the baseline price-demand scenario, vaccine price begins

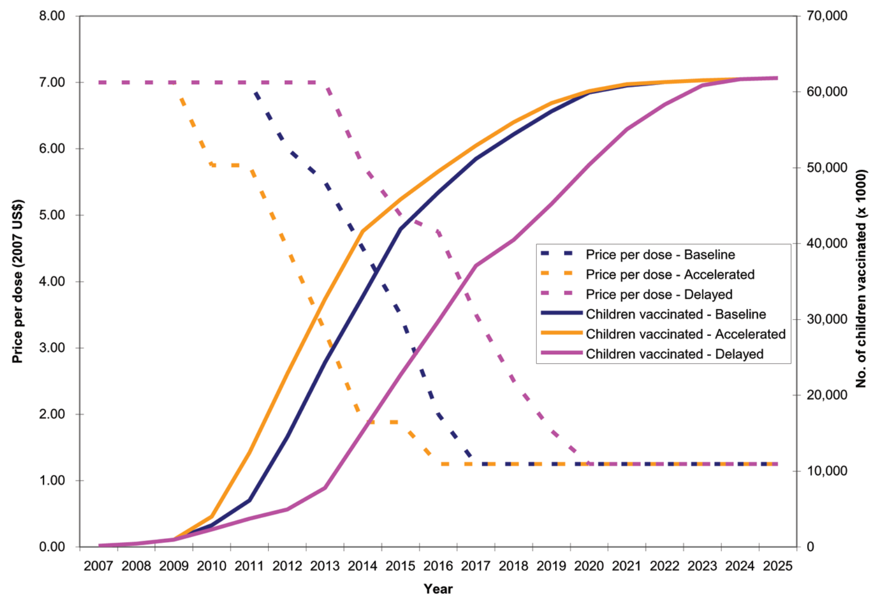

Figure 1. Annual price per dose for a 2-dose rotavirus vaccine and the number of children vaccinated for 3 price-demand scenarios.

to decrease in 2012, when new market entrants are expected, with price stabilizing at $1.25 per dose by 2017. In the accelerated price-demand scenario, vaccine price decreases sooner (2010) to reflect potentially earlier entry of additional products and stabilizes at $1.25 per dose by 2016. For the delayed price-demand scenario, price first decreases in 2014 and does not stabilize at $1.25 per dose until 2020. The delayed scenario represents potential delays in new market entrants because of uncertainty of product development success and timelines. We projected that the last countries to adopt universal rotavirus vaccination will reach vaccine coverage targets in 2021 and will realize the full benefits of vaccination by 2025.

Country adoption schedules. Demand estimates require predictions about which countries will adopt vaccine and about the timing of their adoption. Early adopters, projected to introduce vaccine during 2008–2011, included countries in Latin America and Eastern Europe where vaccine efficacy and safety have been confirmed in clinical trials for these or similar populations. Countries in Africa and Asia likely to await results of ongoing clinical trials before vaccine introduction are projected to adopt from 2011 through 2018. For purposes of the analysis, we accounted for the likely scenario that some countries will not adopt before 2025 for reasons of political instability and/or very poor vaccine adoption history. Although we cannot predict with certainty which countries these will be, we have excluded 8 countries, representing 10% of the GAVI-eligible birth cohort. Countries are presented by adoption timing and WHO region in Table 2.

We used a criteria-based prediction process to estimate the year of vaccine introduction within the 2 major adoption periods. Countries that have (1) relatively high coverage rates of the third dose of DTP ($\geqslant$80%), (2) introduced hepatitis B and/or *Haemophilus influenzae* type b vaccine, (3) a significant burden of rotavirus disease, and (4) expressed an interest in adopting rotavirus vaccine were predicted to adopt early. Countries that met most but not all of these criteria were next in the adoption schedule. This criteria-based prediction process continued until all countries were included. On the basis of the introduction patterns of hepatitis B vaccine, we assumed that countries would need 2–4 years after vaccine introduction to reach maximum expected coverage levels.

Summary Outcomes

The 2 primary outcome measures were the number of deaths averted (total and per 1000 children vaccinated) and incremental cost-effectiveness. The ICER is the net cost of vaccination from the health care system perspective divided by the change in DALYs attributable to rotavirus, compared with current vaccination practice. The ICER was calculated for each year, country, region, and demand scenario.

Sensitivity and Uncertainty Analyses

One-way sensitivity analyses were conducted to assess the impact of specific variables on the number of deaths averted and cost-effectiveness of vaccination for the baseline price-demand scenario. Variables included rotavirus mortality incidence, vaccine efficacy against hospitalization and mortality, relative coverage (ability to reach children at highest risk of death), vaccination systems costs, and timing of vaccine dosing. The 2 alternative price-demand scenarios (accelerated and delayed) were also included in the sensitivity analysis.

A probabilistic uncertainty analysis was done to assess the combined effect of multiple uncertain variables on vaccination impact (deaths averted) and cost-effectiveness (US$ per DALY averted). 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 (tenth and 90th percentiles of the output distributions).

RESULTS

Demand forecast and uptake. The expected trajectory of price decrease and uptake for the 3 price-demand scenarios are shown in Figure 1. For all scenarios, vaccination is expected to reach almost 62 million children in 2025.

Vaccine impact. Projected impact and cost-effectiveness estimates for the 64 countries included in this analysis are presented by region in Table 3. From 2007 through 2025, by using the baseline scenario, universal vaccination would result in 2.4 million fewer deaths due to rotavirus and in >82 million fewer DALYs, primarily in the Southeast Asian and African regions. Vaccination would result in 137 medical visits averted and $857 in medical expenses averted for every 1000 children vaccinated. For every 1000 children vaccinated, the medical costs averted are highest in Latin America ($2533) and lowest in sub-Saharan Africa ($913) and Southeast Asia ($617). Conversely, the health benefits are greatest in Africa (180 DALYs averted) and Southeast Asia (102 DALYs averted) and lowest in Latin America (45 DALYs averted).

Figure 2 shows the estimated annual numbers of deaths averted and deaths averted per 1000 children vaccinated over time for each of the 3 price-demand scenarios. For the baseline scenario, the annual number of deaths averted climbs from 10,000 in 2008 to ~150,000 by 2014, reaching a sustained level of 225,000 annual deaths averted by 2021. The number of deaths averted per 1000 children vaccinated increases from 1.0 in 2008 to ~3.0 in 2011 and ~3.5 after 2018. For the baseline scenario, the number of annual deaths averted climbs rapidly between 2010 and 2020. The annual numbers of deaths averted and deaths averted per 1000 children vaccinated are similar for the baseline and accelerated scenarios. In the delayed scenario, the initial increase in the number of annual deaths averted occurs in 2013 and approaches a maximum only after 2023. The delayed uptake would result in 543,720 fewer deaths averted, compared with the baseline price-demand scenario.

Cost-effectiveness. For the baseline scenario, the cost-effectiveness ratio of rotavirus vaccination in GAVI-eligible countries would be $43 per DALY averted for the entire period during 2007–2025 (Table 3). The ICER ranges from $22 per DALY averted in Africa to $118 per DALY averted in Latin America. The *World Health Report* (2002) suggests that "very cost-effective interventions" are those that "avert each additional DALY at a cost less than GDP [gross domestic product]

Table 3. Projected Impact and Cost-Effectiveness of Rotavirus Vaccination by Region and Total for GAVI-Eligible Countries during the Period 2007–2025

	WHO region						
Variable	AMR	EUR	AFR	EMR	SEAR	WPR	All GAVI Alliance regions
Regional GDP per capita (population-weighted),[a] mean US$	1900	2100	670	880	1020	800	970
Total impact							
Total no. of deaths averted	16,322	53,174	1,025,084	188,859	1,113,609	57,479	2,431,922
Total DALYs averted	577,411	1,813,693	34,915,277	6,437,204	37,957,729	1,961,122	82,872,424
Impact per 1000 children vaccinated							
No. of deaths averted (10%–90% uncertainty)	1.3 (0.8–1.5)	2.3 (1.3–2.5)	5.3 (3.3–5.7)	3.0 (1.6–3.1)	3.0 (1.7–3.2)	2.0 (1.0–2.0)	3.6 (2.1–3.7)
DALYs averted	45	80	180	100	102	67	123
Health care visits averted	141	147	132	133	139	139	137
Medical costs averted, 2007 US$	2533	1653	913	1480	617	1152	857
Cost-effectiveness							
Cost/DALY averted ($7.00 per dose), 2007 US$	289	201	78	419	147	210	118
Cost/DALY averted ($1.25 per dose), 2007 US$	26	42	14	66	28	29	21
Cumulative cost/DALY averted (2007–2025), 2007 US$ (10%–90% uncertainty)	118 (111–232)	105 (97–195)	22 (17–31)	33 (25–54)	54 (50–99)	81 (76–151)	43 (39–71)

NOTE. AFR, African region; AMR, region of the Americas; DALY, disability-adjusted life-year; EMR, eastern Mediterranean region; EUR, European region; GDP, gross domestic product; SEAR, Southeast Asian region; WHO, World Health Organization; WPR, western Pacific region.

[a] Data are from [69, 80].

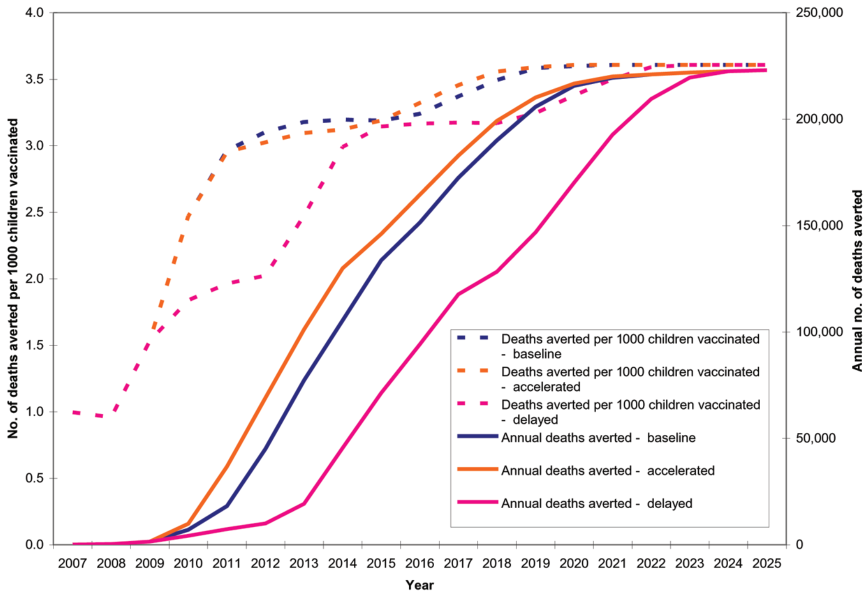

Figure 2. No. of deaths averted per 1000 children vaccinated and total no. of deaths averted annually for the 3 following price-demand scenarios: (1) base-case demand, (2) delayed demand, and (3) accelerated demand.

per capita" [81, p 108] and that interventions with a cost-effectiveness ratio ($/DALY averted) of 1–3 times the gross domestic product per capita are cost-effective. By this standard, rotavirus vaccination would be very cost-effective in all the regions considered over the period. If vaccine prices do not decrease as projected, vaccination would meet only the standard of cost-effectiveness in some countries.

With use of a constant price of $7 per dose for a 2-dose vaccine, the ICER ranges from $78 to $419 per DALY averted. At the projected market mature price of $1.25, the ICER ranges from $14 per DALY averted in sub-Saharan Africa to $66 per DALY averted in the eastern Mediterranean region. At that price, rotavirus vaccines represent a very cost-effective intervention for GAVI-eligible countries in all regions.

Figure 3 shows the estimated cost-effectiveness of vaccination over time, including the annual ICER for each year for the 3 price-demand scenarios and the cumulative ICER for the baseline scenario. For all 3 price-demand scenarios, the annual ICER decreases from >$400 per DALY averted to ~$25 per DALY averted. The cumulative ICER for the baseline scenario decreases over time, reaching $43 per DALY averted.

Sensitivity analysis. Changes in assumptions for key variables resulted in minimal changes in the cost-effectiveness of universal rotavirus vaccination (Figure 4). The cost-effectiveness of the vaccine decreases to a low of $33 per DALY averted based on the accelerated scenario and increases to $73 per DALY averted if vaccine efficacy is only 50%. Even at the highest cost-effectiveness ratio of $73 per DALY averted, the rotavirus vaccine remains a very cost-effective intervention in GAVI-eligible countries for the projected period during 2007–2025. The number of deaths averted ranged from 1.4 million with a vaccine efficacy of 50% to an upper range of 3 million when baseline rotavirus mortality rates are increased by 25%. Upper and lower uncertainty limits from the probabilistic analysis are also presented by region for deaths averted per 1000 children vaccinated and cost-effectiveness in Table 3.

DISCUSSION

Introduction of rotavirus vaccines in GAVI-eligible countries will be cost-effective and could avert the deaths of 2.5 million children from 2007 through 2025, with annual reductions in mortality of up to 225,000 children. Our findings suggest that cost-effectiveness ratios decrease over time and that the impact of vaccination on overall mortality and mortality rates increases. These temporally related outcomes are influenced by similar factors—primarily, decreases in vaccine price over time and vaccine uptake by countries with a higher burden of rotavirus later during the introduction period. Early-adopter countries in Latin American and European regions are burdened by significant morbidity and associated hospital costs related to rotavirus, compared with countries in the African and Asian regions; however, their underlying mortality rates are lower. In addition, the initial vaccine price is anticipated to be higher than in subsequent years. Once countries with a higher burden of rotavirus in Africa and Asia introduce the vaccine, the price is likely to decrease as production in developing countries increases, both global and region-specific cost-effectiveness ratios will improve, and impact will increase substantially.

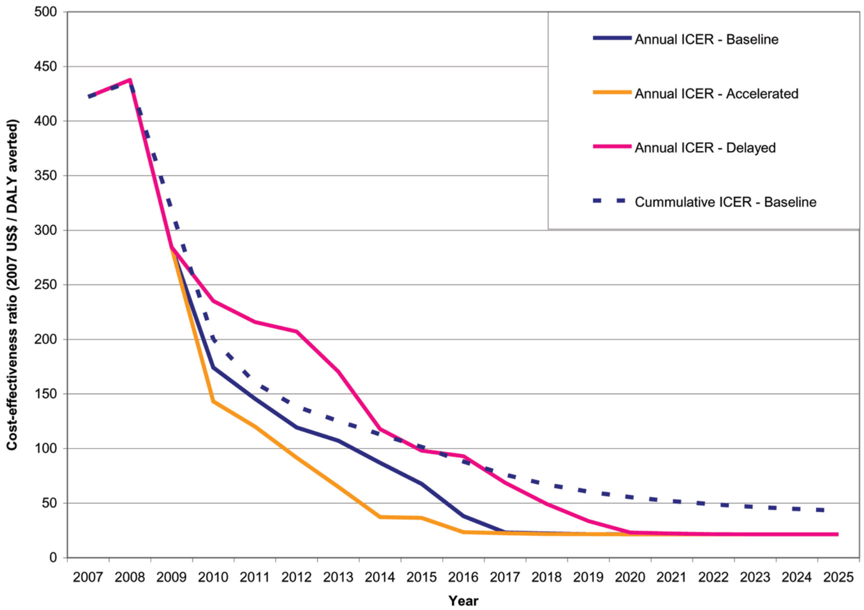

Figure 3. Annual incremental cost-effectiveness ratio (ICER) for 3 price-demand scenarios and cumulative cost-effectiveness ratio for baseline scenario. The annual ICER is calculated for each year. The cumulative ICER is for the period up to that year. DALY, disability-adjusted life-year.

Our sensitivity analysis assessed the impact of variability in rotavirus mortality, vaccine efficacy, relative coverage, timing of administration of vaccine doses, vaccine system costs, and our price-demand scenarios on health outcomes and cost-effectiveness of universal rotavirus vaccination. For all adjustments, rotavirus vaccination remained cost-effective or very cost-effective. Although our sensitivity analysis accounted for changes in vaccination coverage, our model required holding infant and child mortality rates from 2004 constant. Possible secular reductions in diarrhea- and rotavirus-associated mortality because of factors such as economic development or improvements in access to care could result in an overestimate of both the cost-effectiveness and the total impact of universal vaccination. Societal costs and costs associated with the informal health care sector also are not included in this analysis. Although these costs have been shown to have a nominal impact on the incremental cost-effectiveness of vaccination programs, our cost-effectiveness results would be more favorable if we had captured the full extent of medical costs averted through rotavirus vaccination. In addition, although the 3-dose vaccine schedule was not modeled, the conclusions of this analysis would not be expected to differ between the 2- and 3-dose regimens.

Projections are based on several assumptions that could substantially affect the cost-effectiveness and impact of rotavirus vaccination over time. First, our 3 price-demand scenarios assume that results of clinical trials in Africa and Asia will be favorable enough for adoption. Should results not provide com-

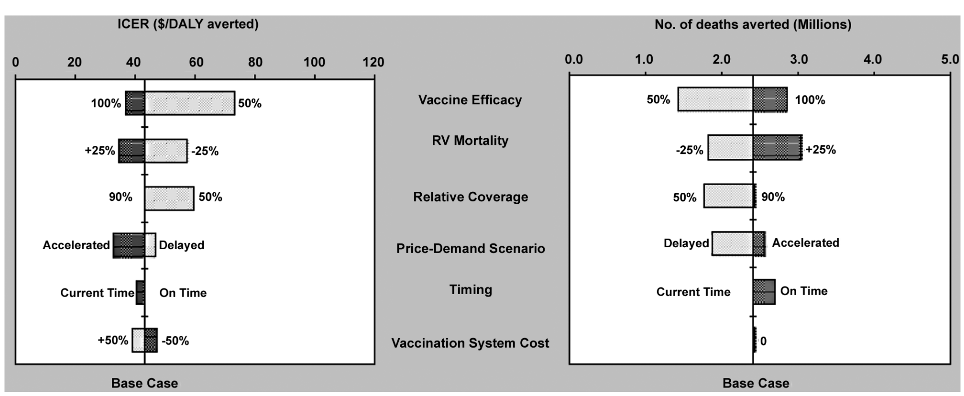

Figure 4. One-way sensitivity analysis of key variables for the cumulative cost per disability-adjusted life-years (DALYs) averted and number of deaths averted during the period 2007–2025. ICER, incremental cost-effectiveness ratio.

pelling evidence for rotavirus vaccine introduction, demand in these regions is likely to be very limited. Second, the scenarios depend on the entry of manufacturers in developing countries in the rotavirus vaccine market. Development efforts by emerging suppliers are underway, but uncertainty regarding the timing and extent of market entry remains and is also dependent on vaccine demand. Finally, although we have used historical trends to predict when countries are likely to introduce rotavirus vaccination, it is difficult to reliably predict adoption patterns. Despite these limitations, our current price-demand scenarios are based on the most reliable data currently available and are broad enough to capture potential delays in both demand and introduction.

For all vaccine prices and price-demand scenarios included in our analysis, universal rotavirus vaccination is very cost-effective or cost-effective in all GAVI-eligible countries and can save the lives of millions of children. However, a program can provide good value for money but remain unaffordable and, thus, unable to achieve and sustain desired results. Initial vaccine prices, although substantially discounted by multinational pharmaceutical companies, are still out of reach for many developing countries, making the subsidies provided by the GAVI Alliance and other potential donors essential for accelerated vaccine introduction. We showed the impact of a modest delay in price decrease and uptake in our delayed scenario, in which the opportunity to save the lives of >540,000 children is missed. Although universal rotavirus vaccination programs would be cost-effective even at the highest vaccine price included in our analysis, subsidies must be sustained or the price of the vaccine must decrease to ensure introduction in low-income, high-burden countries.

In addition to vaccine affordability, decision makers will be influenced by factors such as health system capacity and the costs associated with expanding existing immunization services to accommodate new vaccines. Policy makers must weigh the political, social, and economic considerations of allocating precious resources in the face of many important and often competing health care and development priorities. Because more countries will consider adoption of rotavirus vaccination in the coming years, this analysis was designed to complement existing and forthcoming clinical and epidemiological data to provide the evidence base necessary to make well-informed policy and funding decisions. Our findings indicate that rotavirus vaccination is cost-effective and has the potential to save hundreds of thousands of young children each year in developing countries.

Acknowledgments

We thank Angeline Nanni, for her contributions to the demand forecasting work, and Deborah Phillips, for her assistance in editing the manuscript.

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