Appalachian
STATE UNIVERSITY®
BOONE, NORTH CAROLINA

# Economic Costs of Rotavirus Gastroenteritis and Cost-Effectiveness of Vaccination in Developing Countries

By: Richard D. Rheingans, Lynn Antil, Robert Dreibelbis, Laura Jean Podewils, Joseph S. Bresee,and Umesh D. Parashar

## Abstract

**Background**. Rotavirus is the leading cause of severe gastroenteritis in children worldwide. We evaluated the economic burden of rotavirus and the cost-effectiveness of vaccination from the health care perspective.

**Methods**. Estimates were based on existing epidemiological data, cost estimates, vaccine coverage, and efficacy data, as well as hypothetical vaccine prices. Outcome measures included health care and societal costs of rotavirus and benefits and incremental cost-effectiveness ratio of vaccination. Sensitivity analyses evaluated the impact of estimate uncertainty.

**Results.** Treatment costs increased with income level, and health burden decreased; however, burden varied across regions. On the basis of current vaccination coverage and timing, rotavirus vaccination would annually prevent 228,000 deaths, 13.7 million hospital visits, and 8.7 million disability-adjusted life-years, saving $188 million in treatment costs and $243 million in societal costs. At $5 per dose, the incremental cost-effectiveness ratio in low-, lower-middle–, and upper-middle–income countries was $88, $291, and $329 per disability-adjusted life-year averted, respectively, and $3,015, $9,951 and $11,296 per life saved, respectively. Vaccination would prevent 45% of deaths and     58% of associated medical visits and costs.

**Conclusions**. Vaccination is a cost-effective strategy to reduce the health and economic burden of rotavirus. The cost-effectiveness of vaccination depends mostly on vaccine price and reaching children at highest risk ofmortality

Rotavirus is the most common cause of severe gastro-enteritis in young children worldwide and is estimated to cause >500,000 deaths, >2 million hospitalizations, and >25 million clinic visits each year among children <5 years of age [1]. In addition to the pain and suffering in children, these rotavirus-associated events result in increased medical expenses, lost productivity, and other costs to society and families. Two effective rotavirus vaccines have recently become available and could significantly reduce this burden [2, 3].

Decisions to adopt vaccination programs depend on multiple factors, including the health burden, vaccine effectiveness, and cost-effectiveness of a vaccination program. Although economic analyses have played a central role in the consideration of new childhood vaccines for industrialized countries, decisions to introduce new vaccines in developing countries have traditionally been driven by data on disease burden. However, with

**Table 1. Input Variables and Ranges: General Parameters**

| Parameter | Baseline estimate (range) | Distribution for uncertainty analysis | Reference(s) |
|---|---|---|---|
| Health | | | |
| 5-year risk of hospitalization for rotavirus infection | | | |
|   Low income | 0.016 (0.012–0.02) | Triangular | [8] |
|   Lower-middle income | 0.020 (0.015–0.025) | Triangular | [8] |
|   Upper-middle income | 0.029 (0.022–0.036) | Triangular | [9–14] |
| 5-year risk of an outpatient visit for rotavirus infection | | | |
|   Low income | 0.202 (0.152–0.252) | Triangular | [8] |
|   Lower-middle income | 0.202 (0.152–0.252) | Triangular | [8] |
|   Upper-middle income | 0.233 (0.175–0.291) | Triangular | [8] |
| Hospital length of stay, days | 4.0 (3–5) | Triangular | [9, 11, 14, 15–32] |
| Vaccine efficacy | | | |
| Severe rotavirus GE resulting in hospitalization or death | 0.85 (0.70–0.94) | Log normal | [33] |
| Moderate rotavirus GE resulting in outpatient visit | 0.78 (0.58–0.89) | Log normal | [34, 33] |
| Effectiveness reduction with 1 dose | 0.5 (0.25–0.75) | Uniform | Authors' assumption |
| Effectiveness reduction in subsequent seasons for mild cases | 0.04 (0–0.25) | Uniform | [35] |

**NOTE.** Ranges for triangular and uniform distributions are minimum and maximum values, and ranges for log-normal distributions are 2.5th and 97.5th percentiles. GE, gastroenteritis.

the increased availability of international resources to improve childhood vaccination in developing countries, cost-effectiveness analyses are increasingly used by policy-makers to allocate resources among many competing priority interventions. Economic evaluations of vaccines can assess whether they are cost saving (averted costs are greater than the intervention) and their cost-effectiveness (comparing net costs with the health gains).

In the present study, we examined the economic burden of rotavirus and the cost-effectiveness of vaccination in low- and middle-income countries, which account for the vast majority of the global burden of severe rotavirus gastroenteritis [1]. The current analysis assessed the costs and effects of a rotavirus vaccine, compared with current diarrheal control measures without vaccination.

## METHODS

*Model overview.* We analyzed the economic burden of rotavirus and the cost-effectiveness of routine rotavirus vaccination of infants in low- and middle-income countries. Countries were placed into the regional groups used by the World Health Organization (WHO; African, American, eastern Mediterranean, European, Southeast Asian, and western Pacific regions) [4], and each regional group was further divided into 3 income strata (low, lower middle, and upper middle) [5]. The regional income group was the unit of analysis, and a total of 17 regional income groups were assessed. Countries included in this analysis account for ∼99% of the global rotavirus mortality burden [1] and >90% of the global 2004 birth cohort [6].

A Microsoft Excel–based model was developed to estimate

the health care and social costs of rotavirus gastroenteritis and the cost-effectiveness of vaccination, which has been described in detail elsewhere [7]. The model estimates health outcomes (hospitalizations, outpatient visits, and deaths) of rotavirus disease and their associated costs for an annual birth cohort [6] followed up for a 5-year period. It also estimates the disease burden and health care costs averted as the result of vaccination. The principal model inputs include epidemiological information on disease incidence, health care treatment costs, and the effectiveness and cost of vaccination (Tables 1 and 2).

The primary analysis was conducted from a health care system perspective focusing on direct medical costs from hospitalization and outpatient visits. These include the cost of diagnostic tests, medication, supplies, facilities, and personnel. Secondary analyses of economic burden were conducted from a societal perspective and included transportation costs and productivity losses of caregivers. No economic costs were included for cases resulting in death or for patients not seeking formal medical attention. The health burden of rotavirus was also estimated in terms of disability-adjusted life-years (DALYs), which quantify the years lost because of premature mortality and the years lived with disability [38]. Loss of potential productivity because of mortality was not included in the model. The model also estimated the incremental cost-effectiveness ratio (US$ per DALY averted and US$ per death averted) of rotavirus vaccination. Estimates are expressed in 2007 US dollars, and all future costs and DALY estimates are discounted at a rate of 3%.

*Rotavirus-associated hospitalizations, outpatient visits, and mortality.* For low-, lower-middle–, and upper-middle–in-

**Table 2. Input Variables and Ranges: Region-Specific Parameters**

| Region, income group | Rotavirus-associated mortality rate, deaths per 1000 children <5 years of age | Hospital visit treatment cost, US$ | Outpatient visit treatment cost, US$ | Vaccine administration cost, US$ |
|---|---|---|---|---|
| African | | | | |
| Low | 2.17 | 43.84 | 4.10 | 0.48 |
| Lower-middle | 0.16 | 47.48 | 4.45 | 0.47 |
| Upper-middle | 0.27 | 71.18 | 6.75 | 0.94 |
| Americas | | | | |
| Low | 0.93 | 57.12 | 4.92 | 0.58 |
| Lower-middle | 0.27 | 113.23 | 10.79 | 0.67 |
| Upper-middle | 0.22 | 201.67 | 20.44 | 1.33 |
| Eastern Mediterranean | | | | |
| Low | 1.38 | 67.59 | 7.20 | 0.76 |
| Lower-middle | 0.38 | 88.43 | 8.99 | 0.73 |
| Upper-middle | 0.13 | 237.68 | 24.09 | 1.46 |
| Europe | | | | |
| Low | 0.73 | 71.52 | 6.35 | 1.30 |
| Lower-middle | 0.25 | 102.82 | 9.68 | 1.23 |
| Upper-middle | 0.001 | 174.55 | 19.52 | 2.46 |
| Southeast Asia | | | | |
| Low | 0.95 | 30.47 | 2.31 | 0.37 |
| Lower-middle | 0.26 | 58.27 | 5.02 | 0.25 |
| Western Pacific | | | | |
| Low | 0.69 | 55.82 | 4.56 | 0.27 |
| Lower-middle | 0.32 | 78.44 | 6.70 | 0.38 |
| Upper-middle | 0.06 | 103.78 | 9.12 | 0.77 |

**NOTE.** For the uncertainty analysis, a triangular distribution with bounds of ±50% was used for cost parameters and of ±10% for mortality. Data are from [8, 36, 37].

come countries, we estimated rates of rotavirus-associated hospitalization and outpatient visits on the basis of the approach described by Parashar et al [39]. Rotavirus-attributable hospitalizations and outpatient visits were estimated by multiplying the number of diarrhea-related hospitalizations and outpatient visits by the estimated proportion of diarrhea events attributable to rotavirus [39]. Estimates of rates of hospitalization and outpatient visits in upper-middle–income countries were based on pooled results of studies conducted in 6 countries in this income stratum [9–14]. The rate of outpatient visits was estimated to be 8 times that of hospitalization [8]. Annual rates were converted to 5-year cumulative rates.

Estimates of rotavirus mortality rate for each region-income group were calculated on the basis of the population-weighted mean of country-specific rates estimated by the WHO [1]. Rotavirus-associated hospitalizations and deaths were distributed into the following age categories based on a literature review of the age distribution of rotavirus-associated hospitalizations: 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 [10, 11, 14, 40–65]. The distribution of outpatient visits was assumed to be the same.

The DALY burden from rotavirus mortality was calculated on the basis of the standardized life expectancy at 1 year of age. The DALYs from cases of rotavirus disease resulting in outpatient or hospital visits were calculated on the basis of default disability weights [66] and an estimated illness duration of 6 days [36]. To ensure comparability, DALY calculations included age weights and a discount rate of 3% [67].

***Economic costs associated with rotavirus.*** The direct medical cost includes the costs of a visit or hospital stay and diagnostic tests and medications. Inpatient and outpatient visit costs were estimated using standardized unit costs from the WHO Choosing Interventions that are Cost Effective (CHOICE) project, which estimates per diem hospitalization costs and outpatient visit costs by geographical region and mortality stratum [36]. The published function was used to estimate country-specific hospital per diem costs for the present study. The mean hospital and outpatient unit cost of each regional income group was calculated by determining a population-weighted mean of the country-specific cost estimates. The mean length of hospital stay was estimated to be 4 days [9, 11, 14, 15–32]. Diagnostic and medication costs were estimated as a proportion of the per diem and per visit costs from studies in

10 countries [68, 69]. Transportation cost and productivity losses to care providers were estimated in the same manner. Cost estimates were converted from 2000 international dollars to 2007 US dollars with use of the Consumer Price Index [70], purchasing power parity, and official exchange rates [71].

*Vaccination: effectiveness and costs.* The vaccine evaluated was a live attenuated monovalent human rotavirus vaccine administered orally with the first and second doses of diphtheria, tetanus, and pertussis vaccine (DTP) at ∼2 and ∼4 months of age, respectively [34]. To estimate vaccination effectiveness, the model combined information on vaccine coverage, vaccine efficacy, and the relative coverage of children at high risk of infection. Vaccine coverage was based on DTP coverage (doses 1 and 2) for each age category with use of 17 demographic and health surveys conducted in low- and lower-middle–income countries [72]. Demographic and health survey estimates were similar to WHO–United Nations Children's Fund (UNICEF) best estimates for DTP coverage [37]. For the European region, WHO-UNICEF estimates for DTP coverage were used because of limited availability of DHS data, and it was assumed that vaccination occurred at the recommended time. Because few DHS data were available for upper-middle–income countries, vaccine timing and coverage were assumed to be the same as those in lower-middle–income countries.

Several studies suggest that infants who die of diarrhea are less likely to have access to routine vaccinations [62, 73–75]. The model assumed that children who would die of diarrhea in the absence of rotavirus vaccination have a lower level of vaccination coverage. For the base case, vaccination coverage among children at high risk of infection was assumed to be 90% (range, 50%–100%) that among children at low risk of infection.

Vaccine efficacy against severe rotavirus disease resulting in hospitalization was 85%, based on data from Latin America [33]. This efficacy was also assumed for mortality. Efficacy against outpatient visits was estimated as the mean efficacy reported for severe (85%) [33] and any (70%) [34] rotavirus gastroenteritis. The efficacy of receiving 1 dose was assumed to be 50% of that of a full course.

The cost of vaccination includes administration costs, the price of each dose, and expected losses from waste. Administration costs for the low- and lower-middle–income countries were estimated using the WHO Global Immunization Vision and Strategy costing model [76]. Costs for the upper-middle–income countries were assumed to be twice those for the lower-middle–income group for each region. Because the current and future price of rotavirus vaccines is currently unknown, the analysis used a price range of $2–$15 per 2-dose course. A 10% vaccine wastage rate was assumed. The cost of adverse events associated with vaccination was not included, because the vaccine has a safety profile equivalent to that of placebo [34].

*Cost-effectiveness.* The primary measures of cost-effectiveness in this study are the incremental cost per DALY averted and incremental cost per death averted. The incremental cost is the difference in the costs with and without vaccination (costs of vaccination minus the averted costs from prevented cases). The incremental cost-effectiveness ratio (ICER) is defined as the incremental costs divided by the difference in the DALYs (or deaths) with and without vaccination. Cost-effectiveness was assessed from the health care system perspective for comparability with other published studies. The break-even price, which is the price per vaccine dose at which the costs averted because of vaccination exactly offset the costs of vaccination, was calculated from the health care system and societal perspective.

*Uncertainty and sensitivity analyses.* One-way sensitivity analyses were completed by varying the individual values for key model inputs among a high, low, and baseline estimate. Variables included hospitalization, outpatient, and mortality rates; vaccine efficacy; relative coverage; and vaccine coverage. The model assumed that rotavirus vaccine coverage would be the same as current coverage and timing for DTP doses 1 and 2. Scenario analyses were conducted to consider on-time coverage, with children vaccinated at the recommended 2 and 4 months of age, and theoretical coverage, assuming both an optimistic level of coverage based on WHO-UNICEF best estimates of coverage [37] and on-time vaccine delivery.

A probabilistic sensitivity analysis was conducted to develop a range of estimates of burden and cost-effectiveness and to identify specific variables that have substantial influence on outcomes and that may merit additional data collection. A Monte Carlo simulation model was developed using distributions for key input variables. Multiple iterations (10,000) generated output distributions and uncertainty limits (5% and 95%) for key variables [77]. Contribution to variance analysis was conducted to determine which input variables contributed the most to the uncertainty in the outputs. Variables used in the model can be found in tables 1–3.

## RESULTS

*Health and economic burden.* Annually, rotavirus accounts for 527,025 deaths and 147 DALYs per 1000 children in all countries included in this analysis (Table 3). Rotavirus-associated outpatient visits and hospitalizations result in direct medical treatment costs of $325 million ($202 million–$453 million) and total societal costs of $423 million ($262 million–$590 million) each year. In general, there is an inverse relationship between the health burden and economic burden of rotavirus, with health burden concentrated in low-income countries and the economic burden concentrated in upper-middle–income countries. There is also significant variation in

**Table 3.** Economic and Health Burden of Rotavirus Gastroenteritis by Region-Income Group (Cost per Annual Birth Cohort)

| Region, income level | No. of medical visits | Medical cost | | Societal cost | | No. of deaths | DALYs per 1000 children |
|---|---|---|---|---|---|---|---|
| | | 1000 US$ | US$ per child | 1000 US$ | US$ per child | | |
| Africa | | | | | | | |
| Low | 5,469,819 | 38,095 | 1.52 | 50,122 | 1.99 | 237,606 | 322 |
| Lower-middle | 408,373 | 3370 | 1.83 | 4386 | 2.38 | 1443 | 27 |
| Upper-middle | 30,636 | 426 | 3.64 | 548 | 4.68 | 141 | 41 |
| All | 5,908,828 | 41,891 | 1.55 | 55,056 | 2.03 | 239,190 | 300 |
| Americas | | | | | | | |
| Low | 91,635 | 794 | 1.89 | 1042 | 2.47 | 1736 | 140 |
| Lower-middle | 780,851 | 15,501 | 4.40 | 20,192 | 5.73 | 4682 | 45 |
| Upper-middle | 1,995,810 | 80,980 | 10.62 | 104,493 | 13.71 | 8197 | 37 |
| All | 2,868,296 | 97,275 | 8.41 | 125,727 | 10.87 | 14,615 | 43 |
| Eastern Mediterranean | | | | | | | |
| Low | 1,993,557 | 23,028 | 2.51 | 30,486 | 3.33 | 50,449 | 187 |
| Lower-middle | 1,275,197 | 20,420 | 3.55 | 26,683 | 4.64 | 10,111 | 60 |
| Upper-middle | 274,941 | 13,147 | 12.52 | 16,965 | 16.16 | 592 | 19 |
| All | 3,543,695 | 56,595 | 3.55 | 74,134 | 4.65 | 61,152 | 130 |
| Europe | | | | | | | |
| Low | 328,233 | 3624 | 2.40 | 4756 | 3.15 | 5392 | 122 |
| Lower-middle | 818,298 | 14,658 | 3.97 | 19,081 | 5.17 | 4555 | 42 |
| Upper-middle | 185,127 | 6802 | 9.62 | 8820 | 12.48 | 4 | 0 |
| All | 1,331,658 | 25,084 | 4.25 | 32,657 | 5.53 | 9951 | 57 |
| Southeast Asia[a] | | | | | | | |
| Low | 7,876,061 | 34,172 | 0.94 | 44,501 | 1.23 | 161,253 | 152 |
| Lower-middle | 311,986 | 3034 | 2.16 | 3933 | 2.79 | 1732 | 42 |
| All | 8,188,047 | 37,206 | 0.99 | 48,434 | 1.29 | 162,985 | 148 |
| Western Pacific | | | | | | | |
| Low | 558,083 | 4606 | 1.80 | 6021 | 2.35 | 8090 | 107 |
| Lower-middle | 4,596,693 | 59,937 | 2.89 | 77,653 | 3.74 | 30,890 | 51 |
| Upper-middle | 142,707 | 2802 | 5.14 | 3591 | 6.59 | 152 | 9 |
| All | 5,297,483 | 67,345 | 2.82 | 87,265 | 3.66 | 39,132 | 56 |
| All regions | | | | | | | |
| Low | 16,317,388 | 104,322 | 1.39 | 136,929 | 1.83 | 464,526 | 211 |
| Lower-middle | 8,191,397 | 116,920 | 3.16 | 151,929 | 4.11 | 53,413 | 49 |
| Upper-middle | 2,629,222 | 104,157 | 10.37 | 134,417 | 13.39 | 9086 | 31 |
| All | 27,138,006 | 325,400 | 2.67 | 423,275 | 3.47 | 527,025 | 147 |

**NOTE.** DALYs, disability-adjusted life-years.

[a] No upper-middle–income countries were identified in the Southeast Asian region.

the health and economic burden among countries in different geographic regions that fall into the same income category

*Vaccine effectiveness and cost-effectiveness.* With a national rotavirus vaccination program, an estimated 227,673 lives (209,000–266,000 lives) would be saved in low- and middle-income countries in each annual birth cohort (Table 4). In addition to improving health, vaccination would save $188 million ($121 million–$272 million) in treatment costs and $243 million ($157 million–$354 million) in total societal costs.

From the health care system perspective, vaccination would be cost-saving in lower-middle– and upper-middle–income regions for vaccine prices <$0.53 and <$2.00, respectively (break-even price). Vaccination would require a net financial investment at higher prices and at any price in the low-income region. At a vaccine price of $5 per dose, the ICER was $88 ($79–$126), $291 ($242–$402), and $329 ($173–$547) per DALY averted in the low-, lower-middle–, and upper-middle–income groups, respectively.

Table 5 shows the differences in benefits and cost-effectiveness of vaccination among regions and income groups. In low-income countries, vaccination would result in a smaller percentage reduction in rotavirus-associated deaths and medical

**Table 4.** Costs, Benefits, and Cost-Effectiveness of Rotavirus Vaccination by Income Group

| Variable | Income group | | | |
| --- | --- | --- | --- | --- |
| | Lower | Lower-middle | Upper-middle | All |
| Total medical cost | | | | |
|   Without vaccine | 104,322,143 | 116,920,464 | 104,157,303 | 325,399,910 |
|   With vaccine | 58,988,917 | 41,230,798 | 37,225,355 | 137,445,070 |
|   Averted | 45,333,226 | 75,689,666 | 66,931,948 | 187,954,840 |
|   Percent reduction | 0.43 | 0.65 | 0.64 | 0.58 |
| Total societal costs averted | 59,178,616 | 97,921,712 | 85,991,851 | 243,092,179 |
| Cost of vaccination | | | | |
|   $1/dose | 162,294,905 | 109,857,673 | 46,436,100 | 318,588,677 |
|   $2/dose | 275,851,447 | 182,831,561 | 66,912,285 | 525,595,293 |
|   $3/dose | 389,407,989 | 255,805,449 | 87,388,470 | 732,601,908 |
|   $5/dose | 616,521,073 | 401,753,224 | 128,340,841 | 1,146,615,138 |
|   $7.50/dose | 900,412,428 | 584,187,944 | 179,531,305 | 1,664,131,676 |
| Medical break-even price | −0.03 | 0.53 | 2.00 | 0.37 |
| Societal break-even price | 0.09 | 0.84 | 2.93 | 0.64 |
| DALYs | | | | |
|   Without vaccine | 15,827,898 | 1,827,512 | 311,876 | 17,967,286 |
|   With vaccine | 9,372,297 | 706,807 | 125,357 | 10,204,462 |
| DALYs averted | 6,455,601 | 1,120,705 | 186,519 | 7,762,825 |
| No. of deaths | | | | |
|   Without vaccine | 464,526 | 53,413 | 9086 | 527,025 |
|   With vaccine | 275,057 | 20,645 | 3650 | 299,352 |
|   Averted | 189,469 | 32,768 | 5436 | 227,673 |
| Cost-effectiveness, US$ per DALY | | | | |
|   $1/dose | 18 | 30 | Cost-saving | 17 |
|   $2/dose | 36 | 96 | Cost-saving | 43 |
|   $3/dose | 53 | 161 | 110 | 70 |
|   $5/dose | 88 | 291 | 329 | 123 |
|   $7.50/dose | 132 | 454 | 604 | 190 |
| Cost-effectiveness, US$/death | | | | |
|   $1/dose | 617 | 1043 | Cost-saving | 574 |
|   $2/dose | 1217 | 3270 | Cost-saving | 1483 |
|   $3/dose | 1816 | 5497 | 3763 | 2392 |
|   $5/dose | 3015 | 9951 | 11,296 | 4211 |
|   $7.50/dose | 4513 | 15,518 | 20,713 | 6484 |

**NOTE.** DALYs, disability-adjusted life-years.

visits, particularly in Africa and the eastern Mediterranean region (35%). The lower percentage reductions are attributable to lower coverage rates and greater delays in vaccination in these regions. Nevertheless, vaccination would be most cost-effective in these same low-income countries because of the higher overall rotavirus-associated mortality rates.

*Sensitivity and uncertainty.* Table 6 shows the results of the 1-way sensitivity analysis for individual variables and their contribution to variance in the probabilistic sensitivity analysis. Results are shown for ICER at $5 per dose for each income level. The contribution to variance shows the proportion of overall uncertainty in cost-effectiveness attributable to the individual variable in the probabilistic model.

In low- and lower-middle–income regions, 3 variables contribute the majority of uncertainty to the estimate of cost-effectiveness: vaccine efficacy against rotavirus-associated mortality, rotavirus-associated mortality rate, and relative vaccination coverage among children at the highest risk of rotavirus-associated mortality, compared with children at lower risk. In both income groups, vaccine efficacy contributes over one-half of the overall uncertainty. In the low-income region, economic variables have little effect on overall uncertainty. In lower-middle– and upper-middle–income regions, economic variables, including hospital and outpatient visit costs, contribute more to overall uncertainty regarding cost-effectiveness.

Table 7 shows the estimated impact and cost-effectiveness of

**Table 5.  Benefits and Cost-Effectiveness of Rotavirus Vaccination by Region and Income Group**

| Region, income group | No. (%) of medical visits averted | Medical costs averted 1000 US$ (2007) | Medical costs averted Percentage | Societal costs averted 1000 US$ (2007) | Societal costs averted Percentage | No. (%) of deaths averted | Cost-effectiveness by vaccine price (US$/dose), US$/DALY $1 | $2 | $5 | $7.50 |
|---|---|---|---|---|---|---|---|---|---|---|
| **Africa** | | | | | | | | | | |
| Low | 1,928,025 (35) | 13,944 | 37 | 18,264 | 36 | 83,950 (35) | 13 | 25 | 61 | 91 |
| Lower-middle | 274,149 (67) | 2353 | 70 | 3049 | 70 | 958 (66) | 95 | 211 | 561 | 852 |
| Upper-middle | 20,612 (67) | 299 | 70 | 383 | 70 | 94 (66) | 47 | 123 | 351 | 541 |
| All | 2,222,785 (38) | 16,597 | 40 | 21,696 | 39 | 85,001 (36) | 13 | 27 | 67 | 100 |
| **Americas** | | | | | | | | | | |
| Low | 49,095 (54) | 442 | 56 | 577 | 55 | 927 (53) | 24 | 48 | 122 | 184 |
| Lower-middle | 468,339 (60) | 9664 | 62 | 12,532 | 62 | 2774 (59) | 19 | 95 | 321 | 510 |
| Upper-middle | 1,199,654 (60) | 50,709 | 63 | 65,139 | 62 | 4857 (59) | ...[a] | ...[a] | 274 | 506 |
| All | 1,717,088 (60) | 60,816 | 63 | 78,248 | 62 | 8558 (59) | 22 | 44 | 109 | 163 |
| **Eastern Mediterranean** | | | | | | | | | | |
| Low | 702,697 (35) | 8404 | 36 | 11,077 | 36 | 17,824 (35) | 21 | 42 | 104 | 156 |
| Lower-middle | 856,065 (67) | 14,231 | 70 | 18,512 | 69 | 6712 (66) | 25 | 77 | 234 | 364 |
| Upper-middle | 184,975 (67) | 9217 | 70 | 11,839 | 70 | 393 (66) | ...[a] | ...[a] | 340 | 743 |
| All | 1,743,737 (49) | 31,851 | 56 | 41,428 | 56 | 24,929 (41) | 17 | 49 | 143 | 222 |
| **Europe** | | | | | | | | | | |
| Low | 221,525 (67) | 2538 | 70 | 3316 | 70 | 3611 (67) | 35 | 60 | 136 | 199 |
| Lower-middle | 550,786 (67) | 10,261 | 70 | 13,297 | 70 | 3037 (67) | 56 | 129 | 348 | 531 |
| Upper-middle | 129,686 (70) | 4955 | 73 | 6395 | 73 | 3 (69) | ...[a] | 6647 | 27,602 | 45,065 |
| All | 901,997 (68) | 17,754 | 71 | 23,008 | 70 | 6651 (67) | 44 | 98 | 259 | 393 |
| **Southeast Asian** | | | | | | | | | | |
| Low | 3,902,554 (50) | 17,631 | 52 | 22,857 | 51 | 79,184 (49) | 22 | 44 | 109 | 163 |
| Lower-middle | 186,269 (60) | 1888 | 62 | 2436 | 62 | 1024 (59) | 40 | 117 | 348 | 540 |
| All | 4,088,823 (50) | 19,519 | 52 | 25,292 | 52 | 80,208 (49) | 23 | 45 | 112 | 168 |
| **Western Pacific** | | | | | | | | | | |
| Low | 276,528 (50) | 2373 | 52 | 3087 | 51 | 3973 (49) | 20 | 51 | 142 | 219 |
| Lower-middle | 2,744,419 (60) | 37,293 | 62 | 48,097 | 62 | 18,262 (59) | 26 | 90 | 280 | 439 |
| Upper-middle | 85,388 (60) | 1752 | 63 | 2236 | 62 | 90 (59) | 7 | 339 | 1336 | 2167 |
| All | 3,106,334 (59) | 41,418 | 62 | 53,420 | 61 | 22,324 (57) | 25 | 84 | 260 | 407 |
| **All regions** | | | | | | | | | | |
| Low | 7,080,424 (43) | 45,333 | 43 | 59,179 | 43 | 189,469 (41) | 18 | 36 | 88 | 132 |
| Lower-middle | 5,080,027 (62) | 75,690 | 65 | 97,922 | 64 | 32,768 (61) | 30 | 96 | 291 | 454 |
| Upper-middle | 1,620,314 (62) | 66,932 | 64 | 85,992 | 64 | 5436 (60) | ...[a] | ...[a] | 329 | 604 |
| All | 13,780,765 (51) | 187,955 | 58 | 243,092 | 57 | 227,673 (43) | 17 | 43 | 123 | 190 |

[a] Vaccination is cost saving at this price.

**Table 6. Sensitivity and Uncertainty Analysis: Best and Worst Case Estimates of Cost-Effectiveness for Individual Variables (1-Way Sensitivity Analysis) and Overall Contribution to Variance (Probabilistic Analysis)**

| | Cost-effectiveness, US$/DALY at $5/dose | | | | | | | | |
| | Low income | | | Lower-middle income | | | Upper-middle income | | |
| Variable | Worst | Best | Contribution to variance, % | Worst | Best | Contribution to variance, % | Worst | Best | Contribution to variance, % |
|---|---|---|---|---|---|---|---|---|---|
| Vaccine efficacy against mortality | 122 | 82 | 65.9 | 386 | 261 | 55.7 | 449 | 305 | 12.4 |
| Relative immunization coverage of children at high risk of infection | 103 | 88 | 16.7 | 326 | 279 | 13.6 | 380 | 325 | 2.8 |
| Rotavirus-associated mortality rate | 100 | 87 | 12.3 | 317 | 276 | 9.6 | 369 | 322 | 1.7 |
| Vaccination program cost | 96 | 91 | 1.7 | 305 | 285 | 2.0 | 389 | 299 | 6.3 |
| Outpatient visit treatment cost | 95 | 91 | 1.0 | 310 | 280 | 5.6 | 420 | 268 | 19.4 |
| Hospital visit treatment cost | 95 | 91 | 1.2 | 313 | 277 | 8.4 | 448 | 240 | 37.3 |
| 1-dose efficacy | 94 | 92 | <1 | 298 | 292 | <1 | 351 | 337 | <1 |
| Vaccine efficacy for outpatient visits | 94 | 92 | <1 | 305 | 289 | 1.4 | 394 | 313 | 4.7 |
| Vaccine efficacy for hospital visits | 94 | 93 | <1 | 303 | 290 | <1 | 393 | 317 | 4.0 |
| Outpatient visit rate | 94 | 92 | <1 | 300 | 290 | <1 | 370 | 318 | 2.2 |
| Hospital visit rate | 94 | 93 | <1 | 301 | 289 | 1.0 | 380 | 309 | 4.7 |
| Length of hospital stay | 94 | 93 | <1 | 301 | 289 | 1.0 | 379 | 309 | 4.5 |

**NOTE.** Ranges and distribution of individual variables are shown in table 1.

vaccination for the 3 immunization scenarios examined: current timing, on-time, and theoretical (on-time and increased coverage). On-time immunization would increase the impact of vaccination on mortality, particularly in low-income regions. In the low-income countries in Africa, it would increase mortality reduction by one-third and reduce the cost-effectiveness ratio by 25%. The theoretical immunization scenario would result in further increases in mortality reduction but no changes in cost-effectiveness.

## DISCUSSION

Rotavirus gastroenteritis annually results in 27 million hospital and outpatient visits and 527,000 deaths among children <5 years of age in developing countries, at an estimated treatment cost of $325 million and total societal costs of $423 million. Assuming current vaccination coverage and timing, the integration of a rotavirus vaccine into national vaccination programs could prevent an estimated 227,000 deaths, 13.8 million medical visits, and 7.8 million DALYs, saving $188 million in treatment costs and $243 million in total costs. Vaccination would not be cost-saving at most of the prices considered in this analysis. However, the World Health Report (from 2002) suggests that interventions are very cost-effective if the ICER is less than the country's per capita gross domestic product and are cost-effective if the ICER is <3 times the per capita gross domestic product [78]. With use of these standards, rotavirus vaccination is very cost-effective in all income groups for a range of vaccine prices evaluated in the analysis.

The value of rotavirus vaccination as a health investment also depends on the other interventions available for improving child health and the availability of financial resources. On the basis of WHO-CHOICE, point-of-use water disinfection with education is the most cost-effective water and sanitation intervention in most regions, ranging from $161 per DALY in countries in Africa with high mortality to $1092 per DALY in countries in Latin America with low mortality. Introduction of expanded oral rehydration therapy coverage to 50% as a part of supplementation interventions had an ICER of <$25 per DALY in Africa and >$1200 per DALY in Latin America [79]. These comparisons suggest that rotavirus vaccination could be as cost-effective as other interventions for prevention or treatment of diarrhea, depending on vaccine price. However, differences in the nature of these interventions and the lack of empirical, directly compared cost-effectiveness trials limit the comparability of these results.

Three factors that greatly affected the estimated performance of a rotavirus vaccination program were the timing of vaccine delivery, the overall vaccine coverage, and the relative vaccine coverage among children who die of rotavirus, compared with all children. If a rotavirus vaccine was delivered on time at the age of 2 and 4 months and without the delays assumed in the model, an additional 46,000 rotavirus deaths (total of 274,000 deaths) could be averted. Improving vaccination coverage to the 90th percentile of coverage for each region and income level and optimizing timing of vaccine delivery could prevent an additional 125,978 deaths, compared with current vaccination practices. In low-income countries, vaccination would prevent 41% of rotavirus-related deaths with the current timing and coverage, compared with 67% with optimal levels.

The sensitivity analyses identified several factors that are

**Table 7. Rotavirus Vaccination Impact and Cost-Effectiveness (at US$5/dose) by Immunization Scenario and Region-Income Group**

| Region, income group | Current vaccination | | | On-time | | | Theoretical | | |
|---|---|---|---|---|---|---|---|---|---|
| | No. of deaths averted | Reduction, %[a] | US$/DALY | No. of deaths averted | Reduction, %[a] | US$/DALY | No. of deaths averted | Reduction, %[a] | US$/DALY |
| Africa | | | | | | | | | |
| Low | 83,950 | 35 | 61 | 112,856 | 47 | 47 | 158,269 | 67 | 47 |
| Lower-middle | 958 | 66 | 561 | 995 | 69 | 551 | 1019 | 71 | 551 |
| Upper-middle | 94 | 66 | 351 | 97 | 69 | 344 | 100 | 71 | 344 |
| Americas | | | | | | | | | |
| Low | 927 | 53 | 122 | 1111 | 64 | 107 | 1156 | 67 | 107 |
| Lower-middle | 2774 | 59 | 321 | 3169 | 68 | 279 | 3306 | 71 | 279 |
| Upper-middle | 4857 | 59 | 274 | 5548 | 68 | 216 | 5787 | 71 | 216 |
| Eastern Mediterranean | | | | | | | | | |
| Low | 17,824 | 35 | 104 | 23,962 | 47 | 80 | 33,604 | 67 | 80 |
| Lower-middle | 6712 | 66 | 234 | 6973 | 69 | 229 | 7139 | 71 | 229 |
| Upper-middle | 393 | 66 | 340 | 408 | 69 | 325 | 418 | 71 | 325 |
| Europe | | | | | | | | | |
| Low | 3611 | 67 | 136 | 3611 | 67 | 136 | 3695 | 69 | 136 |
| Lower-middle | 3037 | 67 | 348 | 3037 | 67 | 348 | 3216 | 71 | 348 |
| Upper-middle | 3 | 69 | 27,602 | 3 | 69 | 27,602 | 3 | 71 | 27,602 |
| Southeast Asia | | | | | | | | | |
| Low | 79,184 | 49 | 109 | 86,940 | 54 | 102 | 107,410 | 67 | 102 |
| Lower-middle | 1024 | 59 | 348 | 1091 | 63 | 329 | 1223 | 71 | 329 |
| Western Pacific | | | | | | | | | |
| Low | 3973 | 49 | 142 | 4362 | 54 | 133 | 5389 | 67 | 133 |
| Lower-middle | 18,262 | 59 | 280 | 19,452 | 63 | 264 | 21,809 | 71 | 264 |
| Upper-middle | 90 | 59 | 1336 | 96 | 63 | 1,247 | 107 | 71 | 1,247 |
| All regions | | | | | | | | | |
| Low | 189,469 | 41 | 88 | 232,841 | 50 | 75 | 309,524 | 67 | 75 |
| Lower-middle | 32,768 | 61 | 291 | 34,717 | 65 | 278 | 37,712 | 71 | 278 |
| Upper-middle | 5436 | 60 | 329 | 6152 | 68 | 274 | 6415 | 71 | 274 |

[a] Compared with baseline.

likely to influence the actual impact and cost-effectiveness of vaccination. In low-income regions, the effectiveness of vaccination will be affected by the efficacy of vaccination in those settings and the ability of vaccination to reach children at high risk of infection on time. Several studies have identified a relationship between immunization status and mortality, which suggests that infants who have been vaccinated are less likely to die than are infants who are not fully immunized [62, 73–75]. If those who die are less likely to have been vaccinated, the effectiveness (and cost-effectiveness) of vaccination will be reduced. Targeted efforts to increase the coverage of children at the greatest risk of mortality could improve the impact of vaccination programs.

Several limitations of this study should be considered in the interpretation of the findings. First, estimates of health burden and the impact of vaccination were based on a limited number of publications that may not be generalizable to all countries within income-region strata. Second, there are few empirical data on resource use and cost for rotavirus gastroenteritis, particularly in developing countries. For this reason, a standardized approach developed by the WHO for its WHO-CHOICE project was used. Additional information on treatment and societal costs may provide additional information on the economic benefits of vaccination and potential cost offsets. Third, vaccine price has a significant influence on the cost-effectiveness of vaccination, but precise information on current and future costs are not available. Additional analyses are needed to explore the effect of likely prices on vaccine introduction and cost-effectiveness. Finally, potential herd immunity of rotavirus vaccination was not factored into our analysis; however, any herd immunity effects of rotavirus vaccination would only improve the overall cost-effectiveness of vaccination.

In conclusion, our findings indicate that vaccination can effectively reduce the tremendous health and economic burden of rotavirus gastroenteritis. Timing of vaccination, vaccination coverage, and the ability of vaccination programs to reach children at risk of death due to rotavirus disease will substantially impact the effectiveness of vaccination. Although rotavirus vaccination is unlikely to be cost-saving from the health care perspective at the prices considered, vaccination is cost-effective across a range of prices using several standards. Compared with other interventions to reduce diarrhea-associated mortality, the benefits of rotavirus vaccination may be achieved quickly because of the ability of the vaccine to be incorporated into existing immunization programs and the short time between vaccination and averted mortality. Although rotavirus vaccination may be considered to be cost-effective, it will require an investment of resources to procure and deliver the vaccine, the magnitude of which is determined by vaccine price. Although some of these costs will be defrayed by averted medical costs, additional national or international resources will likely be needed to bring vaccines to children in the poorest countries who need them the most. In the short term, external resources may be available from international donors, such as funding from the GAVI Alliance for eligible low-income countries; however, countries will need to identify internal resources for rotavirus vaccination program sustainability.

## References

1. World Health Organization. Global and national estimates of deaths under age five attributable to rotavirus infection: 2004. Geneva: World Health Organization, **2006**.
2. Ruiz-Palacios GM, Perez-Schael I, Velazquez FR, et al.; the Human Rotavirus Vaccine Study. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. N Engl J Med **2006**; 354:11–22.
3. Vesikari T, Matson DO, Dennehy P, et al.; the Rotavirus Efficacy and Safety Trial Study. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. N Engl J Med **2006**; 354:23–33.
4. World Health Organization (WHO). The World Health Report: reducing risks, promoting healthy life. Geneva: WHO, **2002**.
5. World Bank. World Development Indicators Database. World Bank list of economies. **2002**. Available at: http://devdata.worldbank.org/external/CPProfile.asp?PTYPE = CP&CCODE = BRN. Accessed 21 February 2008.
6. United Nations Children's Fund (UNICEF). State of the world's children 2004. New York: UNICEF, **2003**.
7. Rheingans R, Constenla D, Antil L, Innis B, Breuer T. Potential cost-effectiveness of vaccination for rotavirus gastroenteritis in eight Latin American and Caribbean countries. Rev Panam Salud Publica **2007**; 21:205–16.
8. Parashar UD, Hummelman EG, Bresee JS, Miller MA, Glass RI. Global illness and deaths caused by rotavirus disease in children. Emerg Infect Dis **2003**; 9:565–72.
9. Ehrenkranz P, Lanata CF, Penny ME, Salazar-Lindo E, Glass RI. Rotavirus diarrhea disease burden in Peru: the need for a rotavirus vaccine and its potential cost savings. Rev Panam Salud Publica **2001**; 10:240–8.
10. Gomez JA, Sordo ME, Gentile A. Epidemiologic patterns of diarrheal disease in Argentina: estimation of rotavirus disease burden. Pediatr Infect Dis J **2002**; 21:843–50.
11. Mrukowicz JZ, Krobicka B, Duplaga M, et al. Epidemiology and impact of rotavirus diarrhoea in Poland. Acta Paediatr Suppl **1999**; 88:53–60.
12. O'Ryan M, Perez-Schael I, Mamani N, et al. Rotavirus-associated medical visits and hospitalizations in South America: a prospective study at three large sentinel hospitals. Pediatr Infect Dis J **2001**; 20:685–93.
13. Perez-Schael I. The impact of rotavirus disease in Venezuela. J Infect Dis **1996**; 174(Suppl 1):S19–21.
14. Szücs G, Uj M, Mihály I, Deák J. Burden of human rotavirus-associated hospitalizations in three geographic regions of Hungary. Acta Paediatr Suppl **1999**; 88:61–5.
15. Chan PK, Tam JS, Nelson EA, et al. Rotavirus infection in Hong Kong: epidemiology and estimates of disease burden. Epidemiol Infect **1998**; 120:321–5.
16. Fang ZY, Yang H, Zhang J, et al. Child rotavirus infection in association with acute gastroenteritis in two Chinese sentinel hospitals. Pediatr Int **2000**; 42:401–5.
17. Ardern-Holmes SL, Lennon D, Pinnock R, et al. Trends in hospitalization and mortality from rotavirus disease in New Zealand infants. Pediatr Infect Dis J **1999**; 18:614–9.
18. Nelson EA, Tam JS, Glass RI, Parashar UD, Fok TF. Incidence of rotavirus diarrhea and intussusception in Hong Kong using standardized hospital discharge data. Pediatr Infect Dis J **2002**; 21:701–3.
19. Berner R, Schumacher RF, Forster J. Survey on rotavirus infections in a German pediatric hospital. Eur J Clin Microbiol Infect Dis **1997**; 16:479–81.

20. Lynch M, O'Halloran F, Whyte D, Fanning S, Cryan B, Glass RI. Rotavirus in Ireland: national estimates of disease burden, 1997 to 1998. Pediatr Infect Dis J 2001; 20:693–8.

21. Noel JS, Parker SP, Choules K, Phillips AD, Walker-Smith J, Cubitt WD. Impact of rotavirus infection on a paediatric hospital in the east end of London. J Clin Pathol 1994; 47:67–70.

22. O'Mahony J, Christie G, Morgan JG, Hill C. Rotavirus gastroenteritis among paediatric patients at Tralee general hospital. Ir Med J 2000; 93:274–7.

23. Vesikari T, Rautanen T, Von Bonsdorff CH. Rotavirus gastroenteritis in Finland: burden of disease and epidemiological features. Acta Paediatrica 1999; 88(Suppl):24–30.

24. Bittencourt SA, Leal Mdo C, Santos MO. Hospitalization due of infectious diarrhea in Rio de Janeiro State. Cadernos de Saude Publica 2002; 18:747–54.

25. Gomez JA, Nates S, De Castagnaro NR, Espul C, Borsa A, Glass RI. Anticipating rotavirus vaccines: review of epidemiologic studies of rotavirus diarrhea in Argentina. Rev Panam Salud Publica 1998; 3:69–78.

26. Effler PV, Holman RC, Parashar UD, Glass RI. Diarrhea-associated hospitalizations among children in Hawaii. Hawaii Med J 2000; 59: 362–5.

27. Ford-Jones EL, Wang E, Petric M, Corey P, Moineddin R, Fearon M. Hospitalization for community-acquired, rotavirus-associated diarrhea: a prospective, longitudinal, population-based study during the seasonal outbreak. The Greater Toronto Area/Peel Region PRESI Study Group. Pediatric Rotavirus Epidemiology Study for Immunization. Arch Pediatr Adolesc Med 2000; 154:578–85.

28. Parashar UD, Holman RC, Clarke MJ, Bresee JS, Glass RI. Hospitalizations associated with rotavirus diarrhea in the United States, 1993 through 1995: surveillance based on the new ICD-9-CM rotavirus-specific diagnostic code. J Infect Dis 1998; 177:13–7.

29. Parashar UD, Holman RC, Bresee JS, et al. Epidemiology of diarrheal disease among children enrolled in four West Coast health maintenance organizations. Vaccine Safety Datalink Team. Pediatr Infect Dis J 1998; 17:605–11.

30. Buigues R, Duval B, Rochette L, at al. Hospitalizations for diarrhea in Quebec children from 1985 to 1998: Estimates of rotavirus-associated diarrhea. Can J Infect Dis 2002; 13:239–44.

31. Carlin JB, Jackson T, Lane L, Bishop RF, Barnes GL. Cost effectiveness of rotavirus vaccination in Australia. Aust N Z J Public Health 1999; 23: 611–6.

32. Berner R, Schumacher RF, Hameister S, Forster J. Occurrence and impact of community-acquired and nosocomial rotavirus infections— a hospital-based study over 10 y. Acta Paediatrica 1999; 88(Suppl): 48–52.

33. Velazquez F, Abate H, Clemens S-A, Espinoza F, Gillard P, Linhares AC. The human monovalent G1P[8]rotavirus vaccine, Rotarix™ is highly efficacious and provides cross-protection against G1 and non-G1 serotypes. In: Program and abstracts of the 23rd Annual Meeting of the European Society for Paediatric Infectious Diseases (Valencia, Spain). 2005.

34. De Vos B, Vesikari T, Linhares A, et al. A rotavirus vaccine for prophylaxis of infants against rotavirus gastroenteritis. Pediatr Infect Dis J 2004; 23(Suppl):S179–82.

35. Vesikari T, Karvonen A, Puustinen L, et al. Efficacy of RIX4414 live attenuated human rotavirus vaccine in Finnish infants. Pediatr Infect Dis J 2004; 23:937–43.

36. World Health Organization. Results of unit costs for patient services for the 14 GBD regions. Available at: http://www.who.int/choice/costs/unit_regions/en/index.html. Accessed 4 September 2009.

37. WHO-UNICEF. WHO and UNICEF estimates of national immunization coverage. 2002. Available at: http://www.who.int/vaccines-surveillance/WHOUNICEF_Coverage_Review/. Accessed 19 March 2004.

38. Murray C, Lopez A. The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. Boston: School of Public Health, Harvard University, 1996.

39. Parashar UD, Hummelman EG, Bresee JS, Miller MA, Glass RI. Global illness and deaths caused by rotavirus disease in children. Emerg Infect Dis 2003; 9:565–72.

40. Villa S, Guiscafre H, Martinez H, Munoz O, Gutierrez G. Seasonal diarrhoeal mortality among Mexican children. Bull WHO 1999; 77: 375–80.

41. Velazquez FR, Matson DO, Guerrero ML, et al. Serum antibody as a marker of protection against natural rotavirus infection and disease. J Infect Dis 2000; 182:1602–9.

42. Gonzalez FS, Sordo ME, Rowensztein G, et al. Rotavirus diarrhea: impact in a pediatric hospital of Buenos Aires [in Spanish]. Medicina 1999; 59:321–6.

43. Cardoso DD, Soares CM, Dias e Souza MB, et al. Epidemiological features of rotavirus infection in Goiania, Goias, Brazil, from 1986 to 2000. Memorias do Instituto Oswaldo Cruz 2003; 98:25–9.

44. Bok K, Castagnaro NC, Diaz NE, et al. Rotavirus laboratory network: results after one year of observation [in Spanish]. Revista Argentina de Microbiologia 1999; 31:1–12.

45. Bok K, Castagnaro N, Borsa A, et al. Surveillance for rotavirus in Argentina. J Med Virol 2001; 65:190–8.

46. Barraza P, Avendano LF, Spencer E, Calderon A, Prenzel I, Duarte E. Hospital infection caused by rotaviruses in infants, Santiago, Chile. Boletin de la Oficina Sanitaria Panamericana 1986; 101:328–38.

47. Urrestarazu MI, Liprandi F, De Suarez EP, Gonzalez R, Perez-Schael I. Etiological, clinical, and sociodemographic characteristics of acute diarrhea in Venezuela. Rev Panam Salud Publica 1999; 6:149–56.

48. Perez-Schael I, Gonzalez R, Fernandez R, et al. Epidemiological features of rotavirus infection in Caracas, Venezuela: implications for rotavirus immunization programs. J Med Virol 1999; 59:520–6.

49. Hsu VP, bin Abdul Rahman H, Lan WS, et al. Estimates of the rotavirus disease burden in Malaysia. J Infect Dis 2005; 192(Suppl 1):S80–6.

50. Nelson E, Tam J, Bresee J, et al. Estimates of rotavirus disease burden in Hong Kong: hospital−based surveillance. J Infect Dis 2005; 192(Suppl 1):S71–9.

51. Chen KT, Chen PY, Tang RB, et al. Sentinel hospital surveillance for rotavirus diarrhea in Taiwan, 2001–2003. J Infect Dis 2005; 192(Suppl 1):S44–8.

52. Jiraphongsa C, Bresee J, Pongsuwanna Y, et al. Epidemiology and burden of rotavirus diarrhea in Thailand: results of the sentinel surveillance. J Infect Dis 2005; 192(Suppl 1):S87–93.

53. Cama RI, Parashar UD, Taylor DN, et al. Enteropathogens and other factors associated with severe disease in children with acute watery diarrhea in Lima, Peru. J Infect Dis 1999; 179:1139–44.

54. Cunliffe NA, Gondwe JS, Kirkwood CD, et al. Effect of concomitant HIV infection on presentation and outcome of rotavirus gastroenteritis in Malawian children. Lancet 2001; 358:550–5.

55. Mpabalwani M, Oshitani H, Kasolo F, et al. Rotavirus gastro-enteritis in hospitalized children with acute diarrhoea in Zambia. Ann Trop Paediatr 1995; 15:39–43.

56. Fang Z-Y, Wang B, Kilgore PE, et al. Sentinel hospital surveillance for rotavirus diarrhea in the People's Republic of China, August 2001–July 2003. J Infect Dis 2005; 192(Suppl 1):S94–9.

57. Bahl R, Ray P, Subodh S, et al.; Delhi Rotavirus Study Group. Incidence of severe rotavirus diarrhea in New Delhi, India, and G and P types of the infecting strains. J Infect Dis 2005; 192(Suppl 1):S114–9.

58. De Francisco A, Hall AJ, Schellenberg JR, Greenwood AM, Greenwood BM. The pattern of infant and childhood mortality in Upper River Division, The Gambia. Ann Trop Paediatr 1993; 13:345–52.

59. Jaffar S, Leach A, Greenwood AM, et al. Changes in the pattern of infant and childhood mortality in upper river division, The Gambia, from 1989 to 1993. Trop Med Int Health 1997; 2:28–37.

60. Shamebo D, Muhe L, Sandstrom A, Freij L, Krantz I, Wall S. The Butajira Rural Health Project in Ethiopia: a nested case-referent (control) study of under-5 mortality and its health and behavioural determinants. Ann Trop Paediatr 1994; 14:201–9.

61. Khalique N, Sinha SN, Yunus M, Malik A. Early childhood mortality—a rural study. J R Soc Health **1993**; 113:247–9.

62. Hirve S, Ganatra B. A prospective cohort study on the survival experience of under five children in rural western India. Indian Pediatr **1997**; 34:995–1001.

63. van Tran D, van Thuan C, Tuan T, Dung PH, Persson L, Grabe M. Survey on immunization, diarrhoeal disease and mortality in Quang Ninh Province, Vietnam. J Trop Pediatr **1991**; 37:280–5.

64. Jinadu MK, Olusi SO, Agun JI, Fabiyi AK. Childhood diarrhoea in rural Nigeria. I. Studies on prevalence, mortality and socio-environmental factors. J Diarrhoeal Dis Res **1991**; 9:323–7.

65. Baqui AH, Sabir AA, Begum N, Arifeen SE, Mitra SN, Black RE. Causes of childhood deaths in Bangladesh: an update. Acta Paediatrica **2001**;90:682–90.

66. Murray CJL, Lopez AD. The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries and risk factors in 1990 and projected to 2020. Vol. 1. Cambridge: Harvard University Press, **1996**.

67. Baltussen R, Adam T, Tan Torres T, et al. Generalized cost effectiveness analysis: a guide. Geneva: World Health Organization, **2002**.

68. World Health Organization. Review of treatment cost protocol studies: report of a meeting Geneva, 11–12 December 2000. Geneva: Department of Vaccines and Biologicals, World Health Organization, **2001**: 1–26.

69. Rheingans R, Constenla D, Antil L, Innis B, Breuer T. Economic and health burden of rotavirus gastroenteritis for the 2003 birth cohort in eight Latin American and Caribben countries. Rev Panam Salud Publica **2007**; 21:192–204.

70. Bureau of Labor Statistics. Consumer Price Index, 2000–2002. Available at: http://www.bls.gov/cpi/cpi_dr.htm. Accessed 4 September 2009.

71. World Development Indicators Online. **2004**. Available at: http://ddp-ext.worldbank.org/ext/DDPQQ/member.do?method = getMembers& userid = 1&queryId = 135. Accessed 4 September 2009.

72. Measure DHS. Demographic and health surveys. 1996–2001. Available at: http://www.measuredhs.com/aboutsurveys/search/search_survey_main.cfm?SrvyTp = country. Accessed 4 September 2009.

73. Suwal JV. The main determinants of infant mortality in Nepal. Soc Sci Med **2001**; 53:1667–81.

74. Wang L. Determinants of child mortality in LDCs: empirical findings from demographic and health surveys. Health Policy **2003**; 65:277–99.

75. Terra de Souza AC, Cufino E, Peterson KE, Gardner J, Vasconcelos do Amaral MI, Ascherio A. Variations in infant mortality rates among municipalities in the state of Ceara, Northeast Brazil: an ecological analysis. Int J Epidemiol **1999**; 28:267–75.

76. Wolfson LJ. WHO immunization coverage estimates and trajectories (WHO ICE-T). Geneva: World Health Organization, Department of Immunization, Vaccines, and Biologicals, **2008**.

77. Adam T, Evans DB, Murray JL. Econometric estimation of country-specific hospital costs. Cost Effectiveness and Resource Allocation **2003**; 1:3.

78. World Health Organization. World Health Report 2002: Ch. 5. Some strategies to reduce risk. **2002**:100–144. Available at: http://www.who.int/whr/2002/en/. Accessed 23 January 2004.

79. World Health Organization. Cost-effectiveness results. Available at: http://www.who.int/choice/results/en/. Accessed 4 September 2009.