

Projected Impact and Cost-Effectiveness of a Rotavirus Vaccination Program in India, 2008

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Background. To assess the value of rotavirus vaccination in India, we determined the potential impact and cost-effectiveness of a national rotavirus vaccination program.

Methods. We compared the national rotavirus disease and cost burden with and without a vaccination program and assessed the cost-effectiveness of vaccination. Model inputs included measures of disease and cost burden, vaccine performance, and vaccination coverage and cost. We measured the annual number of health-related events and treatment costs averted, as well as the cost-effectiveness in US dollars per disability-adjusted life-year (DALY) and cost per death averted. One-way sensitivity analyses were performed by individually varying each model input.

Results. With use of a vaccine that has an estimated effectiveness of 50%, a rotavirus vaccination program in India would prevent ~44,000 deaths, ~293,000 hospitalizations, and ~328,000 outpatient visits annually, which would avert \$20.6 million in medical treatment costs. Vaccination would be cost-saving at the GAVI Alliance price of \$0.15 per dose. At \$1.00 per dose, a vaccination program would cost \$49.8 million, which would result in an expenditure of \$21.41 per DALY averted or \$662.94 per life saved. Even at \$7.00 per dose, vaccination would be highly cost-effective. In sensitivity analyses, varying efficacy against severe rotavirus disease and vaccine price had the greatest impact on cost-effectiveness.

Conclusions. A national rotavirus vaccination program in India would prevent substantial rotavirus morbidity and mortality and would be highly cost-effective at a range of vaccine prices. Public health officials can use this locally derived data to evaluate how this highly cost-effective intervention might fit into India's long-term health care goals.

(See the editorial commentary by Nelson et al, on pages 178–179.)

Rotavirus is the most common cause of severe dehydrating gastroenteritis in children <5 years of age worldwide and causes an estimated 527,000 deaths annually [1, 2]. Approximately 23% of these deaths occur in India alone [3]. Because improvements in sanitation and hygiene have had little impact on the incidence of severe rotavirus gastroenteritis, vaccination is considered to be the best means of controlling this disease [4, 5].

Since 2006, 2 safe and effective live, attenuated, oral rotavirus vaccines have become available on the world market [6], and other rotavirus vaccines are under development in India and elsewhere. In June 2009, the World Health Organization (WHO) recommended global use of rotavirus vaccines in infants [7]. To help policy makers to assess the value of a national rotavirus vaccination program in India, we determined the impact of vaccination on rotavirus disease burden and associated health care costs, and we evaluated the cost-effectiveness of vaccination.

METHODS

Model Overview

We used a Microsoft Excel–based model to evaluate the impact and cost-effectiveness of a projected national

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rotavirus immunization program in India by comparing rotavirus disease and cost burden with and without such a program for an annual birth cohort that was followed-up for a 5-year period [8]. Principle model inputs included measures of disease burden (rotavirus-associated rates of childhood death, hospitalization, and outpatient visit), direct treatment costs (cost of hospitalization and outpatient visit), vaccine effectiveness, vaccination coverage rates, and vaccination cost (vaccine price, administration costs, and wastage).

Impact of vaccination on disease and cost burden, which was expressed in terms of annual number of health-related events and costs averted, and cost-effectiveness, which was expressed in US dollars per disability-adjusted life-year (DALY) and cost per death averted, were calculated. DALYs measure “age-specific life expectancy for loss of healthy life due to disability” [9]. In contrast to quality-adjusted life-years (QALY), which measure the addition of healthy years, DALYs measure a loss of healthy years by weighting the incremental loss of health as a result of specific diseases. In keeping with norms for DALY-related analyses, standardized life expectancy at 1 year of age was used to calculate the DALY burden due to rotavirus mortality. A default disability weight of 0.119 and estimated duration of illness of 6 days were used to calculate the DALYs for cases of rotavirus disease that resulted in a hospital or outpatient visit [10]. DALYs included age weights and all future costs, and DALY estimates are discounted at a rate of 3%. All costs and savings are considered exclusively from the health care system perspective and focus on direct medical treatment costs (eg, diagnostic tests, medications and medical supplies, and facility costs), and they are reported in 2008 inflation-adjusted US dollars. Three clinical states were modeled: well, ill (ie, hospitalized or seeking outpatient medical care), and dead. Societal costs (eg, transportation, food, and lodging costs and lost wages of caregivers), economic costs associated with fatalities, and costs for persons ill with rotavirus gastroenteritis who sought care outside of the formal medical system were not considered.

Model Inputs

Rotavirus disease burden and treatment costs. Base-case estimates for the India-specific rotavirus death rate, hospitalization rate, and outpatient visit rate and their associated medical treatment costs among children <5 years of age were obtained from our recently published study (Table 1) [11]. The rotavirus death rate was 108 deaths per 100,000 children <5 years of age. Hospitalizations and outpatient visits occurred at a frequency of 652 hospitalizations and 932 visits per 100,000 children <5 years of age, respectively. We applied a cost of \$68.90 per rotavirus hospitalization; in India, each rotavirus hospitalization averaged 3 days in duration. For each rotavirus-related outpatient visit, a cost of \$2.89 was used.

Rotavirus vaccination effectiveness. Rotavirus vaccine immunogenicity, efficacy, and effectiveness have all been found

to vary by income level of the country where the vaccine is used, and they tend to be lower in lower-income countries than they are in middle- and upper-income countries [12]. Because India-specific rotavirus vaccine performance data do not exist, we assumed a performance similar to that observed in Bangladesh and Viet Nam, which are 2 Asian countries that are comparable to India and which have existing rotavirus vaccine clinical trials data [7, 13]. Data combined from these 2 countries show an efficacy against severe rotavirus disease of ~50%, and we used this figure for the effectiveness of rotavirus vaccination against death and hospitalization due to rotavirus infection in India (Table 1). No data specifying rotavirus vaccine efficacy against outpatient visits exist from a country that is comparable to India. Therefore, we assumed rotavirus vaccine effectiveness against outpatient visits for rotavirus infection to be 10 percentage points lower than the estimated effectiveness of the vaccine against severe disease. The effectiveness of 1 dose was assumed to be one-half that of the full 2-dose series.

Rotavirus vaccination coverage and timing. Our model assumed a 2-dose infant rotavirus vaccination series, administered on the same schedule as the first 2 doses of diphtheria, tetanus, and pertussis (DTP) vaccine. Using WHO–United Nations Children’s Fund vaccination coverage data for DTP vaccination in India, we estimated that India-wide rotavirus vaccination coverage would be 73% for the first dose and 63% for the second dose (Table 1) [14, 15]. Our model assumed on-time administration of all vaccinations. Because children at greatest risk for death due to rotavirus infection may have less access to routine vaccination, we assumed coverage among these children to be 10 percentage points lower than coverage among other children [8].

Rotavirus vaccination cost. Vaccination cost reflects the combination of vaccine price, cost of administration, and loss from waste. The price of rotavirus vaccine for use in the public sector in India is not known. For purposes of this analysis, we varied vaccine price from a low of \$0.15 per dose [16] (the current lowest possible country co-pay price for procurement of vaccine through the GAVI Alliance), a medium price of \$1.00 per dose (a stated target price for rotavirus vaccines that are currently being developed in India), to a high of \$7.00 per dose [17, 18] (the price currently paid by some middle-income developing countries for rotavirus vaccine). We estimated the cost of vaccine administration to be \$0.25 per dose with use of the WHO Global Immunization Vision and Strategy costing model [19], with an expected vaccine loss of 10% due to wastage.

Model Outputs

Rotavirus vaccination impact. Vaccination impact was expressed in terms of annual number of lives saved and annual hospitalizations, outpatient visits, and medical treatment costs

Table 1. Principle Base-Case Values, Sensitivity Ranges, and References and Assumptions of Model Inputs for Estimating Impact and Cost-effectiveness of a National Rotavirus Vaccination Program, India, 2008

Parameter	Base-case estimate	Sensitivity range	References and assumptions
Disease burden^a			
Rotavirus death rate	108	102–112	[11]
Rotavirus hospitalization rate	652	337–816	[11]
Rotavirus outpatient visit rate	932	700–1501	[11]
Treatment costs			
Cost of 3-day hospitalization	\$68.90	\$51.68–\$86.13	[11]
Cost of outpatient visit	\$2.89	\$2.16–\$3.61	[11]
Vaccine performance			
Effectiveness against death, %	50	40–60	[7]
Effectiveness against hospitalization, %	50	40–60	[7]
Effectiveness against clinic visit, %	40	30–50	... ^b
Vaccination coverage^d			
First dose, %	73	63–83	[14]
Second dose, %	63	53–73	[14]

NOTE. All costs are given in 2008 inflation-adjusted US dollars.

^a Expressed as annual rate per 100,000 children <5 years of age.

^b No data available; assumed effectiveness in preventing a clinic visit was 10 percentage points lower than effectiveness against hospitalization and death.

^c Assumes 10% vaccine wastage.

^d Vaccine received by 12 months of age; assumes on-time vaccination.

averted. Impact was also expressed in terms of DALYs averted. DALYs quantify the years lost because of premature death and the years lived with disability [10], and included age weights and a discount rate of 3%.

Rotavirus vaccination cost-effectiveness. Incremental cost-effectiveness ratios (ICERs), which are a measure of cost-effectiveness, were expressed in 2 ways: (1) incremental cost per DALY averted, and (2) incremental cost per life saved, where incremental cost equals the cost of the vaccination program minus the medical cost savings from vaccine-prevented cases. The medical break-even price of vaccination, which is the price per dose of vaccine where the cost of vaccination exactly equals the health care costs averted, was also determined. Finally, we compared ICERs in cost per DALYs averted to the WHO threshold for highly cost-effective interventions [20]. By this standard, an intervention is considered to be highly cost-effective if the cost per DALY averted is less than the country's per capita gross domestic product (GDP). The 2008 GDP for India was \$1017 [21].

Sensitivity analysis. One-way sensitivity analyses were performed by individually varying each base-case model input and observing the effect on cost-effectiveness (Table 1). The upper and lower limits for the rotavirus death rate, the lower limit for the hospitalization rate, and the upper limit for the outpatient visit rate were all taken from the same study that provided the base-case estimates for these parameters, which reflects a difference in calculation methods used by the authors [11]. We also varied the hospitalization rate by +25% and the

outpatient visit rate by -25% to create the upper and lower limits, respectively. Medical treatment costs and vaccination administration costs were varied by $\pm 25\%$ from the base-case estimate. To arrive at upper and lower limits for both rotavirus vaccine efficacy and vaccination coverage, we varied these parameters by $\pm 10\%$. The vaccine price was held at the base-case price of \$1.00 per dose during the sensitivity analyses, except where we evaluated the impact of the vaccine price itself. For this component, we varied vaccine price from the low price of \$0.15 per dose to the high price of \$7.00 per dose.

RESULTS

Rotavirus Vaccination Impact on Disease Burden and Treatment Costs

A national rotavirus vaccination program in India would prevent ~44,000 deaths, ~293,000 hospitalizations, and ~328,000 outpatient visits annually (Table 2). More than 1.3 million DALYs (or 50 DALYs per 1000 children) would be averted by such a program. The reductions in rotavirus disease brought about by vaccination would save the health care system in India \$20.6 million annually in medical treatment costs (\$19.7 million in hospitalization and \$0.9 million in outpatient visit costs), or \$0.76 per child.

Rotavirus Vaccination Cost and Cost-effectiveness

At the low price of \$0.15 per dose, a vaccination program would cost a total of \$15.3 million but would be cost-saving in India (the medical break-even price of vaccine is \$0.28 per dose)

Table 2. Rotavirus Infection–Related Events in Children <5 Years of Age and Associated Medical Treatment Costs with and without Rotavirus Vaccine and Averted by Vaccination and Cost of Intervention, India, 2008

Variable	Without vaccine	With vaccine	Annual averted events or cost (%)
No. of events			
Deaths	147,386	103,423	43,963 (30)
Hospitalizations	884,315	591,229	293,086 (33)
Outpatient visits	1,263,745	935,589	328,156 (26)
DALYs lost	4,564,545	3,203,135	1,361,410 (30)
Medical treatment costs, in millions			
Hospitalization	61.7	42.0	19.7 (32)
Outpatient	3.7	2.8	0.9 (24)
Total	65.4	44.8	20.6 (31)

NOTE. All costs in 2008 inflation-adjusted US dollars. DALY, disability-adjusted life-year.

(Table 3). At the medium price of \$1.00 per dose, a vaccination program would cost a total of \$49.8 million (a net cost of \$29.1 million), which would result in an ICER of \$21.41 per DALY averted or \$662.94 per death averted. At the high price of \$7.00 per dose, a vaccination program would cost a total of \$293.2 million (net cost of \$272.6 million), which would result in an ICER of \$200.21 per DALY averted or \$6199.88 per death averted. With use of the WHO cost-effectiveness criteria, a vaccination program would be highly cost-effective up to a per-dose vaccine price of \$34.41, but at this price a vaccination program in India would cost over \$1.4 billion annually.

One-way Sensitivity Analysis

Using the base-case price of \$1.00 per dose, the ICER (expressed as incremental cost per DALY averted) was most sensitive to changes in rotavirus vaccine efficacy against both death and hospitalization (Table 4). A 10 percentage point decrease in efficacy against death and hospitalization yielded a 25% increase and a 14% increase, respectively, in ICER. Conversely, a 10 percentage point increase in efficacy against

death and hospitalization yielded a 17% decrease and a 14% decrease, respectively, in ICER. Varying vaccine price also had a substantial effect on the ICER. An increase in vaccine price to \$7.00 per dose yielded an 835% increase in the ICER, whereas a decrease to \$0.15 per dose was cost saving. Variations in all other model inputs had negligible effects.

DISCUSSION

In India, rotavirus infection is estimated to cause 122,000–153,000 deaths, 457,000–884,000 hospitalizations, and 2 million outpatient visits among children <5 years of age each year, with associated annual medical treatment costs as high as \$72 million [11]. On the basis of available data on the performance and expected coverage of rotavirus vaccination in India, we show that a national rotavirus vaccination program would save 44,000 lives and avert 293,000 hospitalizations and 328,000 outpatient clinic visits each year, which would save the health care system \$20.6 million in medical treatment costs. From the perspective of the health care system

Table 3. Cost-effectiveness of a National Rotavirus Vaccination Program at Varying Vaccine Prices, India, 2008

Vaccine price per dose, \$	Cost of program in millions, \$ ^a	Net cost of program in millions, \$ ^b	Incremental cost per DALY averted, \$	Incremental cost per death averted, \$
0.15 ^c	15.3	−5.3	Cost-saving	Cost-saving
0.28 ^d	20.6	0	0	0
1.00 ^e	49.8	29.1	21.41	662.94
7.00 ^f	293.2	272.6	200.21	6,199.88

NOTE. All costs in 2008 inflation-adjusted US dollars. DALY, disability-adjusted life-year.

^a Includes stated per-dose vaccine price plus \$0.25 vaccine administration; assumes a 2-dose vaccination schedule and 10% vaccine wastage.

^b Equal to the cost of the vaccination program minus the medical treatment cost savings from averted rotavirus-associated disease (\$20.6 million).

^c Low-price estimate representing the current lowest possible India co-pay price for procurement of vaccine through the GAVI Alliance [16].

^d Medical break-even price of vaccine or the price per dose of vaccine where the cost of the vaccination program exactly equals the health care costs averted by vaccination.

^e Medium base-case price based on stated target price for rotavirus vaccines that are being currently developed in India.

^f The price some middle-income developing countries have paid for vaccine [17, 18].

Table 4. Sensitivity Analysis to Examine the Effect of Rotavirus-associated Disease and Cost Burden, Vaccine Performance, and Vaccination Cost and Coverage on the Cost-effectiveness of a National Rotavirus Vaccination Program, India, 2008

Input parameter	Parameter value	Change in parameter value, %	Cost per DALY averted, %	Change in ICER, %
Rotavirus-associated death rate^a				
Low	102	-6	22.81	+7
Base case	108		21.41	
High	112	+4	20.78	-3
Rotavirus hospitalization rate^a				
Very low	337	-48	28.41	+33
Low	634	3	21.81	+2
Base case	652		21.41	
High	816	+25	17.77	-20
Rotavirus outpatient visit rate^a				
Low	700	-25	21.58	+1
Base case	932		21.41	
High	1501	+61	20.99	-2
Hospitalization cost per child, \$				
Low	51.68	-25	25.03	+17
Base case	68.90		21.41	
High	86.13	+25	17.79	-17
Outpatient visit cost per child, \$				
Low	2.16	-25	21.58	+1
Base case	2.89		21.41	
High	3.61	+25	21.24	-1
Vaccine efficacy against death, %				
Low	40	-10	26.75	+25
Base case	50		21.41	
High	60	+10	17.84	-17
Vaccine efficacy against hospitalization, %				
Low	40	-10	24.31	+14
Base case	50		21.41	
High	60	+10	18.51	-14
Vaccine efficacy against outpatient visit, %				
Low	30	-10	21.58	+1
Base case	40		21.41	
High	50	+10	21.24	-1
Vaccine price per dose, \$				
Low	0.15	-85	Cost-saving	-100
Base-case	1.00		21.41	
High	7.00	+733	200.21	+835
Administration cost per dose, \$				
Low	0.19	-25	19.78	-8
Base-case	0.25		21.41	
High	0.31	+25	23.03	+8
First dose vaccine coverage rate, %				
Low	63	-10	21.46	+0
Base case	73		21.41	
High	83	+10	21.37	-0
Second dose vaccine coverage rate, %				
Low	53	-10	21.35	-0
Base case	63		21.41	
High	73	+10	21.46	+0

NOTE. All costs given in 2008 inflation-adjusted US dollars. ICER, incremental cost-effectiveness ratio.

^a Expressed as annual rate per 100,000 children <5 years of age.

alone, rotavirus vaccination would be cost-saving for India if vaccine is procured at the GAVI Alliance country co-pay price of \$0.15 per dose [16], and it would be highly cost-effective even at the higher vaccine prices that we examined, although program costs would be substantially greater.

Rose et al [22] have recently published another report on the impact and cost-effectiveness of rotavirus vaccination in India, and some important differences between their assumptions and those of our study should be noted. First, unlike our disease burden estimates, which are based on surveillance of rotavirus health outcomes in India, Rose et al [22] extrapolated data from a study conducted in Mexico [23] to model the incidence of infections and clinical outcomes of rotavirus infection in Indian children. Second, although we applied recent data from rotavirus vaccine efficacy trials conducted in Asian countries that had a socioeconomic status similar to that of India, Rose et al [22] used data from rotavirus vaccine trials conducted in the Americas and Europe and in affluent countries in Asia, with adjustment for rotavirus strain patterns in India. Regarding the findings, our base estimates of rotavirus-associated mortality and hospitalization in the absence of vaccination are greater than those of Rose et al [22], but our estimates of vaccine effectiveness and coverage are lower. Consequently, our overall estimates of rotavirus-associated deaths and hospitalizations prevented are very similar to those of Rose et al [22] (44,000 deaths and 293,000 hospitalizations prevented vs 41,000 deaths and 203,000 hospitalizations prevented). Furthermore, at a vaccine price of \$7.00 per dose, the cost-effectiveness reported by Rose et al [22] of \$164 per DALY averted is also similar to our estimate of \$200 per DALY averted at the same vaccine price.

Although rotavirus vaccination is likely to have substantial public health impact in India, our analysis indicates that only approximately one-third of the estimated rotavirus-associated deaths would be averted by vaccination. Efforts to improve vaccination coverage rates in India could further enhance the life-saving benefits and public health impact of this intervention. In addition, research is needed to understand the reasons for the lower immune response and lower effectiveness of rotavirus vaccination in low-income countries, such as India, compared with middle- and high-income countries, as well as to develop targeted strategies to improve rotavirus vaccine performance. Our cost-effectiveness model showed greatest sensitivity to changes in the effectiveness of vaccination in preventing both death and hospitalization, and strategies to improve vaccine performance would benefit both the impact and the cost-effectiveness profile of rotavirus vaccination in India.

These data are subject to several limitations. First, we consider cost-effectiveness only from the health care system perspective and ignore societal costs in our analysis. Including societal costs,

which could be substantial, would improve the overall cost-effectiveness of vaccination. Second, we use a 2-dose rotavirus vaccination schedule in our analysis. It is possible that a 3-dose rotavirus vaccine will ultimately be adopted. If this were the case, administration costs would be higher, but this also would have a relatively limited overall impact on the cost-effectiveness estimate, based on our sensitivity analysis. Vaccine price, however, could increase or remain the same. Third, effectiveness of rotavirus vaccination in India against severe disease (death and hospitalization), which is the parameter with the greatest impact on the cost-effectiveness estimate in our model, is unknown. Although our base-case estimate derives from rotavirus vaccine efficacy trials that were conducted in Asian countries comparable to India, vaccine performance in the Indian environment might differ and could impact rotavirus vaccination cost-effectiveness positively or negatively. Fourth, India is an enormously diverse country with incomplete health and health care cost data. Although we included the best and most current data available, our rotavirus disease and cost burden estimates originate from limited locations within India. Additional, up-to-date, nationally representative data would help to refine estimates of rotavirus vaccination impact and cost-effectiveness. Finally, our model does not consider the future medical costs of individuals whose lives are saved by the intervention, nor do we consider the productive contributions these individuals will make that might offset future medical costs [24].

In conclusion, our findings suggest that a national rotavirus vaccination program, if adopted in India, would be a highly cost-effective means for reducing the tremendous disease and economic burden of rotavirus gastroenteritis in that country. The WHO now recommends inclusion of rotavirus vaccine in the vaccination schedule of all infants worldwide. Given the intense competition for severely limited resources, these data provide additional tools to public health officials and policymakers to objectively decide which of the myriad public health programs and medical interventions to adopt for implementation in India.

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