

Cost-effectiveness analysis of routine rotavirus vaccination in Brazil

Patrícia Coelho de Soárez,¹ Joice Valentim,¹ Ana Marli Christovam Sartori,² and Hillegonda Maria Dutilh Novaes¹

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ABSTRACT

Objective. *The objective of this study was to conduct a cost-effectiveness analysis of a universal rotavirus vaccination program among children ≤ 5 years of age in Brazil.*

Methods. *Considering a hypothetical annual cohort of approximately 3 300 000 newborns followed over 5 years, a decision-tree model was constructed to examine the possible clinical and economic effects of rotavirus infection with and without routine vaccination of children. Probabilities and unit costs were derived from published research and national administrative data. The impact of different estimates for key parameters was studied using sensitivity analysis. The analysis was conducted from both healthcare system and societal perspectives.*

Results. *The vaccination program was estimated to prevent approximately 1 735 351 (54%) of the 3 210 361 cases of rotavirus gastroenteritis and 703 (75%) of 933 rotavirus-associated deaths during the 5-year period. At a vaccine price of 18.6 Brazilian reais (R\$) per dose, this program would cost R\$121 673 966 and would save R\$38 536 514 in direct costs to the public healthcare system and R\$71 778 377 in direct and indirect costs to society. The program was estimated to cost R\$1 028 and R\$1 713 per life-years saved (LYS) from the societal and healthcare system perspectives, respectively.*

Conclusions. *Universal rotavirus vaccination was a cost-effective strategy for both perspectives. However, these findings are highly sensitive to diarrhea incidence rate, proportion of severe cases, vaccine coverage, and vaccine price.*

Key words

Rotavirus vaccines, cost effectiveness analysis, Brazil.

Rotavirus is a common cause of severe diarrhea among children, accounting for as many as 111 million episodes of diarrhea, 25 million

healthcare visits, 2 million hospitalizations, and 440 000 deaths of children ≤ 5 years of age worldwide each year (1). The fact that incidence of rotavirus is similar in developed and developing countries suggests the disease is not adequately controlled with improvements in sanitation alone (1).

Two rotavirus vaccines whose efficacy and safety have been demonstrated in phase 3 trials are commercially available (2–3). The World Health Organization (WHO) has encouraged the introduction of a rota-

virus vaccine into national immunization programs, particularly in poorer countries (4).

In Brazil, morbidity and mortality associated with diarrhea has sharply decreased in the last 30 years. This has been largely attributed to improvements in potable water supply and sanitation, the promotion of breastfeeding, and increased use of oral rehydration therapy countrywide (although major regional and socioeconomic differences remain) (5). With the decrease in bacterial diarrhea, rota-

¹ Departamento de Medicina Preventiva, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brasil. Send correspondence and requests for reprints to: Patrícia C. de Soárez, Departamento de Medicina Preventiva, Faculdade de Medicina da Universidade de São Paulo, Av. Dr. Arnaldo, 455 - 2º andar Cerqueira Cesar, São Paulo 01246-903, Brasil; telephone: +55 (11) 5052 4868; fax: +55 (11) 5052 4868; e-mail: pcsoarez@uol.com.br

² Clínica de Moléstias Infecciosas e Parasitárias, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brasil.

virus infection has gained importance as a cause of diarrhea in children < 5 years of age (6).

Routine immunization of children in Brazil includes all vaccines recommended by WHO's Expanded Programme on Immunization (EPI): tuberculosis (BCG); oral poliomyelitis (OPV); diphtheria-tetanus-pertussis whole-cell and *Haemophilus influenzae* type b (DTPw-Hib); hepatitis B; measles, mumps, and rubella (MMR); and yellow fever. In 2004, coverage of the third dose of the DTPw-Hib vaccine and the third dose of the hepatitis B vaccine in children < 12 months was, respectively, 96% and 90.5% (7). There is continuous pressure from the general population, health professions, and drug manufacturers to include new and increasingly expensive vaccines in the National Immunization Program (*Programa Nacional de Imunizações*, PNI), and public health officials face difficult choices.

Brazil is a large country, with an estimated population of 182 060 108 people in 2004, and an urbanization rate of 83%. Socioeconomic and cultural conditions as well as healthcare systems vary significantly across different regions. Therefore, it should be noted that any analyses conducted from a national perspective, albeit necessary, reflect national averages that include significant contextual variations countrywide.

Cost-effectiveness analyses in other countries have shown rotavirus vaccination to be cost-effective (8–14). However, results of economic evaluations are highly sensitive to local parameters, such as incidence, mortality, healthcare and hospitalization costs, and vaccine costs. Therefore, the objective of this study was to do a cost-effectiveness analysis of a universal childhood vaccination program against rotavirus using local data from both the healthcare system and societal perspectives.

MATERIALS AND METHODS

Model design

Applying a similar approach to those used in other studies (8–14), a decision-

tree model was constructed to examine the possible clinical and economic effects of rotavirus infection with and without routine vaccination of children.

Microsoft Excel was used to develop a model for a hypothetical annual birth cohort of children followed for 5 years in order to estimate health effects and economic costs associated with rotavirus gastroenteritis with and without routine rotavirus vaccination.

A cost-effectiveness analysis was conducted from the public healthcare system perspective, including direct costs, and from the societal perspective, including direct costs as well as transportation costs and indirect costs, such as the losses in productivity that occur when an adult is absent from paid work to care for a sick child (15).

Vaccination strategy

One type of immunization against rotavirus infection was considered: universal vaccination of infants at 2 and 4 months of age. This strategy ("Vaccination Program") was compared with one alternative ("No Vaccination Program") (Figure 1).

As shown in the decision-tree model in Figure 1, one decision node separates the Vaccination Program and No Vaccination Program branches, and one chance node separates the Vaccination Program branch into children who are "vaccinated" versus those who are "unvaccinated." Another chance node separates those who are fully vaccinated ("2 doses") versus those who are partially vaccinated ("1 dose"). Each group considered is separated into children who have diarrhea ("with diarrhea") and those who do not ("no diarrhea"). Those with diarrhea are then separated by severity of illness ("mild," "moderate," or "severe" diarrhea), as the vaccine has specific efficacy in preventing these three different categories of diarrhea. Children for whom the vaccine is efficacious are classified as "protected," and those that develop the disease are classified as "sick."

The study assumes that children who develop mild diarrhea receive only domiciliary treatment (home-

based care), that those who develop moderate diarrhea receive domiciliary treatment and ambulatory treatment (outpatient healthcare facility care), and that both groups of children regain their health (classified as "recovered"). It also assumes that children who develop severe diarrhea receive domiciliary and ambulatory treatment, are hospitalized, and either recover or die (classified as "recovered" or "death"). The structure of the decision tree is identical for all categories of the study population: those in the Vaccination Program branch (fully vaccinated, partially vaccinated, or unvaccinated), and those in the No Vaccination Program branch.

The model estimates the number of domiciliary treatments, ambulatory treatments, hospitalizations, and deaths that would occur over five years with and without the universal immunization program ("Vaccination Program" vs. "No Vaccination Program"). Probabilities assigned to the events detailed in the decision tree are outlined in Table 1.

Valuing outcomes

Using the model, three summary measures were calculated:

1. Incremental cost per case averted,
2. Incremental cost per death averted, and
3. Incremental cost per life-years saved (LYS).

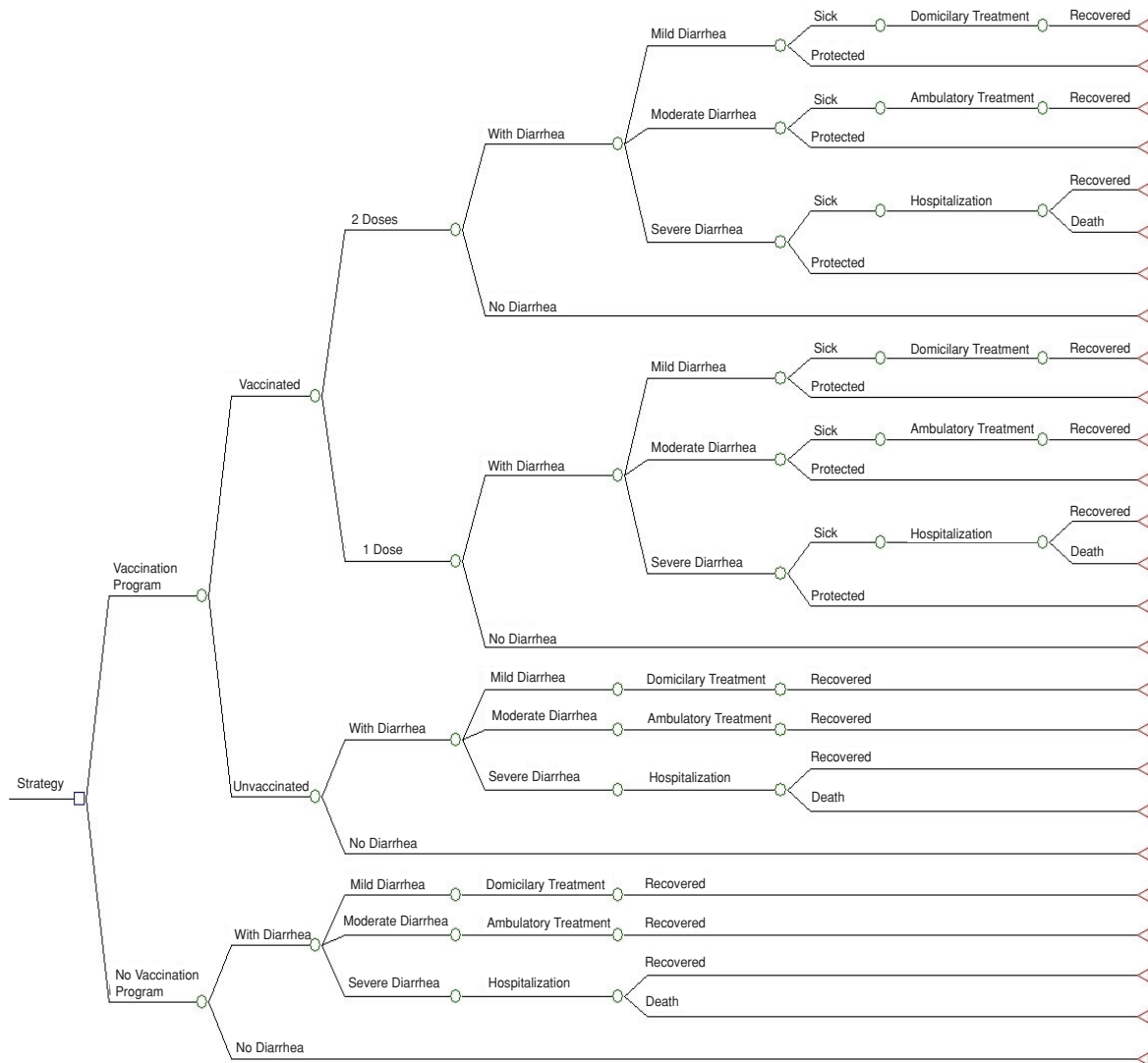
To calculate life-years saved, the following equation was used, assuming a study population life expectancy of 69 years:

$$\text{LYS} = \text{Number of deaths averted} \times 69$$

To calculate the incremental cost-effectiveness ratio (ICER), the following equation was used:

$$\text{ICER} = \frac{\text{Cost with Vaccination Program} - \text{Cost without Vaccination Program}}{\text{(Cases/deaths/LYS) with and without Vaccination Program}}$$

FIGURE 1. Decision-tree model for rotavirus immunization program in Brazil, 2004



Future costs and outcomes were discounted to their present values at a discount rate of 6%—the highest rate suggested by WHO (16), and the one considered most appropriate for developing countries.

Population estimates

The size of the annual birth cohort (3 300 000 newborns) was based on data from the Brazilian Institute of Geography and Statistics (*Instituto Brasileiro de Geografia e Estatística*, IBGE) for 2004 (17).

Morbidity and mortality estimates

Estimates of rotavirus morbidity and mortality were based on the literature review and on data from the national public health database (*Departamento de Informática do Sistema Único de Saúde*, DATASUS) and other sources (18). Rotavirus was estimated to cause 3 525 053 episodes of diarrhea, 655 853 visits to healthcare facilities, 92 453 hospitalizations, and 850 deaths of children ≤ 5 years of age each year in Brazil. The estimated 5-year cumulative incidence of rotavirus diarrhea was 1.2 per child.

Decision-tree linear models do not allow for estimating the effects of multiple disease episodes, so total rotavirus incidence cannot be more than one infection per child. While active acquired immunity after natural infection does not completely protect against reinfection, or mild diarrhea, it does protect against subsequent severe diarrhea (19). Therefore, severe diarrhea is most likely to occur during the first episode of rotavirus infection (19–20). Based on these parameters, the model was used to estimate the incidence of severe and moderate diarrhea only (with the incidence of mild

TABLE 1. Values of input variables in rotavirus vaccine cost-effectiveness model, Brazil, 2004

Model variables	Base-case estimate	Estimates for sensitivity analysis	Reference / basis for calculation of estimates
Disease impact			
Incidence of diarrhea	1	-25 and -50% base case	(18)
Mild diarrhea	0.7437	(0.6392-0.8335)	(5, 18)
Moderate diarrhea	0.2247	(0.1438-0.3218)	(18)
Severe diarrhea	0.0316	(0.0227-0.039)	(18)
Hospitalization ^a	0.9908		(18)
Case-fatality rate ^a	0.0092	±25% base case	(18)
Vaccine coverage			
Unvaccinated	0.10	+25 and +50% base case	(7, Authors' assumption)
Vaccinated	0.90	-25 and -50% base case	(7, Authors' assumption)
2 doses ^b	0.80	-25 and -50% base case	(7, Authors' assumption)
1 dose ^b	0.20	±25 and ±50% base case	(7, Authors' assumption)
Vaccine efficacy			
2 doses			
Against mild diarrhea	0.63	(0.56-0.70)	(22, Authors' assumption)
Against moderate diarrhea	0.63	(0.56-0.70)	(22, Authors' assumption)
Against severe diarrhea	0.847	(0.717-0.924)	(2)
1 dose			
Against mild diarrhea	0.50	(0.44-0.56)	(22, Authors' assumption)
Against moderate diarrhea	0.50	(0.44-0.56)	(22, Authors' assumption)
Against severe diarrhea	0.811	(0.684-0.924)	(2)
Costs^c			
	Society	Healthcare system	
Home-based care ^d	11.80	0.00	e, f
Outpatient healthcare facility care ^d	45.10	19.00	e, f
Hospitalization ^d	388.36	348.00	e, f
Vaccine dose		18.6	±25 and ±50% base case
			±25 and ±50% base case
Discount rate	6%		(3%-8%) (16)

^a Among all cases of severe diarrhea (3.16% of all diarrhea cases), 99.08% were hospitalization cases with recovery and 0.92% resulted in death.

^b Among vaccinated (90% of total population), 80% (72% of total population) received 2 doses and 20% (18% of total population) received 1 dose.

^c In 2004 Brazilian reais (exchange rate: US\$1 = R\$2.65, Brazilian Central Bank).

^d Mean cost per episode.

^e de Soárez PC, Ciconelli RM, Kowalski CC, Ferraz MB, da Silva LJ, Paula Eduardo MB, et al. Estudo prospectivo da diarreia para estimativa da incidência por rotavírus e do custo da gastroenterite por rotavírus em crianças menores de 5 anos. Relatório Técnico. Centro Paulista de Economia da Saúde / Escola Paulista de Medicina / Universidade Federal de São Paulo and Secretaria de Estado da Saúde de São Paulo. September, São Paulo, 2005 [photocopy]. Financed by GlaxoSmithKline Brasil Ltda.

^f de Soárez PC, Ciconelli RM, Kowalski CC, Ferraz MB, da Silva LJ, Paula Eduardo MB, et al. Cost of rotavirus and nonrotavirus diarrhea among young children in Brazil. Poster presented at the 8th Brazilian Congress on Collective Health and the 11th World Congress on Public Health. Brazilian Association for Graduate Studies in Collective Health and The World Federation of Public Health Associations, August 21-25, Rio de Janeiro, 2006.

diarrhea recorded as complementary values for a total incidence of 1). This method was used to ensure that only mild diarrhea would be underestimated. The final numbers for estimated 5-year cumulative incidences of mild, moderate, and severe diarrhea episodes are presented in Table 1.

Vaccine coverage and efficacy estimates

The live attenuated monovalent human G1P[8] rotavirus vaccine was

chosen for universal vaccination in Brazil. The recommended dosage is a 2-dose scheme administered according to a strict schedule, with the first dose given only to children aged between 6 and 14 weeks, and the second dose given one or two months later, to children aged between 14 and 24 weeks.

In 1999, a rhesus-human rotavirus reassortant tetravalent live vaccine (RotaShield[®]) was withdrawn from the market because of a temporal association with intussusception (an intestinal obstruction in which one seg-

ment of bowel becomes infolded within another segment). As no biological mechanism has been established for this syndrome, it is not known whether it may occur with other live rotavirus vaccines. As a precaution, experimental administration of the first dose of the new generation of rotavirus vaccines was restricted to children in the first three months of life, as this age group is less vulnerable to natural intussusception (21). Although the monovalent human G1P[8] rotavirus vaccine has had a reassuring safety profile in a phase 3 trial that en-

rolled more than 60 000 children (2), it has never been used in a large-scale immunization program.

Because “catch-up” vaccination of susceptible older children against rotavirus is not recommended, it was not considered in this model.

Due to possible constraints caused by the strict administration schedule recommended for the rotavirus vaccine, estimated coverage was based on hepatitis B coverage (90.49%), the lowest among vaccines recommended for children under 1 year of age by Brazil’s National Immunization Program in 2004 (7). Data on incomplete hepatitis B and DTPw-Hib vaccination schemes were used to estimate the proportion of children who would receive 1 versus 2 doses of the rotavirus vaccine.

Estimated vaccine efficacy was based on results obtained in clinical trials. Like many other vaccines, rotavirus vaccine is considered more effective against severe disease than against mild or moderate disease. In a phase 3 trial, human G1P[8] rotavirus vaccine efficacy against severe illness was 84.7% (with 2 doses) and 81.1% (with 1 dose) (2), and in a phase 2 Latin America trial, the efficacy of 2 doses of the vaccine against severe diarrhea ranged from 66% to 86%, whereas efficacy against any rotavirus gastroenteritis ranged from 56% to 70%, depending on the vaccine dose ($10^{4.7}$ to $10^{5.8}$ focus-forming unit) (22). Efficacy of the vaccine against mild and moderate disease was not reported (2, 22). Therefore, for this study, the rate of vaccine efficacy against mild diarrhea was estimated, based on the maximum efficacy rate of 70% against “any rotavirus gastroenteritis” (which includes severe diarrhea), and the assumption that this overall maximum efficacy rate would fall above the rate of efficacy against mild diarrhea but below the rate of efficacy against severe diarrhea. Similarly, the efficacy of 1 dose of the vaccine was assumed to be lower than the efficacy of 2 doses.

Possible adverse events after vaccination were not considered in the model because the rates of adverse events in children who received the

human G1P[8] rotavirus vaccine in clinical trials were similar to unvaccinated controls (2, 22).

Potential herd protection (the potential indirect effects of the immunization program for unvaccinated children) was not considered in the model because there was no information about it in the literature.

Cost estimates

Direct and indirect costs included in the model were based on data from the national public health database (DATASUS), demographic surveys (secondary data), and results deemed appropriate for use in national estimates from a recent national study on rotavirus disease-associated costs conducted in two cities in São Paulo state (Rio Claro and Guarulhos) (primary data).^{3,4}

Direct costs

Healthcare costs. Healthcare costs included hospitalizations, physician visits, laboratory tests, medications, and health products. Hospitalization costs were based on the average value paid for hospital care of children \leq 5 years of age due to infectious diarrhea and gastroenteritis (International Classification of Disease, 10th Revision, codes A00 to A09) by the public healthcare system (*Sistema Único de Saúde*, SUS), based on registration records from the SUS Hospital Information

System (*Sistema de Informações Hospitalares*, SIH). Costs for pediatrician visits and laboratory tests were based on values paid by the SUS, based on registration records from its Outpatient Information System (*Sistema de Informações Ambulatoriais*, SIA) (23).

Estimated medications (oral and intravenous rehydration fluids, analgesics, antipyretics, antiemetics, and antibiotics) and products (mainly diapers and baby wipes) were based on information from the 2004 national rotavirus cost study (see footnotes 3 & 4). Home-based care costs included medications and products; outpatient healthcare facility care costs included healthcare system visits, laboratory tests, medications, and products; and hospital care costs included hospitalizations, healthcare system visits, laboratory tests, medications, and products.

It was assumed that home-based care was provided by families, and outpatient healthcare facility and hospital care were provided by the healthcare system. Home-based care costs were not included in the healthcare system perspective analyses.

The private healthcare system in Brazil is responsible for the healthcare of 30% of the population (24). Costs for this system are most likely higher than for the public healthcare system, but no such data is available. Therefore, all healthcare costs were based on estimates for the public healthcare system.

Transportation costs. Transportation costs were calculated by applying the micro-costing method to information obtained in the 2004 national rotavirus cost study (see footnotes 3 & 4). Transportation costs related to outpatient healthcare facility and hospital care were added to the societal perspective.

Indirect costs

Loss of earnings by caregiver. Estimated loss of earnings by caregivers was based on the human capital method (25–26). The value of the referred average monthly wage of families that participated in the 2004 national rotavirus cost study (median

³ de Soárez PC, Ciconelli RM, Kowalski CC, Ferraz MB, da Silva LJ, Paula Eduardo MB, et al. Estudo prospectivo da diarreia para estimativa da incidência por rotavírus e do custo da gastroenterite por rotavírus em crianças menores de 5 anos. Relatório Técnico. Centro Paulista de Economia da Saúde / Escola Paulista de Medicina / Universidade Federal de São Paulo and Secretaria de Estado da Saúde de São Paulo. September, São Paulo, 2005 [photocopy]. Financed by GlaxoSmithKline Brasil Ltda.

⁴ de Soárez PC, Ciconelli RM, Kowalski CC, Ferraz MB, da Silva LJ, Paula Eduardo MB, et al. Cost of rotavirus and nonrotavirus diarrhea among young children in Brazil. Poster presented at the 8th Brazilian Congress on Collective Health and the 11th World Congress on Public Health. Brazilian Association for Graduate Studies in Collective Health and The World Federation of Public Health Associations. August 21–25, Rio de Janeiro, 2006.

between R\$200 and R\$500) was divided by 30 [days] and multiplied by the estimated number of paid workdays lost by parents each month to care for a sick child (3 days) (see footnotes 3 & 4). The valuation of lost paid workdays was added to the societal perspective.

Vaccination costs

Vaccination costs included the price of each dose, the number of doses administered (based on estimates for a 2-dose scheme), administration costs, and expected losses from vaccine waste. The price of each dose was estimated at US\$7 (R\$18.6)⁵ based on the value established in an agreement between the Brazilian Ministry of Health and the vaccine producer, Glaxo-SmithKline Biologicals (Rixenart, Belgium) (J. Barbosa, Health Surveillance Secretariat, Brazilian Ministry of Health, personal communication, September 2005). Since the rotavirus vaccine can be administered at the same time as the current recommended tetravalent DTPw-Hib and OPV vaccines, incremental administration costs were assumed to be low. Both administration costs (US\$1) and expected losses from waste (10% of vaccine doses) were taken from the literature (11), as no local data were available.

As explained above, vaccination costs were calculated only for the public healthcare system. Data from the immunization program of São Paulo state (the state with the largest private healthcare system) indicate a low level of private sector participation in the immunization of children in 2004, covering just 1.3% of the population—a negligible proportion from the national perspective (H.K. Sato, Coordinator, São Paulo State Immunization Program, personal communication, January 2006).

All cost values for each type of care, according to both the societal and healthcare perspectives, are presented in Table 1.

TABLE 2. Health burden associated with rotavirus gastroenteritis, by vaccination status, Brazil, 2004

Disease impact	No Vaccination Program	Vaccination Program
Total cases	3 210 361	1 475 010
Cases averted		1 735 351
Change in number of cases (%)		54%
Total deaths	933	230
Deaths averted		703
Change in number of deaths (%)		75%
Life-years lost	64 399	15 878
Life-years saved		48 521
Change in number of life-years saved (%)		75%

Sensitivity analysis

Due to uncertainty in some key model parameters, a set of univariate sensitivity analyses was carried out to examine the impact of change in these variables on the ICERs. The following parameters were varied one at a time: diarrhea incidence; proportion of severe, moderate, and mild diarrhea cases; case-fatality rate; vaccine coverage rate; vaccine efficacy; vaccine cost; hospitalization costs; and discount rate. Whenever possible, the variation around the base-case values was based on clinical, epidemiological, and social criteria (regional and social differences). For some variables (diarrhea incidence, case-fatality rate, vaccine coverage, vaccine cost, and hospitalization cost), the values were altered by adding or subtracting 10%, 25%, or 50% to/from the base-case scenario.

Best-case and worst-case scenario sensitivity analyses were also conducted. The model was analyzed using the high-range estimate most favorable to the vaccine (“best-case scenario”) and reanalyzed based on a low-range estimate (“worst-case scenario”). In both scenarios, estimates were varied simultaneously and in the same direction.

RESULTS

Base-case estimates

The estimated reduction in the burden of disease using the Vaccination

Program strategy is shown in Table 2. Costs associated with both strategies (“Vaccination Program” and “No Vaccination Program”) are shown in Table 3. Table 4 summarizes the ICERs of both strategies, according to baseline assumptions.

The break-even price for the vaccine (the point at which the vaccination cost would be counterbalanced by the treatments costs averted) would be R\$9.98 and R\$4.24 per dose from the societal and healthcare system perspectives, respectively.

To determine whether this level of cost-effectiveness is currently economically acceptable or viable for Brazil, the national per capita gross domestic product (GDP) was used as a criterion for comparison with cost-effectiveness calculations. This approach is similar to the one recommended by the Commission on Macroeconomics and Health (CMH) and adopted by WHO, which considers an intervention “very cost-effective” when the cost of averting one disability-adjusted life year or DALY (one lost year of “healthy” life due to disability and/or premature mortality) is less than the per capita GDP (27). Because rotavirus-associated diarrhea is generally an acute event, evolving to either full recovery or death, the disability adjustment of life expectancy would contribute little to DALYs. In this case, one DALY averted would cost about the same as one LYS (life-year saved) (28). In 2004, the Brazilian GDP was R\$10 692 (US\$4 035) (29). Because the cost per LYS (R\$1 028 from the societal perspective, and R\$1 713 from the

⁵ 2004 Brazilian real (exchange rate: R\$2.65 = US\$1, Brazilian Central Bank).

TABLE 3. Costs associated with rotavirus gastroenteritis and rotavirus vaccination, by perspective and vaccination status, Brazil, 2004

Variable	Societal perspective		Healthcare system perspective	
	No Vaccination Program (R\$)	Vaccination Program (R\$)	No Vaccination Program (R\$)	Vaccination Program (R\$)
Cost ^a				
Total costs ^b	99 742 391	27 964 014	48 684 898	10 148 384
Costs averted		71 778 377		38 536 514
Change in costs (%)		72%		79%
Intervention cost ^c				
At R\$9.3/dose		67 813 097		67 813 097
At R\$13.9/dose		94 453 957		94 453 957
At R\$18.6/dose		121 673 966		121 673 966
At R\$23.2/dose		148 314 826		148 314 826
At R\$27.8/dose		174 909 456		174 909 456

^a 2004 Brazilian reais (exchange rate: US\$1 = R\$2.65, Brazilian Central Bank).

^b Healthcare system perspective includes direct medical costs; societal perspective includes all direct and indirect costs. Costs were divided into three categories: home-based care, outpatient healthcare facility care, and hospitalization.

^c Intervention cost includes cost of purchasing vaccine for 2-dose course, cost of administering vaccine, and losses due to vaccine waste.

TABLE 4. Cost-effectiveness of rotavirus vaccination, by perspective, Brazil, 2004

Incremental cost-effectiveness ratio	Societal perspective (R\$)	Healthcare system perspective (R\$)
Costs and consequences (undiscounted)		
Cost per case averted	29	48
Cost per death averted	70 955	118 228
Cost per life-years saved	1 028	1 713
Costs and consequences (discounted by 6%)		
Cost per case averted	37	57
Cost per death averted	91 670	138 947
Cost per life-years saved	1 329	2 014

healthcare system perspective) was less than the GDP, the universal rotavirus vaccination program would qualify as very cost-effective.

Sensitivity analysis

The parameters, their variations, and the results of the calculations from both the societal and healthcare system perspectives are summarized in Table 5.

One-way sensitivity analyses showed the study results were most sensitive to four parameters: diarrhea incidence rate; proportion of severe, moderate and mild diarrhea episodes; vaccine coverage; and vaccine cost. For example, a 25% reduction in the diarrhea

incidence rate results in a 49% to 81% increase in the ICER, whereas a 50% reduction in incidence results in a 146% to 244% increase. A change of approximately 19% in the proportion of severe and moderate diarrhea episodes results in a 59% to 80% change in the ICER. If vaccine coverage has been overestimated in the base-case scenario (i.e., actual coverage is 25% less than the value used), the ICER would decrease by 51% (from the assumed value of R\$1 028 to R\$504) per LYS. If actual coverage is even lower (50% less than the value used), the Vaccination Program strategy becomes cost saving. Moreover, although changes in vaccine efficacy have little impact, changes in vaccine price have a great impact: a 25% dif-

ference in price results in a 32% to 55% change in the ICER. From the point of view of society, a 50% decrease in price makes the Vaccination Program strategy cost saving.

All other model variables, including hospitalization costs and discount rate, were less sensitive to variation.

Sensitivity analyses of best- and worst-case scenarios

From both perspectives, the best-case scenario resulted in savings, whereas the worst-case scenario resulted in a cost per LYS of R\$9 247 and R\$10 431 from the societal and healthcare system perspectives, respectively.

DISCUSSION

Based on the decision-tree model, as well as estimates derived from published national research and data from the national public health database, rotavirus vaccination was very cost-effective from both the societal and healthcare system perspectives when using the standard established by WHO (cost per DALY less than per capita GDP). Sensitivity analysis indicated the results were most sensitive to incidence of rotavirus-associated diarrhea, proportion of severe and moderate diarrhea episodes, vaccine coverage, and vaccine costs (a 50% reduction in the vaccine price would make the Vaccination Program strategy cost saving from the societal perspective).

Study limitations include the possible underestimation of hospitalization costs—often an important variable, among other healthcare costs, according to sensitivity analyses in cost-effectiveness studies in developed countries (8–9)—as these costs were based on public healthcare reimbursements rather than total costs in both the public and private healthcare sectors. Nonetheless, even with the extreme values used in the sensitivity analyses of the best- and worst-case scenarios, the Vaccine Program strategy remained cost-effective, based on the criteria recommended by CMH/

TABLE 5. Sensitivity analysis of key parameters' effect on rotavirus vaccination incremental cost-effectiveness ratio, by perspective, Brazil, 2004

Parameters input values	Cost per life-years saved	
	Societal perspective	Healthcare system perspective
Disease impact		
Diarrhea incidence		
Very low (−50%)	3 536	4 221
Low (−25%)	1 864	2 549
Base case (1)	1 028	1 713
Diarrhea (mild, moderate, severe)		
Low (0.8335 / 0.1438 / 0.0227)	1 852	2 716
Base case (0.7437 / 0.2247 / 0.0316)	1 028	1 713
High (0.6392 / 0.3218 / 0.039)	596	1 209
Case-fatality rate		
Low (−25%)	1 369	2 283
Base case (0.0092)	1 028	1 713
High (+25%)	824	1 372
Vaccine coverage		
Vaccinated		
Very low (−50%)	Cost saving	1 124
Low (−25%)	504	1 523
Base case (0.90)	1 028	1 713
High (+10%)	1 168	1 764
2 doses		
Very low (−50%)	652	1 286
Low (−25%)	842	1 502
Base case (0.80)	1 028	1 713
Vaccine efficacy		
Against severe diarrhea (2 doses)		
Low (0.717)	1 260	2 034
Base case (0.847)	1 028	1 713
High (0.924)	916	1 559
Against severe diarrhea (1 dose)		
Low (0.684)	1 089	1 797
Base case (0.811)	1 028	1 713
High (0.924)	984	1 652
Costs^a		
Hospitalization ^b		
Very low (−50%)	1 371	2 021
Low (−25%)	1 200	1 867
Base case (R\$388.36)	1 028	1 713
High (+25%)	857	1 560
Very high (+50%)	685	1 405
Vaccine dose		
Very low (−50%)	Cost saving	603
Low (−25%)	467	1 152
Base case (R\$18.6)	1 028	1 713
High (+25%)	1 577	2 263
Very high (+50%)	2 126	2 811
Discount rate ^c		
Low (3%)	1 179	1 864
Base case (6%)	1 329	2 014
High (8%)	1 428	2 114

^a In 2004 Brazilian reais (exchange rate: US\$1 = R\$2.65, Brazilian Central Bank).

^b The cost of hospitalization used for the healthcare system perspective was R\$348.

^c Costs and health consequences were discounted.

WHO (27). This outcome supports the validity of the decision-tree analysis results.

Another potential limitation stems from the nature of modeling itself,

which simplifies real-life experience. The decision-tree model allowed for the processing of available data—some of it local data—to create realistic ranges that incorporated parameter

uncertainties in study estimates. In a country with huge regional and socioeconomic differences, the use of local data (e.g., direct and indirect costs associated with rotavirus-related diarrhea) to represent national values, resulting in the combination of information from different studies and populations, may have resulted in inaccurate estimates. However, the use of a considerable number of national studies on rotavirus epidemiology as well as a very recent study of costs associated with rotavirus diarrhea (see footnotes 3 & 4) in this study helped mitigate this risk and increased the expected validity of the estimates.

As explained above, as the decision-tree model does not allow for consideration of reinfection, each child was assumed to have one sole episode of rotavirus-associated diarrhea. Based on the 5-year cumulative incidence of diarrhea attributable to rotavirus (estimated at 1.2 per child), this incidence is underestimated in the study model. In addition, as explained above, assuming severe and moderate diarrhea occur mainly during the first rotavirus infection, it was decided that the milder cases of diarrhea that do not require medical treatment should be underestimated. Although the costs associated with these mild events are lower than the costs associated with moderate and severe diarrhea, and several cost-effectiveness studies did not consider them in their analysis (10, 12–13), mild cases are numerous and probably represent significant costs under the societal perspective.

Several other study assumptions regarding the vaccination program require further evaluation. Although both rotavirus vaccines currently available have had a reassuring safety profile in large phase 3 clinical trials, certain rare adverse events may only be detected when a vaccine is introduced in a routine universal program in which millions of children are vaccinated. In addition, the true rate of vaccine coverage may be lower than study estimates; no other vaccine in current use has an administration schedule as strict as the rotavirus vaccine, so there is no baseline for esti-

imating the level of incomplete immunization. In addition, the effectiveness of the vaccine under field conditions may be quite different from the efficacy observed in clinical trials. Finally, the potential indirect effects of the immunization program for unvaccinated children (i.e., herd protection), which would lead to greater vaccine effectiveness than that estimated in the clinical trials, are not considered in the study model. Sensitivity analysis showed that while vaccine efficacy has low impact on vaccine cost-effectiveness, vaccine coverage could have a great impact.

This study considered two different perspectives (societal and healthcare system) because it was recognized that when allocating scarce community resources, the adopted perspective should reach beyond that of the provider (the healthcare system), which can be too restrictive. While it is impossible to consider every cost and consequence of the Vaccination Program strategy to all members of society, an effort was made to take account of all variables that were measurable and considered relevant.

It should also be noted that the value of the Brazilian real versus U.S. dollars has improved considerably since this study was conducted—changing from R\$2.65/US\$1 (December 2004) to R\$1.82/US\$1 (October 2007). This has affected the conversion of the vaccine price to the local currency, resulting in a reduction of 32% in the cost of introducing the vaccine (vs. the cost derived in the 2004 study). The vaccine price may be reduced even further due to a recent technology transfer agreement between the vaccine producer and Brazil's Immunobiological Technology Institute (*Instituto de Tecnologia em Imunobiológicos, Bio-Manguinhos*), the manufacturing arm of the Oswaldo Cruz Foundation (*Fundação Oswaldo Cruz, FIOCRUZ*).

Several new vaccines have become commercially available over the past 12 years—varicella, hepatitis A, pneumococcal 7-valent and meningococcal conjugates, and, more recently, rotavirus (2005) and human papillomavirus (HPV) (2006). Governments must decide whether to include these new vaccines in their routine immunization programs. Any decision to incorporate

a new vaccine into a publicly funded program should be based on whether or not (1) the disease in question is a public health problem, (2) vaccination is the best way to control it, and (3) the vaccine program is sustainable from both an organizational and economic perspective. Economic evaluations, increasingly used in developed countries, are a valuable tool to aid the decision-making process.

In March 2006, a routine rotavirus vaccination (the attenuated monovalent human G1P[8]) was added to Brazil's National Immunization Program, with recommended administration to all children at 2 and 4 months of age. The decision was based on public healthcare considerations, prior to the availability of economic evaluations. The results of this study support that decision.

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RESUMEN

Análisis de la relación costo-efectividad de la vacunación programada contra rotavirus en Brasil

Objetivo. Analizar la relación costo-efectividad de un programa universal de vacunación contra rotavirus en niños de hasta 5 años en Brasil.

Métodos. Se consideró una cohorte hipotética anual de aproximadamente 3 300 000 recién nacidos con un seguimiento de 5 años. Mediante un modelo de árbol de decisión se analizaron los posibles efectos clínicos y económicos de la infección por rotavirus con la vacunación programada de niños y sin ella. Las probabilidades y los costos unitarios se tomaron de investigaciones publicadas y de los datos oficiales nacionales. Para evaluar el impacto de diferentes estimados de los parámetros clave se realizó un análisis de sensibilidad. El análisis se efectuó tanto desde la perspectiva del sistema sanitario como de la sociedad.

Resultados. Se estimó que el programa de vacunación evitaría aproximadamente 1 735 351 (54%) de los 3 210 361 casos de gastroenteritis por rotavirus y 703 (75%) de las 933 muertes asociadas con la infección por rotavirus en un período de 5 años. A un precio de la vacuna de 18,6 reales brasileños (R\$) por dosis, este programa costaría R\$ 121 673 966 y ahorraría R\$ 38 536 514 en costos directos al sistema de salud pública y R\$ 71 778 377 en costos directos e indirectos a la sociedad. El costo estimado del programa por año de vida salvado sería de R\$ 1 028 y R\$ 1 713, desde el punto de vista de la sociedad y del sistema de salud, respectivamente.

Conclusiones. La estrategia de vacunación universal contra rotavirus presentó una buena relación costo-efectividad según ambas perspectivas. Sin embargo, estos resultados son muy sensibles a cambios en la incidencia de diarreas, la proporción de casos graves, la cobertura de vacunación y el precio de la vacuna.

Palabras clave

Vacunas contra rotavirus, análisis costo-beneficio, Brasil.