Potential cost-effectiveness of vaccination for rotavirus gastroenteritis in eight Latin American and Caribbean countries

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ABSTRACT

Objectives. *To estimate the costs, benefits and cost-effectiveness of vaccination for rotavirus gastroenteritis in eight Latin American and Caribbean countries: Argentina, Brazil, Chile, the Dominican Republic, Honduras, Mexico, Panama, and Venezuela.*

Methods. *An economic model was constructed to estimate the cost-effectiveness of vaccination from the health care system perspective, using national administrative and published epidemiological evidence, country-specific cost estimates, and vaccine efficacy data. The model was applied to the first five years of life for the 2003 birth cohort in each country. The main health outcome was the disability-adjusted life year (DALY), and the main summary measure was the incremental cost per DALY averted. A 3% discount rate was used for all predicted costs and benefits. Sensitivity analyses evaluated the impact of uncertainty regarding key variables on cost-effectiveness estimates.*

Results. *According to the estimates obtained with the economic model, vaccination would prevent more than 65% of the medical visits, deaths, and treatment costs associated with rotavirus gastroenteritis in the eight countries analyzed here. At a cost of US$ 24 per course (for a two-dose vaccine), the incremental cost-effectiveness ratio ranged from US$ 269/DALY in Honduras to US$ 10 656/DALY in Chile. Cost-effectiveness ratios were sensitive to assumptions about vaccine price, mortality, and vaccine efficacy.*

Conclusions. *Vaccination would effectively reduce the disease burden and health care costs of rotavirus gastroenteritis in the Latin American and Caribbean countries analyzed here. From the health care system perspective, universal vaccination of infants is predicted to be cost-effective, based on current standards.*

Key words Rotavirus; rotavirus vaccines; cost-benefit analysis; models, economic; Latin America; Caribbean Region.

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Rotavirus infection, the single most important cause of gastroenteritis, leads to dehydration and death in small children in developed and developing countries (1, 2). Gastrointestinal infections in children have a wide range of impacts on their families and society, including increased medical expenditures, lost productivity, other costs to households for the care of children, and pain and suffering caused to children and their families. Universal vaccination of infants with an effective rotavirus vaccine would likely reduce the incidence of moderate and severe gastroenteritis,

as well as its burden on families and society.

A previous study estimated that rotavirus gastroenteritis is responsible for more than 15 000 deaths in children under 5 years of age in Latin America (1). In addition, several studies in Latin America have documented that rotavirus gastroenteritis is a common cause of hospitalization in children under 5 years of age (1–7). Rotavirus has also been shown to generate substantial economic costs for the health care system and society as a whole (6, 8). Cost-effectiveness studies elsewhere suggest that vaccination may be a cost-effective strategy for reducing this health and economic burden (9, 10).

The main impact of rotavirus gastroenteritis is the morbidity and mortality it causes in children, and information on the economic burden of disease and the cost-effectiveness of vaccination can aid decisionmakers in choosing interventions to improve health. Effective vaccines are now available for preventing rotavirus gastroenteritis (11, 12), but investments in medical advances such as new vaccines compete against other interventions for health sector resources. Information about the cost-effectiveness of vaccination provides an estimate of the health benefits resulting from the investment in vaccination, and such estimates can then be compared to the potential benefits of other interventions.

The objective of this analysis is to provide an estimate of the cost-effectiveness of universal rotavirus vaccination in eight Latin American and Caribbean countries. The estimates were developed using a spreadsheet-based decision-analytic model populated with a combination of country-specific data and estimates extrapolated from other countries for which data were lacking. Simulation techniques were used to develop ranges for these estimates, and to identify key data needs. In order to characterize vaccination benefits, the model used secondary data on the efficacy of *Rotarix* (GlaxoSmithKline Biologicals, Rixensart, Belgium), a live attenuated monovalent human rotavirus vaccine administered orally to infants at 2 and 4 months of age (11).

METHODS

Model overview

A decision-analytic model was developed using Excel software to estimate the economic burden of rotavirus gastroenteritis and the cost-effectiveness of vaccination in eight countries: Argentina, Brazil, Chile, the Dominican Republic, Honduras, Mexico, Panama, and Venezuela. These countries were selected because they comprise a large proportion of the population in Latin America and the Caribbean, and the eight nations also represent varying geographic areas, health standards, and income levels. They were also part of a related project to characterize the economic burden of disease in representative Latin American countries (8). The model estimated the expected health outcomes and costs associated with rotavirus gastroenteritis, and the events and costs that might be averted with vaccination of an annual birth cohort of children during the first five years of their life in each country (8). The principal inputs in the model included epidemiological information on disease incidence, health care costs associated with different types of cases, and the effectiveness and cost of vaccination.

The validity of the model was tested in several ways. The initial model was reviewed by a group of external experts convened by the Centers for Disease Control and Prevention and the Rotavirus Vaccine Program in Geneva, Switzerland, in February 2004. The predictive validity was assessed through a structured comparison to an independent alternative rotavirus cost-effectiveness model at a second meeting held in March 2006. Internal validity was also checked by testing the results obtained when extreme values were used in the model.

The primary perspective for this analysis was the health care system, which we analyzed in terms of direct medical costs associated with medical treatment in formal inpatient and outpatient settings. Direct medical costs included the costs of diagnostic tests, medication, supplies, facilities, and personnel needed for treatment, but excluded costs such as nonmedical costs to households, costs of informal medical treatment, or productivity losses to caregivers. The main health outcome measure was the disability-adjusted life year (DALY). Rotavirus vaccination was compared to current practice (no universal vaccination and current use of oral rehydration therapy). All estimates were based on the expected events and costs for the 2003 annual birth cohort until 5 years of age. Estimates were expressed in 2003 US$. All future costs and DALY estimates were discounted at a rate of 3%.

Rotavirus disease and economic burden

For each country, the disease burden was estimated as the expected number of rotavirus-associated events (hospitalizations, outpatient visits, and deaths) during the first five years of life for the 2003 birth cohort. The risk of rotavirus-related hospitalization, outpatient visit, and death are based on the cumulative risk of each event due to acute gastroenteritis by the age of 5 years, and the proportion of these events attributed to rotavirus. A detailed explanation of the methods used to estimate disease burden can be found in Rheingans et al. (8). Estimates of the number of events were based on the size of the birth cohort and the estimated age distribution of each event.

Disease burden was also estimated in terms of DALYs. This aggregate measure makes it possible to compare outcomes for other diseases and interventions by quantifying the years of life lost (YLLs) due to premature mortality, and the years lived with disability (YLDs) (13). The average country-specific life expectancies at birth and 1 year of age (14) were used to calculate YLLs. Only morbidity from disease severe enough to require medical care was considered to calculate YLDs.

Estimates for years lived with disability were calculated with default disability weights from the Global Burden of Disease Study (13), the World Health Organization (WHO) guidelines for cost-effectiveness studies (15), and an estimated duration of illness of six days (16). For rotavirus gastroenteritis, the DALYs were almost entirely based on the YLLs because disability from rotavirus infections is usually brief. A discount rate of 3% and age weighting were included to ensure comparability (15).

The economic burden of rotavirus gastroenteritis for each country was estimated by combining estimates of the number of each type of event with information on the costs associated with the event. Country-specific estimates of direct medical costs, nonmedical direct costs, and productivity losses were developed for hospital and outpatient rotavirus events. For a complete description of the methods used to calculate the economic burden, see Rheingans et al. (8).

Vaccination effectiveness and costs

Vaccine efficacy from clinical trials provides an upper-bound estimate of the potential effectiveness in real world situations. In order to estimate the effectiveness of vaccination, we also considered information on the expected coverage, timing of illness, and the effectiveness of vaccination against different outcomes. The temporal pattern of these parameters must be considered since vaccination can only affect events that would have occurred after the vaccine was received. A decision-analytic model was developed to combine information on disease burden, coverage, and effectiveness in a temporally explicit fashion.

The age distribution of disease was estimated for each of the key rotavirus outcomes (death, hospitalization, and outpatient visits) on the basis of published studies (4, 5, 7, 16–23). The estimated total number of events for the annual birth cohort was then divided 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.

Next, the model considered the expected immunization status of children in each age category. It was assumed that the timing of the two-dose rotavirus vaccine would correspond to the delivery of the first and second diphtheria, pertussis, and tetanus (DPT) doses at 2 and 4 months of age. In the baseline analysis, national coverage of rotavirus vaccination was based on DPT3 coverage at 1 year of age for the year 2003, which ranged from 65% in the Dominican Republic to 99% in Chile (24, 25). Because rotavirus vaccination would occur with DPT doses one and two, but standardized coverage data are available only for the third DPT dose, this approach may underestimate the proportion of children who would receive both rotavirus vaccine doses. In addition, it was assumed that all children would receive the vaccine at the recommended time.

Information on the efficacy of the *Rotarix* two-dose vaccine against clinical trial endpoints was converted to efficacy against epidemiologically relevant outcomes. Ruiz-Palacios and colleagues reported the efficacy for hospitalization from severe rotavirus gastroenteritis as 85% during the first year (11). Efficacy against rotavirus gastroenteritis resulting in outpatient visits was estimated as the reported mean of the efficacy against severe (85%) (11) and any (70%) (26) rotavirus gastroenteritis. Clinical trial data in Latin America have shown that vaccine efficacy increases with disease severity (26), and it was assumed that efficacy against mortality would be the same as efficacy against hospitalization. For the baseline analysis it was further assumed that one dose of the vaccine would have the same effectiveness as a full course during the inter-dosing period, as demonstrated in a clinical trial in Latin America (27).

The effectiveness of vaccination was estimated by following the 2003 birth cohort through the age periods identified above, to the age of 5 years. The predicted reduction in the number of hospitalizations, outpatient visits, and deaths during this period was estimated based on vaccine coverage and efficacy.

Calculations of cost-effectiveness also require estimates of vaccination costs. For this analysis, these costs included the cost of administration, the price of the vaccine, the number of doses given (based on coverage level), and expected losses from waste (assumed to be 10%). Administrative costs consist of the cost of health personnel and training, cold chain maintenance, storage space, and public education. No costs for adverse events were included, since the safety profile of the vaccine is no different from that of a placebo (11, 27). The analysis assumed that the rotavirus vaccine would be administered along with the current Expanded Program on Immunization (EPI) vaccines; therefore, incremental administrative costs would be low. Earlier studies estimated the cost of immunization for current EPI vaccines (28–31); however, there were no data on the incremental cost of adding a vaccine to the current EPI regimen. Based on the range of estimates in previous immunization cost studies and the assumption of low incremental costs, the model assumed an administration cost of US$ 1.00 per course. Given that the actual price was unknown, vaccine cost was assumed to be US$ 24 per course for the two-dose vaccine, and alternative values were used in the sensitivity analysis.

Cost-effectiveness analysis

The cost-effectiveness summary measure was the net cost per DALY averted (US$/DALY). All costs are reported in 2003 US$. From the health care system perspective, net costs are defined as the cost of vaccination (administration and vaccine itself) minus the averted medical costs. Averted DALYs were calculated as the difference between the health burden without vaccination and the health burden with vaccination. The incremental cost-effectiveness ratio (ICER) is the ratio of the net costs to the net health benefits (US$/DALY). This ratio rep-

resents the net investment required to avert one DALY; thus, a lower ICER implies greater cost-effectiveness. The net cost per death averted was also calculated.

Several standards can be used to determine whether an intervention is cost-effective in terms of US$/DALY. The appropriateness of the different approaches depends on the perspective of the decisionmaker. The results presented here for rotavirus vaccination are intended to estimate cost-effectiveness from the health care perspective. The *World Health Report 2002* suggests that "very cost-effective interventions" are those that "avert each additional DALY at a cost less than GDP [gross domestic product] per capita." In addition, the WHO considers interventions with a cost-effectiveness ratio (US$/DALY) between one and three times the per capita GDP as cost-effective (32).

In addition to the ICER, break-even price was calculated as a secondary outcome measure. The break-even price for each country was calculated as the price per course for which the cost of vaccination (procurement and delivery) equaled the expected cost savings to the health care system.

Sensitivity and uncertainty analyses

The model described above required country-specific data on the epidemiology of the disease, the costs associated with different outcomes, and vaccine effectiveness. Although some of these data were available, the quality and relevance were limited for others. These data limitations create uncertainties regarding the final estimates of costs and cost-effectiveness. Two approaches were used to address this uncertainty: sensitivity and uncertainty analyses.

A one-way sensitivity analysis was conducted to assess the impact of changes in individual parameters on the ICER for each country, and to assess the robustness of the analysis. The variables included in this analysis were incidence of hospitalization, outpatient visits, and death from rotavirus gastroenteritis; costs associated with different events; vaccine efficacy; and vaccine price.

An uncertainty analysis was conducted to evaluate the overall impact of these uncertainties on quantitative estimates, and to assess the need for additional data collection. A Monte Carlo model was developed based on the model of rotavirus disease burden and vaccination cost-effectiveness described above. In Monte Carlo analysis, individual point estimates of parameters are replaced with distributions of potential values (33). In a series of iterations, individual values are randomly selected from each of the distributions, and the results are calculated and stored. The process is repeated for a large number of iterations (10 000 in this case). The final product is a distribution of potential outcomes that describe the likely range of actual expected results.

For national disease burden variables, distributions were used to characterize the cumulative incidence of illness outcomes (hospitalization, outpatient visits, and death) in each country, and the proportion of each outcome due to rotavirus. The distributions specified a range around the value chosen for the analysis, and described the likelihood that the value chosen was representative of the true population value. Wider distributions were used for countries for which the estimates were extrapolated from foreign data. For cost variables, distributions were based on the cost estimates presented in Rheingans et al. (8). For estimates of vaccine effectiveness, distributions were used for efficacy (in protecting against rotavirus hospitalization, outpatient visits, and mortality), based on the reported confidence intervals from clinical trials (11, 26). Distributions were also included for the reduction in efficacy from using only one dose, and the reduction in efficacy during subsequent seasons. Table 1 summarizes the best estimates and distributions used in the analysis, including location parameters.

Uncertainty limits (5% and 95%) were estimated for key output parameters, including vaccine benefit (costs and DALYs averted) and the incremental cost-effectiveness ratio. Uncertainty analysis was also used to estimate the likelihood that vaccination would result in different levels of cost-effectiveness. In addition, a contribution-to-variance analysis was conducted to determine the contribution of the individual input parameters to the ICER.

RESULTS

Vaccination benefits

Table 2 shows the expected rotavirus-associated events (deaths, hospitalizations, and outpatient visits) and associated medical costs, without and with vaccination. According to our model, vaccination of the entire 2003 birth cohort would prevent 68% of rotavirus deaths and 69% of the health care costs associated with treatment for rotavirus (Table 2 and Table 3). For the eight countries studied here, vaccination would prevent 3 435 deaths for the 2003 annual birth cohort that is vaccinated. In addition, vaccination would prevent US$ 43.4 million in health care treatment costs and an additional US$ 16.8 million in societal costs (including nonmedical direct costs and productivity losses).

Cost-effectiveness analysis

Table 3 shows the results of the cost-effectiveness analysis, and summarizes the estimated treatment costs, deaths, and DALYs that would be averted with vaccination in each country. The cost of vaccination (administrative and procurement) is shown for an assumed vaccine price of US$ 24 per course. The break-even prices, below which vaccination would be cost-saving from the health care system perspective, range from US$ 1.47 per course in the Dominican Republic to US$ 10.33 in Chile. The incremental cost-effectiveness ratio was calculated as the net cost of vaccination (from the health care system perspective) divided by the DALY averted. At the baseline price of US$ 24 per course for

TABLE 1. Input variables and ranges for estimates of cost-effectiveness of rotavirus vaccination of the 2003 birth cohort in eight Latin American and Caribbean countries (all costs reported in 2003 US$)

Country-specific input variables (source)	Argentina	Brazil	Chile	Dominican Republic	Honduras	Mexico	Panama	Venezuela
2003 birth cohort (35)	726 000	3 471 000	286 000	203 000	206 000	2 285 000	70 000	582 000
5-year risk of hospitalization for gastroenteritis (2, 36–41)[a]	0.093	0.112	0.060	0.065	0.038	0.018	0.065	0.070
Upper and lower bounds[b]	0.08, 0.11	0.10, 0.13	0.05, 0.07	0.05, 0.08	0.03, 0.04	0.01, 0.02	0.05, 0.08	0.06, 0.08
Proportion of gastroenteritis hospitalizations due to rotavirus (2, 5, 6, 36, 42–50)[a]	0.34	0.31	0.47	0.37	0.37	0.40	0.37	0.33
Upper and lower bounds	0.29, 0.39	0.26, 0.36	0.40, 0.54	0.30, 0.44	0.30, 0.44	0.34, 0.46	0.30, 0.44	0.28, 0.38
5-year risk of an outpatient visit for gastroenteritis (2, 35, 38–40, 51, 52)[a]	1.38	1.08	0.69	1.08	1.07	1.06	1.13	1.15
Upper and lower bounds	1.17, 1.59	0.81, 1.35	0.59, 0.79	0.81, 1.35	0.91, 1.23	0.90, 1.22	0.96, 1.30	0.98, 1.32
Proportion of gastroenteritis outpatient visits due to rotavirus (2, 5, 6, 36, 42, 53–56)[a]	0.26	0.19	0.34	0.25	0.25	0.25	0.25	0.23
Upper and lower bounds	0.22, 0.30	0.16, 0.22	0.29, 0.39	0.20, 0.30	0.20, 0.30	0.20, 0.30	0.20, 0.30	0.20, 0.27
5-year risk of death for gastroenteritis (per 1 000 births) (35, 57–61)[a]	0.40	2.30	0.10	5.90	8.70	1.01	1.44	2.00
Upper and lower bounds	0.34, 0.46	1.96, 2.65	0.09, 0.12	5.02, 6.79	7.40, 10.01	0.86, 1.16	1.22, 1.66	1.70, 2.30
Proportion of gastroenteritis deaths due to rotavirus[c]	0.34	0.31	0.47	0.37	0.37	0.40	0.37	0.33
Upper and lower bounds	0.27, 0.41	0.25, 0.37	0.38, 0.56	0.30, 0.44	0.30, 0.44	0.32, 0.48	0.30, 0.44	0.26, 0.40
Vaccine coverage (%) (24, 25)	88	96	99	65	92	93	86	68
Average life expectancy (years) (14)	74.2	68.9	75.8	69.6	69.1	74.0	74.1	73.8

[a] The shape of the distribution was defined as triangular distribution since the true population value was more likely to be closer to the chosen value for the analysis than the minimum or maximum values defined by the range.
[b] The upper and lower bounds of the distributions were the ones used in the sensitivity and uncertainty analyses.
[c] The proportion of gastroenteritis mortality attributable to rotavirus was based on the proportion of hospitalizations attributable to it. The shape of the distribution was defined as uniform since the true population value was equally likely to be any value within the specified range.

TABLE 2. Estimated health burden associated with rotavirus in eight Latin American and Caribbean countries with and without rotavirus vaccination of the 2003 birth cohort

	Argentina	Brazil	Chile	Dominican Republic	Honduras	Mexico	Panama	Venezuela
2003 birth cohort (35)	726 000	3 471 000	286 000	203 000	206 000	2 285 000	70 000	582 000
Without vaccination								
Deaths	99	2 475	13	443	663	923	37	384
Hospitalizations	22 956	120 513	8 008	4 882	2 896	16 086	1 684	13 502
Outpatient visits	260 489	712 249	66 924	54 810	55 105	605 525	19 775	153 648
With vaccination								
Deaths	33	671	3	224	200	273	13	186
Hospitalizations	7 044	29 386	1 763	2 383	798	4 328	543	6 270
Outpatient visits	92 310	210 598	18 315	28 672	17 911	193 258	7 298	76 994
Averted with vaccination								
Deaths	66	1 804	10	219	463	651	24	198
Hospitalizations	15 912	91 127	6 245	2 500	2 099	11 758	1 140	7 232
Outpatient visits	168 179	501 651	48 609	26 138	37 194	412 267	12 477	76 654

TABLE 3. Estimated burden of rotavirus and the cost-effectiveness of rotavirus vaccination of the 2003 birth cohort in eight Latin American and Caribbean countries (costs reported in 2003 US$)

	Argentina	Brazil	Chile	Dominican Republic	Honduras	Mexico	Panama	Venezuela
Total medical costs								
Without vaccine	7 061 108	25 332 499	4 641 283	696 601	1 511 679	17 242 669	862 387	5 154 096
With vaccine	2 329 495	6 576 304	1 152 529	352 416	474 980	5 361 075	303 986	2 523 021
Medical costs averted	4 731 614	18 756 195	3 488 755	344 185	1 036 699	11 881 594	558 401	2 631 074
Percent reduction	67%	74%	75%	49%	69%	69%	65%	51%
Vaccination cost [a]	17 505 312	91 301 184	7 758 036	3 615 430	5 192 848	58 101 152	1 649 480	10 843 824
Medical break-even price (US$)[b]	5.84	4.22	10.33	1.47	4.09	4.18	7.56	5.16
Societal break-even price (US$)[b]	6.86	5.83	12.15	2.59	4.88	7.30	10.36	6.36
DALYs[c]								
Without vaccine	3 549	83 365	543	14 823	22 120	31 768	1 277	13 098
With vaccine	1 192	22 686	142	7 510	6 672	9 438	445	6 345
DALYs averted	2 357	60 679	401	7 313	15 448	22 330	832	6 753
Percent reduction	66%	73%	74%	49%	70%	70%	65%	52%
Number of deaths								
Without vaccine	99	2 475	13	443	663	923	37	384
With vaccine	33	671	3	224	200	273	13	186
Number of deaths averted	66	1 804	10	219	463	651	24	198
Percent reduction	67%	73%	75%	49%	70%	70%	65%	52%
ICER (US$/DALY)[d]	5 419	1 196	10 656	447	269	2 070	1 311	1 216
Uncertainty range	4 554 to 7 177	1 003 to 1 576	8 324 to 14 348	375 to 589	225 to 359	1 739 to 2 751	1 080 to 1 773	1 018 to 1 622
ICER (US$/death averted)	193 609	40 212	422 497	14 956	8 972	71 052	44 798	41 408
Uncertainty range	161 099 to 259 118	33 574 to 53 707	324 308 to 585 404	12 521 to 19 764	7 476 to 11 885	59 315 to 94 728	36 665 to 61 296	34 443 to 55 286

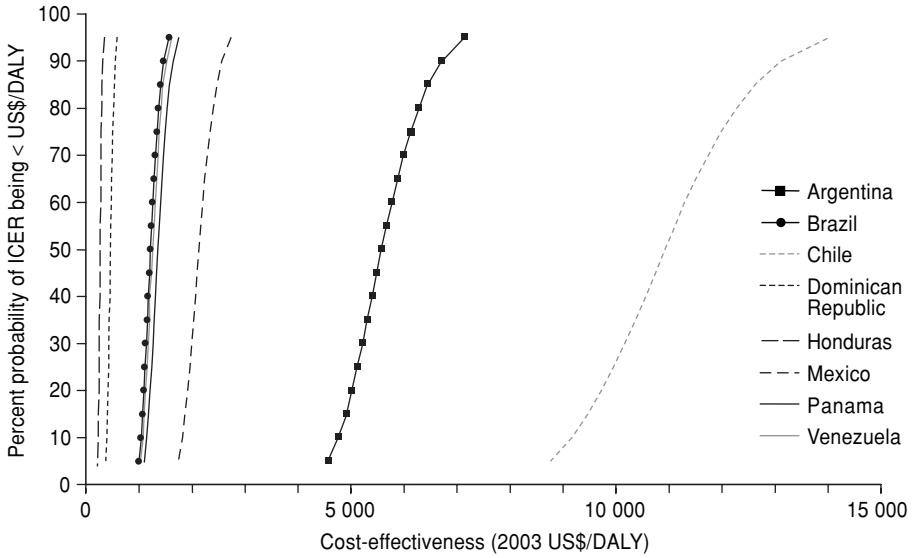
[a] Vaccination cost includes the cost of the vaccine (US$ 24/course) and cost of administering the vaccine.
[b] Medical and societal vaccine break-even prices per course are the prices at which the cost of vaccination would exactly offset the costs of treatment from the health care system or societal perspective. At vaccine prices below the break-even threshold, vaccination would be cost-saving.
[c] DALYs = disability-adjusted life years.
[d] ICER = incremental cost-effectiveness ratio, calculated as the difference in cost with and without the vaccine (vaccination cost minus averted medical costs) divided by the difference in health outcomes (DALYs or deaths) without and with the vaccine.

the two-dose regimen, the ICER ranged from US$ 269/DALY in Honduras to US$ 10 656/DALY in Chile. Cost-effectiveness was also expressed as cost per death averted, which ranged from US$ 8 972 per death averted in Honduras to US$ 422 497 per death averted in Chile.

Sensitivity and uncertainty analyses

Upper and lower uncertainty limits generated by the Monte Carlo analysis are shown in Table 3. These bounds provide an overall measure of the likely incremental cost-effectiveness, given uncertainty in the many input parameters. An alternative way to view these results is using "cost-acceptability" curves. The results in Figure 1 are based on the cumulative distribution of the estimated ICERs from the Monte Carlo analysis. For each country, Figure 1 shows the likelihood (vertical axis) that vaccination would have an ICER less than a specific US$/DALY level (horizontal axis). To estimate the likelihood that vaccination would meet the standard for "very cost-effective" (ICER < per capita GDP) in a given country, a vertical line should be extrapolated from the horizontal axis at the country's per capita GDP to the curve for that country. The value on the vertical axis at this point would be the likelihood that the intervention meets this standard. For Mexico, for example, the vertical line would drawn at US$ 6 121, the per capita GDP for Mexico. Since the entire curve for Mexico is to the left of that vertical line, the likelihood that vaccination will be very cost-effective for Mexico (ICER < US$ 6 121/DALY) is more than 95%. For six of the eight countries, the likelihood that vaccination would be considered very cost-effective was greater than 95%. In the two remaining countries, vaccination had a greater than 90% chance of being

FIGURE 1. Estimated cost-acceptability curves for rotavirus vaccination of the 2003 birth cohort in eight Latin American and Caribbean countries, at US$ 24 per course[a]



[a] The vertical axis plots the likelihood that vaccination would have an incremental cost-effectiveness ratio (ICER) less than the specific US$/DALY (disability-adjusted life year) plotted on the horizontal axis.

considered cost-effective based on the standard of ICER < three times the per capita GDP.

The results of one-way sensitivity analyses are presented in Table 4, and show the effect of changes in individual input parameters on the ICER for vaccination at the baseline price of US$ 24 per course. In most countries, the ICER estimates were most sensitive to changes in assumptions regarding rotavirus mortality and vaccine efficacy against mortality. For example, a 20% change in rotavirus mortality rate resulted in a 15% to 25% change in the ICER for all eight countries. The ICER was also significantly affected by the vaccine price used in the analysis. At a price of US$ 16 per course, the ICER ranged from US$ 161/DALY to US$ 4 437/DALY.

The contribution-to-variance analysis revealed the proportion of variance in the estimated ICER at US$ 24/course that was attributable to each of the input variables. In all countries, the primary sources of uncertainty in ICER estimates were overall diarrheal mortality, accounting for 15% to 22%; the proportion of diarrheal mortality attributable to rotavirus, accounting for 19% to 39%; and vaccine efficacy against mortality, accounting for 20% to 36%. Uncertainty in the direct costs of rotavirus hospitalization and outpatient visits accounted for 1% or less of the variance in all countries except Chile, where the costs of hospitalization and outpatient visits accounted for 17% and 2% of the uncertainty in the estimated ICER, respectively.

DISCUSSION

Benefits of vaccination

The results demonstrate that the incorporation of a rotavirus vaccine into routine vaccination schedules could effectively reduce the health and economic burden associated with rotavirus gastroenteritis in the eight countries analyzed here. In terms of effectiveness, it is estimated that introduction of a vaccination program would reduce mortality and the medical costs associated with treating illness by 67% to 72%. These benefits would be greatest in countries with the highest disease burden and the highest vaccine coverage rates. Although vaccine efficacy against mortality was assumed to be the same as for hospitalized cases (85%), the true efficacy (and, as a result, effectiveness) against mortality is unknown. Because the estimates suggest that vaccine efficacy would increase with increasing severity of illness (11), the assumption of equal vaccine efficacy against mortality appeared justified, and was explored further in the sensitivity analysis.

Economic evaluation of vaccination

From the health care system perspective, health interventions that result in negative net costs are excellent investments since they result in both improved health and cost savings. In practice, very few interventions meet this standard of cost savings (see Table 5). The analysis presented here suggests that although rotavirus vaccination would not be cost-saving in the countries studied, it would be very cost-effective, or at least cost-effective.

The cost-effectiveness analysis compared the net health care costs to the improvement in health, expressed as

TABLE 4. Effect of key variables on the estimated incremental cost-effectiveness ratio of rotavirus vaccination (assuming a cost of US$ 24/course) of the 2003 birth cohort in eight Latin American and Caribbean countries (all costs reported in 2003 US$)

Variable	Argentina	Brazil	Chile	Dominican Republic	Honduras	Mexico	Panama	Venezuela
Incidence of hospitalization for rotavirus								
–20%	5 636	1 240	11 526	452	272	2 089	1 362	1 243
Base case	5 419	1 196	10 656	447	269	2 070	1 311	1 216
+20%	5 202	1 151	9 786	442	266	2 051	1 260	1 190
Incidence of outpatient visits for rotavirus								
–20%	5 607	1 213	11 541	452	279	2 157	1 394	1 268
Base case	5 419	1 196	10 656	447	269	2 070	1 311	1 216
+20%	5 231	1 178	9 773	443	259	1 982	1 228	1 165
Rotavirus mortality rate								
–20%	6 677	1 490	12 843	559	336	2 574	1 632	1 516
Base case	5 419	1 196	10 656	447	269	2 070	1 311	1 216
+20%	4 560	998	9 106	373	224	1 731	1 095	1 016
Efficacy against rotavirus mortality								
70%	6 499	1 448	12 541	543	327	2 503	1 587	1 473
Base (85%)	5 419	1 196	10 656	447	269	2 070	1 311	1 216
94%	4 927	1 082	9 775	405	243	1 875	1 187	1 101
Efficacy against rotavirus hospitalization								
70%	5 612	1 235	11 434	452	272	2 087	1 356	1 240
Base (85%)	5 419	1 196	10 656	447	269	2 070	1 311	1 216
94%	5 303	1 172	10 190	445	267	2 060	1 284	1 202
Direct medical costs, hospitalization								
–20%	5 635	1 240	11 525	452	272	2 089	1 362	1 243
Base case	5 419	1 196	10 656	447	269	2 070	1 311	1 216
+20%	5 202	1 151	9 787	442	266	2 051	1 260	1 190
Direct medical costs, outpatient visits								
–20%	5 604	1 213	11 529	452	279	2 157	1 394	1 268
Base case	5 419	1 196	10 656	447	269	2 070	1 311	1 216
+20%	5 234	1 178	9 784	443	259	1 983	1 228	1 165
Vaccine price								
US$ 16/course	3 034	712	4 437	289	161	1 234	674	700
Base	5 419	1 196	10 656	447	269	2 070	1 311	1 216
US$ 32/course	7 804	1 679	16 875	606	377	2 906	1 947	1 732

the ICER. The interpretation of whether an intervention is cost-effective depends on the ICER and the standard to which it is compared. The standard should reflect how much a decisionmaker is willing to invest to avert one DALY or to prevent one death. Several standards have been suggested to determine whether an intervention is cost-effective. Using the *World Health Report 2002* standard of cost-effectiveness (ICER < three times the per capita GDP) or very cost-effective interventions (ICER < per capita GDP), rotavirus vaccination at a vaccine price of US$ 24/course would be very cost-effective in six of the countries, and cost-effective in the two other countries analyzed here.

Alternatively, national decisionmakers could compare the cost-effectiveness of rotavirus vaccination in their country to the cost-effectiveness of other health interventions being considered, including other strategies for diarrheal prevention, child nutrition, and immunization. Ideally, the most cost-effective intervention would be chosen first. Unfortunately, country-specific information is often unavailable and incomplete. The WHO-CHOICE project provides cost-effectiveness estimates of diarrheal prevention interventions by region (34). For developing countries in the Region of the Americas, the cost-effectiveness ratio for point-of-use water treatment and expansion of oral rehydration therapy are approximately US$ 1 000/DALY (34). Although this estimate may not be applicable for higher-income countries, the cost-effectiveness of rotavirus vaccination is comparable to this standard for most of the countries analyzed here. For purposes of comparison, additional cost-effectiveness ratios for other health interventions are shown in Table 5. However, caution should be used when comparing across studies, since there may be differences in the currency base year and in analytical assumptions. Ide-

TABLE 5. Comparison of the cost-effectiveness of various health interventions

Intervention	Location	Cost-effectiveness ratio (US$/DALY)[a]	Source
Diarrheal disease			
Rotavirus vaccination (US$ 24/course)	8 Latin American countries	269 to 10 656	Current study
Rotavirus vaccination (US$ 16/course)	8 Latin American countries	161 to 4 437	Current study
Oral rehydration therapy expansion to 50%	Latin America (low mortality)[b]	1 085	(34)
Point of use water treatment	Latin America (low mortality)[b]	1 092	(34)
Water supply and sanitation	Global	13 00	(62)
Hygiene education	Global	9 to 150	(62)
Breast-feeding promotion	Brazil, Honduras, Mexico	12 to 19	(63)
Child health			
Zinc supplementation (children < 5 yr)	Latin America (low mortality)[b]	102	(34)
Vitamin A supplementation	Latin America (low mortality)[b]	521	(34)
Integrated management of childhood illness	Global	40 to 140	(62)

[a] Costs have been converted to 2003 US$ for comparison; DALY = disability-adjusted life year.
[b] Countries are classified by the World Health Organization according to region and mortality stratum. All eight countries selected for this study are classified as having low child and low adult mortality. Within Latin America, the following countries are classified as having high child and high adult mortality: Bolivia, Ecuador, Guatemala, Haiti, Nicaragua, and Peru (64).

ally, vaccination should be compared to country-specific analyses of the cost-effectiveness of alternative health investments being considered in that country, assuming that the studies use similar methods.

Although a given intervention may be considered highly cost-effective, it may not be affordable because of national financial constraints. In this situation, the WHO *World Health Report 2002* suggests that external resources should be made available for the investment (32). The results presented here demonstrate that vaccination would prevent substantial costs associated with rotavirus gastroenteritis. These averted treatment costs could partially offset the costs of vaccination.

Sensitivity and uncertainty analyses

In addition to providing an overall assessment of confidence in our estimates of economic burden and cost-effectiveness, the uncertainty analysis provides a method for identifying variables that were likely to significantly affect our final estimates of burden and cost-effectiveness. These variables should be targeted in future efforts to collect more precise country-specific estimates. Although improved estimates of rotavirus-associated mortality and vaccine efficacy against mortality would allow for more accurate estimates of vaccination cost-effectiveness, improved estimates of these parameters may be difficult to obtain. In spite of these data limitations, the uncertainty analysis showed that our estimates of cost-effectiveness were robust, and provided information that is potentially useful for decision-making.

Limitations of the study

The primary limitations of this study relate to the incompleteness of some epidemiological and vaccine effectiveness parameters identified in the uncertainty analysis, and the need to rely on secondary data. Although uncertainties in these parameters affect the estimated cost-effectiveness of vaccination, the magnitude of this impact was systematically assessed in the uncertainty and sensitivity analyses. The uncertainty analysis included those parameters that were expected to significantly influence cost-effectiveness; however, some factors were not considered. In particular, this analysis did not explicitly consider two factors that may impact the results of the study. First, delays in the timing of routine vaccinations might preclude the prevention of rotavirus-associated events occurring very early in childhood. Second, it is not known whether those children who are at the greatest risk of dying from rotavirus infection have the same vaccination coverage as the general population.

A final study limitation is that this analysis considered the direct effects of vaccination but did not consider the potential indirect protective effect of herd immunity for persons unprotected by the vaccine. Three groups of people could benefit if vaccination provided herd immunity: children prior to receiving the first dose of the vaccine, children who are not vaccinated, and children who are vaccinated but in whom immunization is unsuccessful. Unfortunately, there are no data on the magnitude of the herd immunity that might be conferred by partial penetration of vaccination in a population, although partial vaccination is a plausible scenario since children might be exposed to the vaccine strain shed by vaccinated children, and thus might be less exposed to the wild-type rotavirus. By analogy to other vaccine-preventable infectious diseases, the effect of herd immunity might be substantial, and might offset gaps in the delivery of full-course on-time vaccination. Therefore, herd immunity might contribute to the cost-effectiveness of rotavirus vaccination.

In conclusion, given the limits to financial resources available from national governments and donors, vaccination is potentially a cost-effective option for improving child health and

reducing mortality in the Latin American and Caribbean countries analyzed here. The results of this study suggest that immunization of the entire annual birth cohort with an effective rotavirus vaccine could greatly reduce the disease burden and costs associated with rotavirus gastroenteritis. In addition, vaccination is a potentially cost-effective investment compared to other options to control childhood gastroenteritis across a range of vaccine prices.

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RESUMEN

Efectividad potencial en función del costo de la vacunación contra la gastroenteritis por rotavirus en ocho países de América Latina y el Caribe

Objetivos. Estimar los costos, los beneficios y la efectividad en función del costo de la vacunación contra la gastroenteritis por rotavirus en ocho países de América Latina y el Caribe: Argentina, Brasil, Chile, Honduras, México, Panamá, República Dominicana y Venezuela.

Métodos. Se elaboró un modelo económico para estimar la efectividad en función del costo de la vacunación, desde la perspectiva del sistema de salud, a partir de las constancias epidemiológicas nacionales oficiales y publicadas, los estimados de costos específicos de cada país y los datos de eficacia de la vacuna. El modelo se aplicó a los primeros cinco años de vida de la cohorte de nacidos en 2003 en cada uno de esos países. La principal medida de salud fueron los años de vida ajustados por discapacidad (AVAD) y la principal medida sintética fue el costo incremental por AVAD evitado. Se empleó una tasa de descuento de 3% para el pronóstico de los costos y beneficios. El impacto de la incertidumbre relacionada con las variables clave sobre la efectividad en función del costo se realizó mediante el análisis de sensibilidad.

Resultados. Según los estimados obtenidos mediante el modelo económico, la vacunación podría evitar más de 65% de las consultas médicas, de las muertes y del costo de tratamiento asociados con la gastroenteritis por rotavirus en los ocho países analizados. Con un costo total de US$ 24,00 (por las dos dosis de la vacuna), la razón incremental de la efectividad en función del costo varió entre US$ 269/AVAD en Honduras y US$ 10 656/AVAD en Chile. Las razones de la efectividad en función del costo fueron sensibles a las diversas hipótesis sobre el precio de la vacuna, la mortalidad y la eficacia de la vacuna.

Conclusiones. La vacunación permitiría reducir eficazmente la carga de morbilidad y los costos de la atención sanitaria de la gastroenteritis por rotavirus en los países analizados de América Latina y el Caribe. Desde la perspectiva de los sistemas de salud, se prevé que la vacunación universal de todos los niños será efectiva en función del costo, según los estándares vigentes en la actualidad.

Palabras clave Rotavirus, vacunas contra rotavirus, análisis costo-beneficio, modelos económicos, América Latina, Región del Caribe.