Published in final edited form as:

Vaccine. 2013 December 9; 31(51): . doi:10.1016/j.vaccine.2013.10.022.

Cost-Effectiveness of a new Rotavirus Vaccination Program in Pakistan: a Decision Tree Model

Hiten D. Patel^{a,b}, Eric T. Roberts^c, and Dagna O. Constenla^d

^aJames Buchanan Brady Urological Institute, Johns Hopkins Medical Institutions, Baltimore, MD

^bEpidemiology and Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

^cDepartment of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

^dDepartment of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Abstract

Background—Rotavirus gastroenteritis places a significant health and economic burden on Pakistan. To determine the public health impact of a national rotavirus vaccination program, we performed a cost-effectiveness study from the perspective of the health care system.

Methods—A decision tree model was developed to assess the cost-effectiveness of a national vaccination program in Pakistan. Disease and cost burden with the program were compared to the current state. Disease parameters, vaccine-related costs, and medical treatment costs were based on published epidemiological and economic data, which were specific to Pakistan when possible. An annual birth cohort of children was followed for 5 years to model the public health impact of vaccination on health-related events and costs. The cost-effectiveness was assessed and quantified in cost (2012 US\$) per disability-adjusted life-year (DALY) averted and cost per death averted. Sensitivity analyses were performed to assess the robustness of the incremental cost-effectiveness ratios (ICERs).

Results—The base case results showed vaccination prevented 1.2 million cases of rotavirus gastroenteritis, 93,000 outpatient visits, 43,000 hospitalizations, and 6,700 deaths by 5 years of age for an annual birth cohort scaled from 6% current coverage to DPT3 levels (85%). The medical cost savings would be US\$1.4 million from hospitalizations and US\$200,000 from outpatient visit costs. The vaccination program would cost US\$35 million at a vaccine price of US\$5.00. The ICER was US\$149.50 per DALY averted or US\$4,972 per death averted. Sensitivity analyses showed changes in case-fatality ratio, vaccine efficacy, and vaccine cost exerted the greatest influence on the ICER.

Conclusions—Across a range of sensitivity analyses, a national rotavirus vaccination program was predicted to decrease health and economic burden due to rotavirus gastroenteritis in Pakistan by ~40%. Vaccination was highly cost-effective in this context. As discussions of implementing

© 2013 Elsevier Ltd. All rights reserved.

Corresponding Author: Hiten D. Patel, 615 N. Wolfe St., E8-132, Baltimore, MD 21205, Phone: 618-534-4942, Fax: 443-287-6714, hitenpatel@jhmi.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

the intervention intensify, future studies should address affordability, efficiency, and equity of vaccination introduction.

Keywords

rotavirus; gastroenteritis; cost-effectiveness; vaccination; Pakistan

Introduction

Globally, the number of diarrheal deaths for children younger than 5 years of age decreased significantly from 1.8 million in 2003 to perhaps 700,000 in 2011 as part of a general trend in overall mortality for this age group [1,2]. About 453,000 of these deaths are due to diarrhea caused by rotavirus with Pakistan alone accounting for about 23,000 to 39,000 [2–4]. Rotavirus gastroenteritis (RVGE) accounts for 30–40% of diarrheal hospitalizations in this age group and places a significant health and economic burden on Pakistan as it does on many other middle- and low-income Asian and African countries [5–8]. Vaccination is an extremely promising strategy to reduce the burden of RVGE, and the World Health Organization (WHO) recommends implementing routine rotavirus vaccination for infants globally [9,10].

The efficacies of two different oral rotavirus vaccines were demonstrated in 2006 and in a Cochrane Review in 2012 to prevent about 85%–95% of RVGE-associated hospitalizations [11–13]. The results were similar for high-income Asian countries, but the first clinical trial of vaccination in developing Asian countries reported a reduced, yet encouraging, efficacy of 48.3% against severe RVGE [14,15]. A clinical trial sponsored by the Program for Appropriate Technology in Health (PATH) in Karachi, Pakistan recently completed data collection in December 2012 for the primary outcome but has not reported any results to date [16]. Notably, the Global Alliance for Vaccines and Immunisation (GAVI) has secured a 67% reduction in price of the vaccine as they provide vaccines to an increasing number of developing countries [17]. While the efficacies appear comparable, we focus on RIX4414 (Rotarix®) in the present analysis because it requires only two doses instead of three and was chosen for the clinical trial in Karachi [13,18].

In Asia, the Philippines became the first country to implement a national rotavirus vaccination program in July 2012, but no GAVI-eligible countries on the continent have followed suit [19]. South Asian countries carry a significant proportion of the burden of disease with most cost-effectiveness analyses focusing on India [20–22]. Pakistan was included in an analysis of GAVI-eligible countries but has received little dedicated attention [8,23]. We evaluated cost-effectiveness of a national rotavirus vaccination program compared to current practice for a birth cohort in Pakistan (an estimated 4.8 million children in 2012) by calculating incremental cost-effectiveness ratios (ICERs) from the perspective of the health care system to aid policy makers in their decision regarding vaccine introduction [24].

Data and Methods

Model Overview

We developed a decision tree model using Microsoft Excel to estimate health outcomes and costs associated with a rotavirus vaccination program in a hypothetical annual birth cohort of children for a five-year period (Figure 1). The analytic horizon constitutes the lifetime of the cohort. The estimates were developed using a generalized model populated with a combination of country-specific data and extrapolation from other countries where data were lacking. Costs and health outcomes were analyzed from the healthcare perspective.

Children either died or survived after RVGE. Children who survived experienced a number of different events: a response to treatment at home, in the hospital, or in an outpatient setting or subsequent death. The impact of vaccination on costs was broken down into costs related to vaccine program implementation and costs averted due to the reduced burden of disease. All costs were inflated to 2012 Pakistani Rupees and converted to 2012 US\$ using the appropriate exchange rates. The effects were quantified as deaths and disability-adjusted life-years (DALYs) averted due to vaccination.

Model Inputs

Demographic and disease data—The size of the 2012 birth cohort was estimated based on the United Nations World Population Prospects 2010 data, and life expectancy at age one was derived from WHO Member States Life Tables (Table 1) [24,25]. Rates of hospitalization were estimated from a surveillance study in Karachi, Pakistan while rates of outpatient visits and the proportion of rotavirus diarrheal cases that were treated in the community were estimated using data from India as no Pakistan-specific data are available [4,20,26,27]. The proportion of RVGE in the community was multiplied by age-specific incidence rates of RVGE, which are similar globally, to arrive at the rate of RVGE in Pakistan requiring only home-care [28,29]. The annual incidence of RVGE requiring hospitalization, outpatient visits, and home-care were summed to arrive at the overall annual incidence of RVGE infection, which was then converted to a 5-year cumulative incidence. Re-infection was not a consideration in our model to maintain a conservative estimate of the cumulative incidence. The case-fatality rate for children with RVGE was determined from the estimated number of deaths in the under-five year old population in Pakistan due to RVGE relative to the under-five year old population infected with RVGE [4,24].

Vaccine-related costs and assumptions—The vaccination course should be completed by 32 weeks of age according to the Advisory Committee on Immunization Practices in the United States [30]. Therefore, all vaccine-related costs are assumed to occur during the first year of life for the birth cohort, and discounting does not affect the costs. The current rotavirus vaccine coverage in Pakistan is estimated using the average of 6% for the WHO Eastern Mediterranean region (EMR) [31]. However, current coverage is likely concentrated amongst privileged families where the burden of disease is lowest, so the current analysis may underestimate differences in the benefit of publically vs. privately funded vaccination programs. The expected vaccine coverage under a national immunization program is estimated by current coverage of the final dose of diphtheria, pertussis, and tetanus vaccination (DPT3) at 85% [32]. The unit cost for the vaccine is US\$5.00 according to the reduced price secured by GAVI with a sensitivity range of US\$1.00 to US\$7.50 based on prior studies (Table 2) [17,22,33,34]. Wolfson et al (2008) calculated and partitioned costs associated with scaling up general vaccination coverage (for all types of vaccines) by WHO region to achieve WHO-UNICEF Global Immunization Vision and Strategy goals by 2015 and noted that 60% of overall costs are for the actual vaccines and 40% for components of scaling up [34]. Following this logic, we applied gross-costing and increased the cost of vaccines by 66.7% to account for scaling up rotavirus coverage to DPT3 levels and also factored in a 10% wastage rate to arrive at US\$9.26 for total cost of vaccination per child.

Disease-related costs and assumptions—The WHO-CHOICE health care services unit cost database was utilized to assess disease-related costs to the health care system (Table 2) [35]. The average length of hospital stay for a child with RVGE is 4 days [20,36]. We equally weighted hospital costs from primary, secondary, and teaching hospitals for a 4-day length of stay, inflation-adjusted to 2012 currency, and discounted at a rate of 3% over 5 years to arrive at an average hospitalization cost of US\$33.40. Similarly, for outpatient visits

we equally weighted health centers with and without beds, primary health care services, and secondary health care services with discounting at a rate of 3% over 5 years to arrive at an average outpatient visit cost of US\$2.13. We assumed children treated with home-care did not contribute to costs from the health care system perspective.

Model Outputs

Effects—The effects of interest were the number of deaths averted as well as health care costs averted due to reduced hospitalizations and outpatient visits. The impact of the vaccination program was also expressed in terms of DALYs averted. DALYs are the sum of years of life lost due to premature death and years lived with a disability. Age-weights ($K=1, \beta=0.04$) and an annual discount rate of 3% were employed. The disability weight for RVGE was set as the value for severe diarrhea (0.281) with an average duration of 7 days [37,38]. For modeling purposes, RVGE was assumed to occur at 13 months of age, the average age of infection for children in India, and life expectancy was based on life tables for Pakistan [25,39]. One death was weighted at approximately 33.1 DALYs discounted and 67 DALYs undiscounted.

Cost-effectiveness—We tabulated incremental costs and effects to calculate ICERs comparing a national vaccination program to the current vaccine coverage rate. ICERs were reported as both incremental cost per DALY averted as well as incremental cost per life saved. Incremental costs were determined by summing the costs associated with vaccination and anticipated costs of medical treatment under the national vaccination program and subtracting the same costs under the current program. The medical cost savings due to vaccine-prevented cases was also reported separately. WHO thresholds for cost-effectiveness in terms of cost per DALY were used as the standard of comparison [40]. An ICER between one and three times the country's gross domestic product (GDP) per capita is considered cost-effective while an ICER less than the country's GDP per capita is considered highly cost-effective. A league table is also developed for comparison.

Sensitivity analysis—We performed one-way sensitivity and extreme value analyses to test robustness and identify the most important variables influencing cost-effectiveness of the national program. Each base-case model input was varied independently according to the upper and lower limits from the relevant literature (Tables 1 and 2). The ranges used for hospitalization rates, vaccine efficacy, and vaccination costs were based on the relevant studies [5,12,22,33,34]. We chose a range of 0.50 to 1.00 for cumulative incidence of RVGE by 5 years of age because it is well established that most unvaccinated children will be infected with rotavirus during the first 5 years of life [30]. The case-fatality ratio for RVGE varies drastically between high-income and developing countries. We varied our estimate for Pakistan to cover the full range of case-fatality ratios from 8% for Guinea-Bissau to 0.07% for high-income European countries [41,42]. This simulates the potential effect a decreasing case-fatality ratio in future years in Pakistan may have on the ICER. Medical treatment costs were varied by $\pm 25\%$ from the base-case estimates with “high” treatment costs referring to $+25\%$ of both hospitalization and outpatient visit costs and “low” treatment costs referring to -25% of the same. We also varied discounting rates separately for costs and DALYs from 0% to 10% to assess the impact of discounting on the ICER.

Results

Base Case

The decision tree model (Figure 1) was populated with disease parameters from Table 1 and cost inputs from Table 2 to calculate the impact on the Pakistani health care system under the base case. For a yearly birth cohort of 4.8 million children in Pakistan followed for 5

years, implementing a national rotavirus vaccination program would prevent 1.2 million cases of RVGE, 43,000 hospitalizations, 93,000 outpatient visits, and 6,700 deaths (Table 3). This is 40% of the burden of RVGE in Pakistan, and roughly 223,000 total DALYs or 4.7 DALYS per 100 children would be averted. The medical cost savings would amount to US\$1.4 million in hospitalization and US\$200,000 in outpatient visit costs. Assuming a current 6% coverage rate, increasing rotavirus vaccination coverage to 85% would cost US\$35 million or a net US\$33.3 million after factoring in cost savings from reduced health care utilization. This corresponds to an incremental cost of US\$8.83 per fully vaccinated child under the new program. The ICERs under base case parameters are US\$4,972 per death averted and US\$149.50 per DALY averted. The ICER of US\$149.50 per DALY averted compares favorably with the WHO thresholds for cost-effectiveness falling in the highly cost-effective range based on Pakistan's GDP per capita of US\$1,182 in 2011 [43]. A league table shows rotavirus vaccination also compares favorably with cost-effectiveness analyses of other interventions in Pakistan (Table 4) [44–47].

Sensitivity analysis

One-way sensitivity analysis revealed several individual parameters that significantly affected the ICER. Notably, and as expected, varying the case-fatality ratio over the full range observed in developing and high-income countries had a great impact on the ICER (Figure 2). The lower limit of 0.07% from high-income European countries increased the ICER over 7-fold but the value (US\$1,147 per DALY averted) was still comparable to Pakistan's GDP per capita, and a threshold case-fatality ratio of 0.0679% was calculated using GDP per capita as the upper ICER limit [43]. A more reasonable reduction in case-fatality ratio of 25% resulted in an ICER of US\$199.02 per DALY averted (33% increase). Discounting DALYs also had a notable impact on the ICER increasing it 3.5-fold at a rate of 10% and decreasing it by half at a rate of 0%. Discounting costs had a negligible impact with a <1% change.

The lower end of the 95% confidence interval for vaccine efficacy increased the ICER by 122% (US\$332.29) while the higher end decreased it by 28% (US\$107.28). Vaccine price was also important with a price of US\$7.50 and US\$1.00 resulting in a 52% increase (US\$227.89) and 84% decrease (US\$24.08) in ICER, respectively. A threshold vaccine price was calculated at \$34.74 (total vaccination cost per child of \$64.34). Varying the cumulative incidence of RVGE decreased ICER by 35% (US\$96.67) when assuming all children would experience RVGE and increased ICER by 34% (US\$200.61) when assuming only half would experience RVGE. Varying treatment costs and hospitalization rates exerted a negligible impact on the ICER (~1%). Lastly, extreme case analyses showed the ICER ranged from US\$889.32 to US\$6.32 when the four major factors (case-fatality ratio (+/- 25%), vaccine efficacy, vaccine price, and cumulative incidence) were varied according to their respective bounds.

Discussion

The health and economic burden due to RVGE in Pakistan is substantial, and based on available data, we show about 40% of this burden could be prevented with a new national rotavirus vaccination program. Our conservative modeling approach assumes a low estimate for number of RVGE deaths under the current program at ~17,000 while some epidemiologic estimates range up to double this number [2–4]. Even so, base case analysis predicts a vaccination program would prevent 1.2 million cases of RVGE, 93,000 outpatient visits, 43,000 hospitalizations, and 6,700 deaths by 5 years of age for children born in given year in Pakistan at an incremental cost of US\$149.50 per DALY averted or US\$4,972 per death averted. These values are the same for annual events prevented in the country assuming five sequential equally sized birth cohorts.

From a health care system perspective, the costs for implementing a new vaccination program (~US\$35 million) are much greater than the savings from reduced medical treatment costs (~US\$1.6 million). Sensitivity analysis showed the ICER was most influenced by changes in the case-fatality ratio for RVGE, vaccine efficacy, vaccination costs, and cumulative incidence of RVGE. However, no scenario on one-way analysis resulted in an ICER greater than the GDP per capita of Pakistan, and the only situation approaching this threshold would be a reduction in lethality of RVGE in Pakistan to that of high-income European countries [42]. A vaccination program, and other health care improvements, will hopefully begin a trend to reduce the case-fatality ratio, but a significant change in the short-term is unlikely. A number of factors such as age of infection and malnutrition contribute to geographic variation in case-fatality ratios for infectious disease [48]. Therefore, cost of vaccination and the reduced efficacy of rotavirus vaccination in low-income countries are major players driving the ICER, and further insight into vaccine performance in these countries is needed [22]. The reduction in vaccine price negotiated by GAVI and their co-financing policy, requiring countries to co-finance a portion of the costs for requested vaccines based on income, will be key components going forward [17]. Pakistan, although eligible, has yet to submit a rotavirus vaccine application, but the implementation of the pneumococcal vaccine in 2012 with GAVI support may make tackling rotavirus the next logical step [19].

The results of the present analysis are comparable to cost-effectiveness studies in India reporting ICERs of \$165-\$200 per DALY averted for similar vaccine prices (~\$7) [21,22]. Podewils et al (2005) estimated ICERs of \$212, \$434, and \$1653 (in 2002 US\$) per DALY averted for low, middle, and high-income Asian countries at \$20/vaccine course [7]. Only one unpublished study has presented preliminary results on the impact and cost-effectiveness of rotavirus vaccination, specifically RotaTeq®, in Pakistan [23]. Despite differences in methods to assess vaccine program costs, the discussion paper reports an ICER of \$201 per DALY averted and 5,700 deaths prevented annually, which is comparable to our estimate of US\$149.50 per DALY averted and 6,700 deaths prevented. From the health care system perspective, rotavirus vaccination would be a cost-effective intervention to reduce the health burden of RVGE in Pakistan. Hospitalization costs, in particular, may be substantial when paid out-of-pocket. We expect the ICER would be even more cost-effective from a societal perspective, but country-specific data to assess broader societal benefits were not available. Health equity considerations for decision-makers might make it more effective to immunize poorer children in the country first since they may harbor a larger burden of disease.

There are several limitations to the present analysis. Firstly, as mentioned, data to adopt a societal perspective were not readily available. Second, most parameters were estimated based on data specific to Pakistan, but outpatient visit rates were based on estimates for India, and current vaccine coverage rate was based on the EMR according to WHO [4,20,31]. Similarly, the age of infection parameter (13 months) may overestimate the impact of vaccination because cases may occur before the age of the second Rotarix® dose. Third, vaccine efficacy is based on a study of RotaTeq® in developing countries in Asia, which we believe is a good estimate for Pakistan, but the actual efficacy of Rotarix® in Karachi has yet to be reported [15,16]. Lastly, we have simplified some concepts related to immunity. Although natural infection confers protection against subsequent infections, the rate is not reduced to zero, and recurrent infections may occur [49]. Also, similar to the majority of rotavirus vaccination model analyses, we did not factor in the effects of herd immunity [21]. Both of these assumptions work to overestimate the ICER and lead to more conservative results from our analysis.

Conclusions

Based on our results, a national rotavirus vaccination program in Pakistan would be a cost-effective intervention to reduce the economic and health burden of RVGE for children <5 years of age. After India, Pakistan accounts for the second highest number of RVGE deaths in Asia but has received much less attention in terms of disease surveillance and cost analyses for how it impacts the health care system. A combination of studies on vaccine efficacy, surveillance, and cost will be vital as Pakistan considers implementing a national vaccination program in line with WHO recommendations by utilizing support from GAVI.

Acknowledgments

This project was supported, in part, by the Predoctoral Clinical Research Training Program and the Johns Hopkins Institute for Clinical and Translational Research.”

Abbreviations and Acronyms

DALYs	disability-adjusted life-years
DPT3	final dose of diphtheria, pertussis, and tetanus vaccination
EMR	Eastern Mediterranean region
GAVI	Global Alliance for Vaccines and Immunisation
GDP	gross domestic product
ICER	incremental cost-effectiveness ratio
PATH	Program for Appropriate Technology in Health
RVGE	rotavirus gastroenteritis
WHO	World Health Organization

References

1. Bryce J, Boschi-Pinto C, Shibuya K, Black RE. WHO Child Health Epidemiology Reference Group. WHO estimates of the causes of death in children. *Lancet*. 2005; 365:1147–52. [PubMed: 15794969]
2. Walker CL, Rudan I, Liu L, Nair H, Theodoratou E, Bhutta ZA, et al. Global burden of childhood pneumonia and diarrhoea. *Lancet*. 2013; 20:381:1405–16.
3. Tate JE, Burton AH, Boschi-Pinto C, Steele AD, Duque J, Parashar UD, et al. 2008 estimate of worldwide rotavirus-associated mortality in children younger than 5 years before the introduction of universal rotavirus vaccination programmes: a systematic review and meta-analysis. *Lancet Infect Dis*. 2012; 12:136–141. [PubMed: 22030330]
4. Kawai K, O'Brien MA, Goveia MG, Mast TC, El Khoury AC. Burden of rotavirus gastroenteritis and distribution of rotavirus strains in Asia: a systematic review. *Vaccine*. 2012; 30:1244–54. [PubMed: 22212128]
5. Khattak, TA.; Ali, S.; Safdar, CA.; Aslam, MS. [Accessed 31 January 2013] Frequency of rotavirus infection in children with acute diarrhea; Pakistan Armed Forces Medical Journal. 2011. p. 1<http://www.pafmj.org/showdetails.php?id=427&t=o>
6. Khan ZT, Hayat A, Asim S, Ehsan IA, Piracha UG, Javed I, et al. Burden of rotavirus gastroenteritis in children less than 5 years of age in Rawalpindi, Pakistan. *J Rawal Med Coll*. 2006; 10:61–5.
7. Podewils LJ, Antil L, Hummelman E, Bresee J, Parashar UD, Rheingans R. Projected cost-effectiveness of rotavirus vaccination for children in Asia. *J Infect Dis*. 2005; 192:S133–145. [PubMed: 16088797]

8. Kim SY, Sweet S, Slichter D, Goldie SJ. Health and economic impact of rotavirus vaccination in GAVI-eligible countries. *BMC Public Health*. 2010; 10:253. [PubMed: 20470426]
9. Parashar UD, Burton A, Lanata C, Boschi-Pinto C, Shibuya K, Steele D, et al. Global mortality associated with rotavirus disease among children in 2004. *J Infect Dis*. 2009; 200:S9–S15. [PubMed: 19817620]
10. World Health Organization. Rotavirus vaccines: an update. *Wkly Epidemiol Rec*. 2009; 84:533–540. [PubMed: 20034143]
11. Ruiz-Palacios GM, Pérez-Schael I, Velázquez FR, Abate H, Breuer T, Clemens SC, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *N Engl J Med*. 2006; 354(1):11–22. [PubMed: 16394298]
12. Vesikari T, Matson DO, Dennehy P, Van Damme P, Santosham M, Rodriguez Z, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N Engl J Med*. 2006; 354(1):23–33. [PubMed: 16394299]
13. Soares-Weiser K, Macle hose H, Bergman H, Ben-Aharon I, Nagpal S, Goldberg E, et al. Vaccines for preventing rotavirus diarrhoea: vaccines in use. *Cochrane Database Syst Rev*. 2012; 11:CD008521. [PubMed: 23152260]
14. Phua KB, Lim FS, Lau YL, Nelson EA, Huang LM, Quak SH, et al. Safety and efficacy of human rotavirus vaccine during the first 2 years of life in Asian infants: Randomised, double-blind, controlled study. *Vaccine*. 2009; 27:5936–5941. [PubMed: 19679216]
15. Zaman K, Dang DA, Victor JC, Shin S, Yunus M, Dallas MJ, et al. Efficacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in Asia: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2010; 376:615–623. [PubMed: 20692031]
16. [Accessed 31 January 2013] NCT01199874 Immunogenicity of Rotavirus Vaccine. <http://clinicaltrials.gov/ct2/show/NCT01199874>
17. GAVI Alliance secures lower price for rotavirus vaccine. GAVI Alliance; <http://www.gavialliance.org/library/news/press-releases/2012/gavi-secures-lower-price-rotavirus-vaccine/> [Accessed 31 January 2013]
18. Plosker GL. Pharmacoeconomic spotlight on rotavirus vaccine RIX4414 (Rotarix™) in the prevention of rotavirus gastroenteritis in developing countries. *Paediatr Drugs*. 2012; 14:429–33. [PubMed: 23013458]
19. Rotavirus vaccine support. GAVI Alliance; <http://www.gavialliance.org/support/nvs/rotavirus/> [Accessed 11 March 2013]
20. Tate JE, Chitambar S, Esposito DH, Sarkar R, Gladstone B, Ramani S, et al. Disease and economic burden of rotavirus diarrhoea in India. *Vaccine*. 2009; 27:F18–24. [PubMed: 19931713]
21. Rose J, Hawthorn RL, Watts B, Singer ME. Public health impact and cost effectiveness of mass vaccination with live attenuated human rotavirus vaccine (RIX4414) in India: model based analysis. *BMJ*. 2009; 339:b3653. [PubMed: 19783581]
22. Esposito DH, Tate JE, Kang G, Parashar UD. Projected impact and cost-effectiveness of a rotavirus vaccination program in India, 2008. *Clin Infect Dis*. 2011; 52:171–7. [PubMed: 21288839]
23. Brenzel, L.; Sanderson, C.; Galayda, V.; Masud, T.; ul Hap, I. HNP Discussion Paper. World Bank; Cost-effectiveness and Financial Consequences of New Vaccine Introduction in Pakistan. <http://siteresources.worldbank.org/HEALTHNUTRITIONANDPOPULATION/Resources/281627-1095698140167/VaccineIntroPakistan.pdf>. Published online October 2011 [Accessed February 24, 2013]
24. World Population Prospects: The 2010 Revision. United Nations; 2011.
25. [Accessed 1 March 2013] WHO Member States Life Tables. Global Health Observatory. 2009. http://www.who.int/healthinfo/statistics/mortality_life_tables/en/
26. Qazi R, Sultana S, Sundar S, Warraich H, un-Nisa T, Rais A, et al. Population-based surveillance for severe rotavirus gastroenteritis in children in Karachi, Pakistan. *Vaccine*. 2009; 27:F25–30. [PubMed: 19931714]

27. Banerjee I, Ramani S, Primrose B, Moses P, Iturriza-Gomara M, Gray JJ, et al. Comparative study of the epidemiology of rotavirus in children from a community-based birth cohort and a hospital in South India. *J Clin Microbiol.* 2006; 44:2468–74. [PubMed: 16825366]
28. Kosek M, Bern C, Guerrant RL. The global burden of diarrhoeal disease, as estimated from studies published between 1992 and 2000. *Bull World Health Organ.* 2003; 81:197–204. [PubMed: 12764516]
29. 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. [PubMed: 12737740]
30. O’Ryan M, Linhares AC. Update on Rotarix: an oral human rotavirus vaccine. *Expert Rev Vaccines.* 2009; 8:1627–41. [PubMed: 19943758]
31. Global Routine Vaccination Coverage, 2011. *MMWR.* 2012; 61:883–885. [PubMed: 23114256]
32. WHO. Immunization profile—Pakistan. Geneva: WHO; 2010. http://apps.who.int/immunization_monitoring/en/globalsummary/countryprofileselect.cfm [Accessed 1 March 2013]
33. de Oliveira LH, Danovaro-Holliday MC, Matus CR, Andrus JK. Rotavirus vaccine introduction in the Americas: progress and lessons learned. *Expert Rev Vaccines.* 2008; 7:345–53. [PubMed: 18393604]
34. Wolfson LJ, Gasse F, Lee-Martin SP, Lydon P, Magan A, Tibouti A, et al. Estimating the costs of achieving the WHO-UNICEF Global Immunization Vision and Strategy, 2006–2015. *Bull World Health Organ.* 2008; 86:27–39. [PubMed: 18235887]
35. [Accessed 31 January 2013] WHO-CHOICE (Choosing Interventions that are Cost-Effective) health care services unit cost database. http://www.who.int/choice/country/country_specific/en/index.html
36. Wildi-Runge S, Allemann S, Schaad UB, Heininger U. A 4-year study on clinical characteristics of children hospitalized with rotavirus gastroenteritis. *Eur J Pediatr.* 2009; 168:1343–8. [PubMed: 19205732]
37. Salomon JA, Vos T, Hogan DR, Gagnon M, Naghavi M, Mokdad A, et al. Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. *Lancet.* 2012; 380:2129–43. [PubMed: 23245605]
38. Erdo an O, Tanyeri B, Torun E, Gönüllü E, Arslan H, Erenberk U, et al. The comparison of the efficacy of two different probiotics in rotavirus gastroenteritis in children. *J Trop Med.* 2012; 2012:787240. [PubMed: 22778754]
39. Kang G, Arora R, Chitambar SD, Deshpande J, Gupte MD, Kulkarni M, et al. Multicenter, hospitalbased surveillance of rotavirus disease and strains among Indian children aged <5 Years. *J Infect Dis.* 2009; 200:S147–53. [PubMed: 19817593]
40. Tan-Torres Edejer, T.; Baltussen, R.; Adam, T.; Hutubessy, R.; Acharya, A.; Evans, DB., et al. Making choices in health: WHO guide to cost-effectiveness analysis. Geneva: World Health Organization; 2003.
41. Rodrigues A, de Carvalho M, Monteiro S, Mikkelsen CS, Aaby P, Molbak K, et al. Hospital surveillance of rotavirus infection and nosocomial transmission of rotavirus disease among children in Guinea-Bissau. *Pediatr Infect Dis J.* 2007; 26:233–7. [PubMed: 17484220]
42. Soriano-Gabarró M, Mrukowicz J, Vesikari T, Verstraeten T. Burden of rotavirus disease in European Union countries. *Pediatr Infect Dis J.* 2006; 25:S7–S11. [PubMed: 16397431]
43. National Accounts Main Aggregates Database. United Nations; <http://unstats.un.org/unsd/snaama/selbasicFast.asp> [Accessed 31 January 2013]
44. Cook J, Jeuland M, Whittington D, Poulos C, Clemens J, Sur D, et al. The cost-effectiveness of typhoid Vi vaccination programs: calculations for four urban sites in four Asian countries. *Vaccine.* 2008; 26:6305–16. [PubMed: 18835415]
45. Griffiths UK, Wolfson LJ, Quddus A, Younus M, Hafiz RA. Incremental cost-effectiveness of supplementary immunization activities to prevent neonatal tetanus in Pakistan. *Bull World Health Organ.* 2004; 82:643–51. [PubMed: 15628201]
46. Khan MA, Walley JD, Witter SN, Imran A, Safdar N. Costs and cost-effectiveness of different DOT strategies for the treatment of tuberculosis in Pakistan. *Directly Observed Treatment. Health Policy Plan.* 2002; 17:178–86. [PubMed: 12000778]

47. Jafar TH, Islam M, Bux R, Poulter N, Hatcher J, Chaturvedi N, et al. Cost-effectiveness of community-based strategies for blood pressure control in a low-income developing country: findings from a cluster-randomized, factorial-controlled trial. *Circulation*. 2011; 124:1615–25. [PubMed: 21931077]
48. Wolfson LJ, Grais RF, Luquero FJ, Birmingham ME, Strebel PM. Estimates of measles case fatality ratios: a comprehensive review of community-based studies. *Int J Epidemiol*. 2009; 38:192–205. [PubMed: 19188207]
49. Velázquez FR, Matson DO, Calva JJ, Guerrero L, Morrow AL, Carter-Campbell S, et al. Rotavirus infections in infants as protection against subsequent infections. *N Engl J Med*. 1996; 335:1022–8. [PubMed: 8793926]

Highlights

- We model a national rotavirus vaccination program in Pakistan.
- An annual birth cohort is followed through 5 years of age.
- Vaccination would prevent 1.2 million cases of <5 year old gastroenteritis.
- The incremental cost-effectiveness ratio was US\$149.50 per DALY averted.
- The program would avert 6,700 deaths and cost US\$4,972 per death averted.

Figure 1.
National vaccination program arm of the decision tree model.

Figure 2.

Tornado diagram assessing the impact of changes in disease, vaccine, and cost parameters on the incremental cost-effectiveness ratio (ICER) for a national rotavirus vaccination program in Pakistan, 2012.

Table 1

Base-case disease-related parameters and vaccine inputs with upper and lower limits for sensitivity analyses to assess the cost-effectiveness of a national rotavirus vaccination program in Pakistan, 2012.

Parameter	Base-case Value	Low	High	Source
Birth cohort (2012)	4778735	-	-	[24]
Life expectancy at 1 year of age	67.2	-	-	[25]
Disease inputs				
<i>RVGE annual infection rate^a</i>	195.5	147.2	243.9	calculated from [4,20,26–29]
<i>Hospitalization rate^a</i>	6.9	5.7	8.1	[4,26]
<i>Outpatient rate^{ab}</i>	15.0	11.3	18.8	[4,20]
<i>Home-care rate^{ab}</i>	173.6	130.2	217.0	calculated from [27–29]
<i>RVGE cumulative incidence by 5 years</i>	0.663	0.5	1	calculated ^c
<i>Case-Fatality Ratio</i>	0.0055	-	-	calculated ^d
<i>Number of deaths by 5 years^a</i>	3.7	2.8	5.5	calculated ^{cd}
Vaccine inputs				
<i>Efficacy</i>	48.3%	22.3%	66.1%	[15]
<i>Current rotavirus coverage</i>	6.0%	-	-	[31]
<i>DPT3 coverage</i>	85.0%	-	-	[32]
Hospital length of stay (days)	4	3	5	[20,36]

^a Rates are per 1,000 children < 5 years of age

^b Varied +/- 25%

^c from RVGE annual infection rate; low value based on assumption and high based on [29]

^d from [4,24] and RVGE annual infection rate

Table 2

Base-case rotavirus vaccination program costs and rotavirus gastroenteritis medical treatment costs in Pakistan, 2012, with relevant upper and lower limits for sensitivity analyses.

Parameter	Base-case Value	Low	High	Source
Vaccination costs^a				
<i>Vaccine</i>	5.00	1.00	7.50	[17,22,33,34]
<i>Scaling Up</i>	3.34	0.67	5.00	[34]
<i>Cold chain</i>	16.0%	-	-	[34]
<i>Training/supervision</i>	6.0%	-	-	[34]
<i>Vehicles/transport</i>	20.0%	-	-	[34]
<i>Social mobilization</i>	13.0%	-	-	[34]
<i>Surveillance, M&E</i>	18.0%	-	-	[34]
<i>Waste management</i>	1.0%	-	-	[34]
<i>Personnel</i>	22.0%	-	-	[34]
<i>Overhead</i>	4.0%	-	-	[34]
<i>Wastage Rate</i>	10.0%	-	-	assumption
<i>Total cost per child</i>	9.26	1.85	13.89	calculated ^c
Medical treatment costs^a				
<i>Hospitalization (4-day stay)^b</i>	33.40	25.05	41.75	[35]
<i>Outpatient visit^b</i>	2.13	1.60	2.66	[35]

^a All costs reported in 2012 US\$

^b Varied +/- 25%

^c from vaccine cost, scaling up cost, and wastage rate of 10%

Table 3

Expected rotavirus-related clinical events and associated costs with calculation of an incremental cost-effectiveness ratio (ICER) for a national rotavirus vaccination program in Pakistan, 2012.

Variable	Current Program	National Vaccination Program	Incremental events or cost (averted)	Incremental events or cost (incurred)
Hospitalizations				
Outpatient Visits	108,582	65,914	42,668	-
Costs^a	236,047	143,291	92,757	-
Vaccination	2,655,384	37,617,936	-	34,962,553
Hospitalizations				
Outpatient Visits	3,626,892	2,201,676	1,425,216	-
Total	502,442	305,003	197,439	-
Effects	6,784,718	40,124,616	-	33,339,898
Deaths	17,066	10,359	6,706	-
DALYs lost	567,517	344,507	223,010	-
ICER (per death averted)^a	-	4972		
ICER (per DALY averted)^a	-	149.50		

^a All costs reported in 2012 US\$

Table 4

League table comparing a national rotavirus vaccination program in Pakistan, 2012, to estimates of cost-effectiveness for other interventions studied in the country (inflated according to Pakistani inflation index and reported in US\$2012).

Topic of Study	Interventions	Base-Case Cost-Effectiveness	Source
Typhoid Vi vaccination	1 School-based targeting school-age children	1 \$292/DALY averted	[44]
	2 School-based targeting school-age and younger children	2 \$265/DALY averted	
Supplementary tetanus immunization	1 Routine plus supplementary immunization activities	1 \$3.61/DALY averted*	[45]
Directly observed treatment strategies for tuberculosis	1 Supervision by health workers	1 \$339-\$611/case cured	[46]
	2 Supervision by family members	2 \$365/case cured	
	3 Unsupervised	3 \$323/case cured	
Community-based blood pressure control strategies	1 Home health education plus general practitioner	1 \$1548/DALY averted (\$29/mmHg reduction)	[47]
	2 Home health education only	2 Dominated	
	3 General practitioner only	3 Not reported (\$260/mmHg reduction)	
TRIVAC model	1 Haemophilus influenzae type B vaccine	1 \$22/DALY averted	[23]
	2 Pneumococcal conjugate vaccine	2 \$225/DALY averted	
	3 Rotavirus vaccine	3 \$201/DALY averted	
Rotavirus vaccination (current study)	1 National rotavirus vaccination program	1 \$149.50/DALY averted	N/A

* Not inflated according to Pakistani inflation index and exchange rate because year was not reported