

Projecting the effectiveness of RotaTeq[®] against rotavirus-related hospitalizations and deaths in six Asian countries

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Abbreviations: ED, emergency department; M/O/U, mixed, other, untypeable; REST, rotavirus efficacy and safety trial; RGE, rotavirus gastroenteritis; RV5, oral pentavalent rotavirus vaccine; WHO, world health organization

RotaTeq is an oral pentavalent rotavirus vaccine (RV5) that has shown high and consistent efficacy in preventing rotavirus gastroenteritis (RGE) in randomized clinical trials conducted mostly in industrialized countries. We projected the effectiveness of RV5 against RGE-related hospitalizations and deaths in six Asian countries by using a simple mathematical model. Model inputs included rotavirus surveillance data collected during 2006–2007 in China, 2001–2002 in Hong Kong, 2005–2007 in India, 2005–2007 in South Korea, 2005–2007 in Taiwan and 2001–2003 in Thailand; the numbers of rotavirus-related deaths in each country; and published rotavirus serotype-specific efficacy of RV5. The model projected an overall effectiveness in the region of 82% to 89% against RGE-related hospitalizations and a substantial reduction in RGE-related deaths, suggesting that RV5 could substantially reduce the burden of rotavirus disease in Asia.

Introduction

Rotavirus is the leading cause of hospitalization and death from acute gastroenteritis among infants and young children worldwide. The disease causes substantial economic burden on health systems, as well as disruption of the families of children infected by the virus.^{1,2} Globally, more than 2 million hospitalizations and an estimated 527,000 deaths in children <5 years of age are attributed to rotavirus annually.^{3,4}

Rotavirus is associated with a significant disease burden in both developed countries and lower-income countries; however, approximately 82% of rotavirus-related deaths occur in the poorest countries.^{3,5} The most recent data on global mortality associated with rotavirus disease among children show that approximately 42% of total rotavirus-associated deaths occur in Asia (including China), with India alone accounting for almost one fourth of the deaths.^{4,6} The Asian Rotavirus Surveillance Network found that about 45% of all diarrhea hospitalizations in children <5 years old are attributable to rotavirus in the 9 Asian countries and regions that participated.^{5,7}

Based on global surveillance, the 5 most prevalent genotype/serotype combinations, which account for >90% of cases of human rotavirus disease worldwide, are G1P1A[8], G2P1B[4], G3P1A[8], G4P1A[8] and G9P1A[8].⁸⁻¹⁰ However, these 5 genotype/serotype combinations were found to only contribute to 73% of rotavirus serotypes in Asia, highlighting the diversity of

rotavirus serotypes geographically.⁹ The diversity of rotavirus serotypes has important implications for implementation of an effective rotavirus vaccine, particularly in the lower-income regions of Asia where there is the greatest need for a rotavirus vaccine.⁹

Lack of efficacy and effectiveness data in Asia is one of the factors contributing to delays in introducing rotavirus vaccines into national immunization programs.⁵ Decisions to introduce a new vaccine to a previously unvaccinated region require reliable data to estimate disease burden and the potential impact of a vaccination program.⁷ Because it is not feasible to conduct clinical trials in every country, results from previously conducted studies can help to predict disease reduction in other countries, provided that the data are adjusted to account for variations in rotavirus serotype distribution.^{8,11}

RV5 (rotavirus vaccine, live, oral, pentavalent RotaTeq, Merck & Co., Inc., Whitehouse Station, New Jersey) showed high and consistent efficacy in preventing rotavirus gastroenteritis (RGE) in randomized clinical trials that were previously conducted in mostly industrialized countries.¹²⁻¹⁵ The objective of this analysis was to utilize a mathematical model to project the effectiveness of RV5 against RGE-related hospitalizations and deaths in 6 Asian countries.

Results

Projected effectiveness against RGE-related hospitalizations by country. The modeled projected effectiveness of RV5 against

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Table 1. Modeled projected effectiveness of RV5 against RGE-related hospitalizations by country

	Projected effectiveness: Base case scenario [†] (%)	Projected effectiveness: Sensitivity analysis [§] (%)
China	89	83
Hong Kong	94	93
India	82	70
South Korea	91	89
Taiwan	93	90
Thailand	86	75

[†]Base case scenario: assumes 50% efficacy against mixed and nontypeable serotypes. [§]Sensitivity analysis: assumes 0% efficacy against mixed and nontypeable serotypes. RGE, rotavirus gastroenteritis; RV5, oral pentavalent rotavirus vaccine.

RGE-related hospitalizations for each of the 6 Asian countries is shown in Table 1.¹⁶⁻²¹ We estimated the projected effectiveness of RV5 by country to range between 70% and 94%.

Projected effectiveness against RGE-related hospitalizations: regional projections. For the overall region, we estimated the overall effectiveness in the six Asian countries to be between 82% and 89% (Table 2).¹²

Projected reduction in RGE-related deaths. The projected annual reduction in RGE-related deaths attributable to vaccination with RV5 ranged from 98,438 to 113,262 for China, India and Thailand combined, assuming 90% vaccine coverage (Table 3).²²

Discussion

The method applied in this study projected the potential effectiveness of RV5 against rotavirus-related hospitalizations and deaths in Asia. We conducted a sensitivity analysis to account for variations in efficacy against mixed and nontypeable serotypes that may also affect overall vaccine effectiveness.

After weighting serotype-specific efficacy data by serotype prevalence in the 6 Asian countries included in these analyses, this model suggested that RV5 will be 70% to 94% effective against RGE-related hospitalizations in major Asian populations, which included China, Hong Kong, India, South Korea, Taiwan and Thailand. Overall we projected 82% to 89% effectiveness of the vaccine in the region. The model also suggested that RV5 can prevent a substantial number of RGE-related deaths in Asia, with an estimated reduction in deaths of 98,438 to 113,262 in the combined countries included in this analysis.

A study that projected the potential impact of vaccination with RV5 on hospitalizations following the introduction of RV5 in 2006 determined that 45% of AGE-related hospitalizations could be prevented by vaccination in the US.²³ A recent analysis of hospitalization rates for acute gastroenteritis in 18 US states determined that hospitalization rates in 2007 and 2008 were 16% and 45% lower, respectively, compared to the pre-RV5 vaccination period from 2000 to 2006.²⁴ Similar to our analysis, the projections from the US used REST data to assume vaccine efficacy; however, the model for the US used a regression analysis approach and relied on previous estimates of hospitalizations,

efficacy assumptions for 1 and 2 vaccine doses and increasing vaccine coverage rates over time.²³ We opted to use a simple, previously validated mathematical model for this analysis.¹¹

A recent randomized clinical trial of RV5 in Vietnam, a country with resource-constrained medical care, found that the efficacy against severe RGE was 68.1%.²⁵ On the other hand, an effectiveness study in the US showed that RV5 prevented 100% of RGE-related hospitalization and ED visits and 100% of their related costs.²⁶ These results may be indicative of the potential effectiveness of RV5 in certain regions in Asia, depending on how similar their populations and their medical care resources are to those of Vietnam or the US. Overall, the modeled effectiveness for Asia is within the published estimates of efficacy and effectiveness in Vietnam and the US.

Our projected results were based on the efficacy assumed in children who would receive RV5. However, the potential exists for an indirect benefit to the population of unvaccinated children through herd immunity, as was suggested in the US.²⁴ We did not examine the extent to which this could impact vaccine effectiveness in Asia in this analysis. In addition, although we have information available by serotype from the REST trial¹² and for all stool samples that were rotavirus enzyme immunoassay-positive (which include mixed and nontypeable serotypes), we do not have a direct efficacy estimate for only the mixed and nontypeable serotypes. The point estimates for the efficacy against rotavirus disease with any grade of severity and against any sample that was enzyme immunoassay-positive, do not vary substantially.¹² Based on this information, we opted to utilize a conservative estimate of 50% efficacy against mixed and non-typeable serotype for the calculation of our base-case scenario for projected effectiveness.

A limitation to this analysis is that the serotype surveillance data may not be representative of all children <5 years of age in each of the 6 countries evaluated because the studies that we used to inform our modeling sampled data from specific regions within each country (some hospital-based and some community-based data), with some countries having more widespread sampling than others (Table 4). Countries with more widespread sampling from different regional sites were Hong Kong, India and South Korea, whereas studies from China, Taiwan and Thailand collected samples from fewer regional sites and therefore these data may not be geographically representative of the national serotype distribution.

Moreover, studies providing model inputs were conducted several years prior to this analysis and this may affect the accuracy of the results. For instance, data from Hong Kong and Thailand are more than 10 years old, and the data from China, India, South Korea and Taiwan are from approximately 5 to 6 years prior to this analysis. It is also possible that the different assays used for detection and testing of rotavirus antigen and G typing across studies could have influenced rotavirus detection rates.

Our projections related to the number of deaths prevented depended on the projected effectiveness of the vaccine. This also would depend on the population tested and on the availability and location of surveillance data, which may change over time. These projections were based on a compilation of mortality data from the World Health Organization (WHO), which were last published in 2004. Therefore, these data, which are now >6 years

Table 2. Modeled projected effectiveness of RV5 against RGE-related hospitalizations in a group of 6 Asian countries: regional projection

	Proportion of total serotypes in 6 Asian countries (A)	Serotype-specific efficacy of RV5 ¹² (B)	Attributable effectiveness: Base case scenario [†] (%)	Attributable effectiveness: Sensitivity analysis [§] (%)
G1	0.32	0.95	30	30
G2	0.14	0.88	12	12
G3	0.22	0.93	20	20
G4	0.04	0.89	4	4
G9	0.14	1.0	14	14
G12	0.02	1.0	2	2
M/O/U ^{†§}	0.13	-	7	0
Overall weighted effectiveness in the region			89	82

[†]Base case scenario: assumes 50% efficacy against mixed and nontypeable serotypes. [§]Sensitivity analysis: assumes 0% efficacy against mixed and nontypeable serotypes. M/O/U, mixed, other, untypeable; RGE, rotavirus gastroenteritis; RV5, oral pentavalent rotavirus vaccine.

old, could be somewhat out of date as the basis for projecting the number of deaths prevented by vaccination in 2011 and beyond. Data on rotavirus-related deaths were not available for Taiwan, Hong Kong and South Korea; therefore, the projections did not account for potential additional reductions in deaths. Although all models have limitations and given the limitations noted in this analysis, this information derived from region-specific epidemiology and disease burden data coupled with vaccine efficacy data may be valuable in helping policy makers in Asia make decisions about the inclusion of the vaccine on the immunization schedule. A recent WHO-sponsored consultation on the use of rotavirus vaccines in Africa and Asia, concluded that “even vaccines with lesser efficacy in developing countries, compared with industrialized countries, would still lead to substantial public health benefits and would be cost-effective in saving lives in Africa and Asia.”²⁷ The group also concluded that “criteria, such as the WHO mortality strata and local epidemiology of rotavirus infection, would be appropriate measures for extrapolating the clinical data to other regions and countries.”²⁷ Thus, although in the current analysis the effectiveness of RV5 is lesser than the efficacy found in REST, vaccination with RV5 has the potential to have a substantial impact on disease burden in the developing regions of Asia.

This model showed that RV5 is expected to have effectiveness against RGE-related hospitalizations ranging between 82% and 89% and to prevent a substantial number of RGE-related deaths in Asia. The projections indicate that implementation of an effective campaign against rotavirus using RV5 can have a substantial impact on morbidity and mortality in the developed and lower-income countries of Asia. These data may help policy makers decide how to allocate resources to reduce the burden of rotavirus disease in their region.

Methods

This analysis used a previously validated mathematical efficacy projection model, which was developed to project the efficacy of a live attenuated rotavirus vaccine in India.¹¹ The Model was validated by using data from a phase II clinical trial with known rotavirus serotype distribution.

Table 3. Projected annual reduction in RGE-related deaths attributable to vaccination with RV5

	Projected effectiveness of RV5 against RGE-related hospitalizations (%)	WHO 2004 rotavirus-related deaths ²² (N)	Projected reduction in deaths (N)
China	83–89	27,349	22,700–24,341
Hong Kong	93–94	N/A	N/A
India	70–82	122,270	85,589–100,261
South Korea	89–91	N/A	N/A
Taiwan	90–93	N/A	N/A
Thailand	75–86	1,448	1,086–1,245
Total	-	151,067	109,375–125,847
Total assuming 90% vaccine coverage	-	-	98,438–113,262

N/A, not available; RGE, rotavirus gastroenteritis; RV5, oral pentavalent rotavirus vaccine; WHO, World Health Organization.

Our analysis differs from the Rose and Singer model in that we used the term “projected effectiveness” rather than “projected efficacy” to accurately reflect one of our primary objectives of this analysis, which was to project the impact of RV5 on the reduction in RGE-related hospitalizations in Asia. The current analysis adapted the Rose and Singer model to generate the weighted serotype-specific projected effectiveness of RV5 in 6 Asian countries (China, Hong Kong, India, South Korea, Taiwan and Thailand) where clinical trials evaluating efficacy have not yet been conducted.

This was calculated by summing the weighted serotype-specific efficacy in each of the 6 Asian countries using the proportion of locally prevalent serotypes based on literature reviews and known serotype-specific vaccine efficacy results from a large-scale phase III clinical trial (Rotavirus Efficacy and Safety Trial [REST]) of RV5 in infants from 11 countries (US, Finland, Germany, Belgium, Sweden, Italy, Jamaica, Costa Rica, Mexico, Puerto Rico and Guatemala).¹²

Table 4. Key model input: proportion of total rotavirus serotypes in each of the 6 Asian countries and the combined group of countries[†]

	China ¹⁶	Hong Kong ¹⁷	India ¹⁸	South Korea ¹⁹	Taiwan ²⁰	Thailand ²¹	Total [‡]
G1, %	22.4	42.6	27.7	52	41	1.0	32
G2, %	0.2	15.5	31.0	7.5	8.0	17.0	14
G3, %	63.3	30.7	0	23.0	28.0	0	22
G4, %	0	3.5	0	11.0	0	5.0	4
G9, %	2.2	5.3	10.0	0.6	18.0	55.0	14
G12, %	0	0	6.2	0.7	0	0	2.0
M/O/U, %	11.9	2.2	25.1	5.2	5.0	22.0	13

[†]Rotavirus sampling sites and testing (method for G typing specified) and dates from the individual studies of the 6 Asian countries were as follows: In China, samples were collected from 3 sentinel hospitals in mainland China and tested (multiplex seminested reverse transcription polymerase chain reaction [RT-PCR]) from January 2006 to December 2007.¹⁶ In Hong Kong, samples were collected and tested (nested RT-PCR) from a microbiology laboratory of an acute public hospital and a government virology laboratory serving various regions over 1 year, from December 2001 to November 2002.¹⁷ In India, samples were collected from 10 representative hospitals in 7 different cities and tested (RT-PCR) at 4 laboratories in different parts of India from December 2005 to November 2007.¹⁸ In South Korea, samples were collected and tested (1-step RT-PCR) from 8 hospitals located in 3 metropolitan areas and 4 provincial regions from April 2005 to March 2007.¹⁹ In Taiwan, samples were collected from 3 sentinel hospitals in northern, central, and southern Taiwan and testing (1-step real-time RT-PCR) was conducted at the Centers for Disease Control and Prevention in Taiwan from January 2005 to December 2007.¹⁹ In Thailand, samples were collected from 6 general hospitals located throughout Thailand and tested (2-step PCR) at the Thai National Institutes of Health from 2001 to 2003 and from a community-based surveillance program from September 2001 to August 2002.

[‡]Totals for each serotype are rounded to the nearest whole number. M/O/U, mixed, other, untypeable.

Projecting the effectiveness of RV5 against RGE-related hospitalizations in Asia. Published surveillance data collected from 2006 to 2007 in China,¹⁶ from 2001 to 2002 in Hong Kong,¹⁷ from 2005 to 2007 in India,¹⁸ from 2005 to 2007 in South Korea,¹⁹ from 2005 to 2007 in Taiwan,²⁰ and from 2001 to 2003 in Thailand²¹ provided the proportions of rotavirus serotypes attributable to G1, G2, G3, G4, G9 and G12 in children <5 years of age for each of the 6 Asian countries included in this model (Table 4).¹⁶⁻²¹ Published results from REST provided the baseline efficacy data of RV5 against RGE-related hospitalizations and emergency department (ED) visits for serotypes G1 (95%), G2 (88%), G3 (93%), G4 (89%), G9 (100%) and G12 (100%).¹²

To account for the unknown efficacy against mixed and nontypeable serotypes, we conducted sensitivity analyses of modeled effectiveness. The model calculated a base case scenario for projected effectiveness that assumed an efficacy of 50% against mixed and nontypeable serotypes. The sensitivity analysis for projected effectiveness reduced the efficacy against mixed and nontypeable serotypes to 0%.

We conducted calculations for projected effectiveness by country as follows: For example in China, 22.4% of total serotypes was G1. To obtain the projected effectiveness against rotavirus hospitalization, we multiplied this figure by the G1 serotype-specific efficacy of 95% that was reported in REST ($0.224 \times 0.95 = 0.213$). We did the same calculation for G2, G3, G4, G9 and G12. As stated, for mixed and nontypeable serotypes, we assumed 50% efficacy for the base case scenario.

The sum of the weighted serotype-specific data for G1, G2, G3, G4, G9, G12 and mixed and nontypeable serotypes yielded a projected effectiveness of 89% for the base case scenario. The sensitivity analysis applied the same calculation, except with an assumption of 0% efficacy against mixed and nontypeable serotypes, which yielded a projected effectiveness of 83%. Therefore, we estimated the projected effectiveness of RV5 in China to be 83% to 89%.

We used the same methodology to calculate the projected effectiveness of RV5 for Hong Kong, India, South Korea, Taiwan and Thailand. The calculations for overall regional effectiveness projections for Asia used the pooled total proportions of each serotype for the 6 regions.

Projecting the effectiveness of RV5 against RGE-related deaths in Asia. We estimated the projected reduction in RGE-related deaths by applying the projected effectiveness against RGE hospitalizations to the number of RGE-related deaths in 2004 in children <5 years of age (as estimated by the WHO) in each country, assuming vaccine coverage of 90%.^{4,22} Data on WHO estimates of RGE-related deaths in 2004 in children <5 years of age were available for China, India and Thailand.

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