Public health impact and cost effectiveness of mass vaccination with live attenuated human rotavirus vaccine (RIX4414) in India: model based analysis

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ABSTRACT

Objectives To examine the public health impact of mass vaccination with live attenuated human rotavirus vaccine (RIX4414) in a birth cohort in India, and to estimate the cost effectiveness and affordability of such a programme.

Design Decision analytical Markov model encompassing all direct medical costs. Infection risk and severity depended on age, number of previous infections, and vaccination history; probabilities of use of inpatient and outpatient health services depended on symptom severity.

Data sources Published clinical, epidemiological, and economic data. When possible, parameter estimates were based on data specific for India.

Population Simulated Indian birth cohort followed for five years.

Main outcome measures Decrease in rotavirus gastroenteritis episodes (non-severe and severe), deaths, outpatient visits, and admission to hospital; incremental cost effectiveness ratio of vaccination expressed as net cost in 2007 rupees per life year saved.

Results In the base case, vaccination prevented 28 943 (29.7%) symptomatic episodes, 6981 (38.2%) severe episodes, 164 deaths (41.0%), 7178 (33.3%) outpatient visits, and 812 (34.3%) admissions to hospital per 100 000 children. Vaccination cost 8023 rupees (about £100, €113, \$165) per life year saved, less than India's per capita gross domestic product, a common criterion for cost effectiveness. The net programme cost would be equivalent to 11.6% of the 2006-7 budget of the Indian Department of Health and Family Welfare. Model results were most sensitive to variations in access to outpatient care for those with severe symptoms. If this parameter was increased to its upper limit, the incremental cost effectiveness ratio for vaccination still fell between one and three times the per capita gross domestic product, meeting the World Health Organization's criterion for "cost effective" interventions. Uncertainty analysis indicated a 94.7% probability that vaccination would be cost effective according to a criterion of one times per capita gross domestic product per life year saved, and a 97.8%

probability that it would be cost effective according to a criterion of three times per capita gross domestic product.

Conclusions Across a wide range of assumptions, mass RIX4414 vaccination in India would probably prevent substantial morbidity and mortality at a cost per life year saved below typical thresholds of cost effectiveness. The opportunity costs of such a programme in this or similar settings, however, should be weighed up carefully.

INTRODUCTION

Rotavirus is the leading cause of severe gastroenteritis worldwide, infecting virtually every child by the age of 5. Though the incidence of infection is similar around the world and across economic strata,¹⁻⁷ the burden of mortality is borne disproportionately by the world's poorest children.^{8,9} Some 23% of the estimated 527 000 annual rotavirus deaths occur in India.¹⁰

The gastroenteritis caused by rotavirus tends to be more severe than that caused by other viral pathogens. The hallmark triad of fever, diarrhoea, and emesis can bring about rapid dehydration. Indeed, severe emesis tends to preclude the use of oral rehydration in the most severe cases.^{11,12} This fact partially explains the high rotavirus mortality in areas where access to medical care is poor. Given the minimal impact that water and sanitation measures have had on the burden of rotavirus in developing areas, there is wide agreement that effective vaccination represents the most promising prevention strategy against the disease.^{13,14}

Since 2004, two new oral rotavirus vaccines have been introduced: a human-bovine reassortant pentavalent rotavirus vaccine and a monovalent live attenuated human rotavirus vaccine. Both vaccines seem to stimulate protection comparable with the partial protection elicited by a single natural infection.¹⁵⁻¹⁷ We focused on live attenuated human rotavirus vaccine—also known as RIX4414—because of the more diverse population in which its efficacy has been tested and the fact that a full course of RIX4414 requires only two doses compared with the three required for the pentavalent vaccine.¹³

Despite the promising results generated in efficacy trials of RIX4414 in Europe and the Americas,^{15 16 18} the extent to which the vaccine will be effective in poorer Asian nations is unknown. A substantially higher proportion of strains found in these areas is genetically less similar to the vaccine strain in comparison with Western countries, where completed efficacy trials have occurred.^{19 20} Two immunogenic outer capsid proteins, VP7 and VP4, are used to classify rotaviruses into G and P serotypes, respectively. These seem to play a key (though not exclusive) role in eliciting host immune responses and have been the focus in developing existing vaccines against rotavirus. To date, epidemiological studies have identified 42 distinct strains defined by unique G-P serotype combinations.²¹ The vaccine is derived from a G1P[8] strain, believed to be the most common worldwide. Globally, just four strains (G1P[8], G3P[8], G4P[8], and G2P[4]) account for 88.5% of rotavirus diarrhoea. Only 68% of rotavirus cases in Asia, however, are attributable to these strains.²⁰

Studies of both vaccines are ongoing in several developing Asian and African countries; reporting of these data is expected to begin later in 2009.²² Based on preliminary results, the World Health Organization has recently recommended inclusion of rotavirus vaccination in these countries' national immunisation programmes,²³ paving the way for a spate of new rotavirus vaccination programmes in some of the most vulnerable areas beginning as soon as 2010.²²

Accompanying concerns about the vaccine's real world effectiveness in developing settings is a daunting set of economic challenges. The current generation of rotavirus vaccines costs substantially more than traditional childhood vaccines given in these countries.²² Even with manufacturers' commitments to tiered pricing,²⁴ achieving universal vaccination in the world's most affected areas will require substantial help from the international community.²⁵ WHO has emphasised the need for thorough examination of economic issues in the introduction of a rotavirus vaccination programme in any developing country.²⁶

Past models of rotavirus vaccination in developing Asian countries²⁷⁻²⁹ (none have been set in India) have not captured much of the complexity of rotavirus epidemiology. The model we describe here differs fundamentally in that it simulates, in a temporally explicit fashion, the sequence of events from infection to development of symptoms, use of health services, disease outcome, recovery, and reinfection for a birth cohort of heterogeneous individuals. One recent analysis used a similarly sophisticated epidemiological model to examine the impact of vaccination in Vietnam, a country with substantially lower rates of mortality from rotavirus and markedly different distributions of rotavirus strain relative to India.³⁰ In comparison with that model, we use methods allowing us to better predict shifts in the mix of inpatient and outpatient care that might result from decreased severity of symptoms among vaccinated children who become infected.

We estimated the public health impact of mass vaccination with RIX4414 for a birth cohort in India and examined the incremental cost effectiveness and affordability of such a programme.

METHODS

Model overview

We developed an individual based Markov model, which we analysed using Monte Carlo microsimulation methods with TreeAge Pro 2008 software (Williamstown, MA). The base case evaluates only direct medical costs, including those incurred by patients' families or by any public sector entity contributing toward the cost of care. In a secondary analysis from the societal perspective, we also included direct non-medical costs such as transportation expenses for patients' families and indirect costs such as foregone wages of parents caring for sick children. The model's time horizon consisted of 60 one month cycles. We assumed that administration of the vaccine would be piggybacked on the existing WHO expanded programme on immunisation and given concomitantly with other routine vaccinations, including oral polio vaccine.³¹⁻³³

Possible states of individuals in the model were well, rotavirus diarrhoea, and dead (fig 1). At the end of each cycle spent in the well state, individuals faced a risk of rotavirus infection that could be either asymptomatic or symptomatic. Those acquiring asymptomatic infection began the next stage of the model in the well state, while those acquiring symptomatic infection began the next stage in the rotavirus diarrhoea state. In this diarrhoea state, individuals experienced either severe (Vesikari score³⁴ ≥ 11) or non-severe (score < 11) symptoms, the probabilities of which were based on their history of previous infections and vaccination. Symptom severity influenced the likelihood that an individual would receive inpatient, outpatient, or home treatment. At the end of a cycle spent in the diarrhoea state, survivors could either transition to the well state or develop a new symptomatic rotavirus infection, re-entering the diarrhoea state for another cycle.

Each possible chance event in the model was associated with an evidence based probability and the exact sequence and timing of events experienced by a given individual were the results of random number draws occurring at each juncture of the model. We aggregated the experience of 200 000 simulated individuals to predict the expected number of rotavirus infections (up to three per individual); their severity; the number of admissions to hospital, clinic visits, and home treatments for rotavirus gastroenteritis; the total cost of rotavirus related use; and the number of rotavirus related deaths under two different strategies: universal vaccination with RIX4414 at the recommended ages of 2 and 4 months³⁵ versus no vaccination (the status quo).

Incidence, morbidity, and mortality

Rates of rotavirus infection (but not outcomes of infection) are similar worldwide.^{8 36} Accordingly, we chose to base parameters related to infection risk on a

Fig 1 | Schematic of Markov model. Each individual begins life in the well state and thereafter resides in either the well, symptomatic, or dead state during each one month cycle for a total of 60 cycles. Individuals can receive doses of live attenuated human rotavirus vaccine at months two and four only. At the end of each cycle, each individual's risk for rotavirus infection is determined by number of vaccine doses received, time since receiving most recent dose, and number of previous rotavirus infections. If infected, individuals might develop symptoms in which case they will begin the next cycle in symptomatic state. In symptomatic state, gastroenteritis can be non-severe (Vesikari score <11) or severe (Vesikari score ≥ 11). Symptom severity dictates probability that each individual will receive hospital care, outpatient care, or no formal treatment. Those with severe disease who receive no formal treatment are at risk for death. Each month, there is an age dependent background risk of death from non-rotavirus causes (not shown). M in circle represents Markov node; branches emanating from a Markov node represent possible states of being. Open circle represents chance node; branches emanating to right represent possible outcomes of probabilistic process. Left pointing triangle designates terminal node; here, the state in which next cycle should begin is given. [+] signifies that portion of tree has been collapsed because it replicates portion already shown. "Get dose" signifies contingency that individual receives dose of vaccine, "no dose" signifies that they do not

rigorous prospective study of rotavirus incidence in a cohort of 200 Mexican infants followed from birth to 24 months of age.² Velazquez and colleagues² closely monitored children for rotavirus infection with serial stool assays and serum immunoassays (a similar study done in west Africa did not use serum immunoassays and thus probably failed to capture a non-trivial number of infections³⁷). Investigators recorded the time to first and subsequent infections and the severity of each infection (including asymptomatic) for each individual during follow-up. Based on the reported cumulative incidence of the *n*th infection at 6, 12, and 24 month intervals (table 1), we calculated one month hazard rates and converted these to one month transition probabilities corresponding to the appropriate age interval and number of previous infections. Hazard rates for the 12 to 24 month interval formed the basis for transition probability estimates for the *n*th infection after the 24th cycle. Figure 2 shows the cumulative incidence of first to the third rotavirus infection produced by our model for children who were not vaccinated. Data from the same cohort also served as the basis for estimates of probabilities that those infected would experience no symptoms, non-severe symptoms, or severe symptoms with first to the third infections. Severity (or lack) of symptoms did not influence the degree of natural protection conferred against

subsequent rotavirus re-infection.¹⁷ We varied parameters related to disease burden extensively in sensitivity analyses.

Consistent with recent experience in India,^{11,38} individuals receiving formal medical attention (hospital, clinic, or emergency department care) faced no risk of death from rotavirus, irrespective of the severity of gastroenteritis. We determined the model parameter representing probability of death for those with severe rotavirus gastroenteritis who did not receive formal medical attention by using a simple calibration technique. We varied the parameter systematically until the model produced a five year risk of rotavirus mortality in the no vaccination group that matched observed rotavirus mortality in India (one in 250 children¹⁴). We did not explicitly incorporate any additional survival benefit from home oral rehydration as the effect of such treatment at prevailing levels of access and effectiveness should already be implicitly reflected in the Indian rotavirus mortality figure to which we calibrated. Within each cycle all individuals also faced an age dependent probability of death from non-rotavirus causes based on published Indian life tables.³⁹

Vaccine characteristics

We assumed that coverage rates for doses one and two of the vaccine would match rates for doses one and

Table 1 | Disease related parameters. Estimated values, ranges used in sensitivity analysis, and distribution types assumed for uncertainty analysis. Upper and lower limits of ranges correspond to 95% confidence intervals. Standard errors used in creating probability distributions for each parameter were estimated as quarter of range between confidence limits^{56 57}

Parameter	Value	Range	Source/comments	Distribution used in uncertainty analysis
Cumulative incidence of nth infection by 6, 12, and 24 months*:				
First infection	0.34†, 0.67, 0.96	Calculated transition probabilities varied +/- 50%	Velazquez et al ²	Normal
Second infection	0.04, 0.30, 0.69	Calculated transition probabilities varied +/- 50%	Velazquez et al ²	Normal
Third infection	0.00, 0.07, 0.42	Calculated transition probabilities varied +/- 50%	Velazquez et al ²	Normal
Probability that 1st, 2nd, and 3rd infections, respectively, will cause symptoms	0.47, 0.32, 0.25	+/- 50%	Velazquez et al ²	Normal
Probability that symptoms, if present, will be severe‡ (1st, 2nd, 3rd infections)	0.28, 0.19, 0.00	+/- 50%	Velazquez et al ²	Normal
Probability of dying from severe rotavirus disease without formal medical attention	0.068	0.034-0.136	Calibrated to yield known five year rotavirus mortality of 1/250 ¹⁴ in "no vaccination" group	Beta
Prevalence of rotavirus strains with:				
G and P proteins in common with RIX4414	0.275	—	Composite of three recent epidemiological studies from	—
Either G or P in common with RIX4414	0.238	—	Delhi, ⁴² Kolkata, ⁴³ Vellore ³⁸	—
Neither G nor P in common with RIX4414	0.487	—		—

*Hazard rate based on $r = -\ln(1-p) / t_1$ where t_1 = length of interval (for example, 6 months between 6th and 12th months of life) and p = probability of infection n by end of interval given being at risk for infection n at beginning of interval, transition probability calculated from hazard rate as $p = 1 - e^{-rt_2}$ where t_2 = cycle length (one month for present model).

†Based on observation that infections by pathogenic rotavirus strains in first few months of life are rare,¹¹ we set probability of infection before 2 months of age to 0.

‡Severe infections are defined as those with Vesikari score ≥ 11 .³⁴

three of the diphtheria-tetanus-pertussis vaccine in India (given on the same schedule as RIX4414) (table 2).^{22 31} Using a previously validated technique,⁴⁰ we estimated setting specific efficacy based on serotype specific efficacy data^{16 41} and combined prevalence figures from northern,⁴² eastern,⁴³ and southern³⁸ India. Where the figures for serotype specific efficacy from a large trial that took place almost entirely in Latin America¹⁶ were significant, we used these. In the case of G2P⁴ efficacy, where results from this single trial did not reach significance, we relied on data from a recently published meta-analysis that also included data from high income countries of Europe and Singapore.⁴¹ We projected that efficacy against severe disease would be 0.804 in India (compared with 0.847 from the Latin American trial¹⁶ and 0.958 from a trial in six European countries¹⁸).

In the absence of analogous serotype specific data from trials needed to estimate efficacy against any rotavirus symptoms, we estimated this value by adjusting our projected efficacy against severe disease by the ratio of overall (that is, all strains) efficacy against any symptomatic infection to overall efficacy against severe infection from a recent phase III trial.¹⁸ Similarly, to estimate the vaccine's efficacy against asymptomatic infection in India, we adjusted the projected vaccine efficacy against severe infection by the ratio of efficacy against asymptomatic to severe infection reportedly conferred by the first naturally acquired rotavirus infection.²

We considered the efficacy of a single dose of RIX4414 to be 37.5% lower than that of a full two dose course.⁴⁴ The annual rate of waning of efficacy was based on the differential between the first and second

season efficacy in a large Latin American trial⁴⁵ and converted into monthly rates for our model.

We assumed no risk of serious adverse events for those receiving the vaccine. An earlier tetravalent rhinovirus recombinant rotavirus vaccine, Rotashield, was removed from the market in 1999 after it was linked to an increase in intussusception events among recipients in the United States.¹⁴ The combined clinical trial and post-marketing data pertaining to RIX4414 suggest no increased rates of adverse events, including intussusception.⁴⁶

Probabilities related to use of health services

Probabilities that symptomatic individuals would receive inpatient care depended on the severity of symptoms and were derived with Bayes's formula with the following inputs: proportion of rotavirus inpatients in India who have severe/non-severe

Fig 2 | Model projections for cumulative incidence of first, second, and third rotavirus infections during first five years of life in children receiving no vaccination

Table 2 | Vaccine related parameters. Estimated values, ranges used in sensitivity analysis, and distribution types assumed for uncertainty analysis. Upper and lower limits of ranges correspond to estimates of 95% confidence intervals. Standard errors used in creating probability distributions for each parameter were estimated as quarter of range between confidence limits^{56 57}

Parameter	Value (range)	Source/comments	Distribution used in uncertainty analysis
Coverage for dose 1 (age 2 months)	0.81 (0.71 to 0.91)	Based on DPT-1 coverage ³¹	β
Coverage for dose 2 (age 4 months)	0.77 (0.67 to 0.87)	Based on DPT-3 coverage ³¹	β
Efficacy against severe infection caused by rotavirus strains with:			
G and P proteins in common with RIX4414	0.908 (0.705 to 0.982*)	Ruiz-Palacios et al ¹⁶	β
Either G or P in common with RIX4414	0.869 (0.628 to 0.966*)	Ruiz-Palacios et al ¹⁶	β
Neither G nor P in common with RIX4414	0.714 (0.201 to 0.911*)	De Vos et al ⁴¹	β
Ratio of efficacy against any symptomatic rotavirus infection to efficacy against severe infection	0.873 (0.773 to 0.973)	Vesikari et al ¹⁸	β
Ratio of efficacy against asymptomatic infection to efficacy against severe infection	0.437 (0.337 to 0.537)	Velazquez et al ²	β
Proportion of full efficacy conferred by single dose	0.625 (0.425 to 0.825)	Lopez et al ⁴⁴	β
Assumed annual rate of waning in vaccine efficacy	0.049 (0.0 to 0.10)	Based on decline in efficacy between 1st and 2nd seasons in two year trial in Latin America ⁴⁵	β

*Ranges based on actual 95% confidence intervals from trial data.

symptoms,³⁸ five year cumulative incidence of severe/non-severe rotavirus infection (taken directly from the output of our model for the no vaccination strategy), and five year cumulative probability of admission to hospital for rotavirus. We estimated this last input at 1.55% by varying it until the model projected the same probability of admission given any rotavirus symptoms that Parashar et al estimated for low income countries.⁸ We estimated severity dependent probabilities of use of outpatient services in the same manner. Based on mean severity scores of Indian children presenting with rotavirus infection in inpatient versus outpatient settings,⁴⁷ we assumed that the proportion of outpatients whose symptoms were severe would be half that of inpatients.

Using these inputs, we estimated the probability of admission given severe infection as 9.7%, the probability of admission given non-severe infection as 0.72%, the probability of outpatient treatment given severe infection as 57.5%, and the probability of outpatient treatment given non-severe infection as 14.1% (table 3). Those not receiving any formal medical treatment were considered to have been treated at home by the family with a probability of oral rehydration solution use corresponding to known levels of oral rehydration therapy access in India.⁴⁸

Costs

We do not know the precise cost per dose that would be paid as part of a universal RIX4414 vaccination programme in India. The manufacturer (GlaxoSmithKline) has pledged to make the vaccine available at greatly reduced prices to public sector programmes in lower income countries.²⁴ The manufacturer recently sold millions of doses to the government of Brazil at a cost of \$7 (£4, €4.8) per dose.²⁴ We used this figure (converted to 2007 rupees) as a baseline estimate for the vaccine's cost and varied it substantially in sensitivity analysis (table 3). We also do not know the degree of increase in administration costs that would

be incurred by adding RIX4414 to the existing vaccination schedule. Consistent with other investigators,^{28,29} we applied an administration cost equivalent to \$0.50 a dose. We also varied this value over a wide range, given doubts about the adequacy of many poorer countries' cold chain infrastructure to accommodate the added volume of a bulky new oral vaccine.²⁵ We assumed a standard 10% rate of vaccine wastage.^{27,28,49}

We were fortunate to have recent data on direct medical, direct non-medical, and indirect costs from a study of the economic burden of rotavirus treatment in Vellore, India.⁴⁷ Based on WHO guidelines for gathering cost data on treatment of diarrhoea,⁵⁰ the investigators followed hospital, clinic, and emergency department patients (we combined the latter two categories into one "outpatient" category) prospectively in three facilities serving markedly different populations of patients. We weighted the costs reported for each treatment setting (inpatient or outpatient) at each facility by the reported number of encounters in each setting and facility to estimate average costs for inpatient and outpatient treatment.

Cost effectiveness analysis

We determined the incremental cost effectiveness ratio for moving from a strategy of no vaccination to a strategy of universal two dose vaccination with RIX4414. For the base case analysis, this ratio was expressed in 2007 Indian rupees per life year saved and was calculated as the difference in mean cost under the vaccination strategy compared with that under the no vaccination strategy divided by the difference in years of life lost between the two strategies. Costs and benefits were discounted at a standard annual rate of 3%, consistent with previous analyses.^{28,29,49,51} In a secondary analysis, we calculated the incremental cost effectiveness in terms of discounted rupees per disability adjusted life year (DALY) averted (by using standard age weighting and discounting⁵²). Based on the

Table 3 | Utilisation and cost parameters. Estimated values, ranges used in sensitivity analysis, and distribution types assumed for uncertainty analysis. Upper and lower limits of ranges correspond to estimates of 95% confidence intervals. Standard errors used in creating probability distributions for each parameter were estimated as quarter of range between confidence limits^{56 57}

Parameter	Value (range)	Source/comments	Distribution used in uncertainty analysis
Probabilities related to use of health services			
Probability of admission to hospital given:			
Non-severe infection	0.00721 (0.00361 to 0.0108)	Calculated based on ^{8 38*}	β
Severe infection	0.0973 (0.0487 to 0.146)	Calculated based on ^{8 38*}	β
Probability of outpatient treatment given:			
Non-severe infection	0.141 (0.0705 to 0.212)	Calculated based on ^{8 38*}	β
Severe infection	0.575 (0.288 to 0.863)	Calculated based on ^{8 38*}	β
Probability of access to oral rehydration solution at home	0.30 (0.0 to 1.0)	Jain et al ⁴⁸	β
Costs (in 2007 rupees)†			
Cost of one dose of RIX4414	285.2 (142.6 to 570.4)	Based on price paid by Brazilian government ²⁵	Triangular
Cost of administering vaccine (per dose)	20.4 (10.2 to 81.6)	Podewils et al, ²⁸ Isakbaeva et al ²⁹	Triangular
Hospital treatment of rotavirus infection:			
Direct medical:			
Paid by patient's family	2444.3 (1833.2 to 3055.4)	Mendelsohn et al ⁴⁷	Normal
Subsidised by government	189.4 (142.1 to 236.8)	Mendelsohn et al ⁴⁷	Normal
Direct non-medical	39.9 (29.9 to 49.9)	Mendelsohn et al ⁴⁷	Normal
Indirect	0	Mendelsohn et al ⁴⁷	NA
Outpatient treatment of rotavirus infection:			
Direct medical:			
Paid by patient's family	156.2 (117.2 to 195.3)	Mendelsohn et al ⁴⁷	Normal
Subsidised by government	52.1 (39.1 to 65.1)	Mendelsohn et al ⁴⁷	Normal
Direct non-medical	23.6 (17.7 to 29.5)	Mendelsohn et al ⁴⁷	Normal
Indirect	1.8 (1.4 to 2.3)	Mendelsohn et al ⁴⁷	Normal
Oral rehydration solution (per course)	15.4 (11.3 to 18.8)	Patel et al ⁸⁰	Normal
Discount rates			
For costs	3% (0% to 3%)	—	—
For benefits	3% (0% to 3%)	—	—

NA=not applicable.

*General formula: $p(\text{site severity}) = [p(\text{severity site}) * p(\text{site})]/p(\text{severity})$.

†In 2007 1 rupee = \$0.025.

age specific disability weight for diarrhoea reported in the Global Burden of Disease Study⁵³ and a typical duration of symptoms of one week,¹⁹ we used a disability weight of 0.0023 per symptomatic episode.

Often, a threshold of one^{28 49 51} to two⁵⁴ times a country's per capita gross domestic product is used as a criterion to gauge whether the incremental cost of an intervention per life year saved or per DALY averted can be considered sufficiently cost effective. WHO describes interventions costing less than a country's per capita gross domestic product per DALY averted as "very cost effective" and those costing between one and three times per capita gross domestic product as "cost effective."⁵⁵ Though our main cost effectiveness measure was cost per life year saved—not per DALY averted—we chose a threshold of one times per capita gross domestic product. This approach is slightly more conservative than basing the threshold on DALYs averted as life years saved do not capture the non-financial benefits of reducing symptoms in non-fatal cases.⁵¹

Sensitivity and uncertainty analyses

To assess the overall robustness of our model and to identify influential parameters for which better empirical data are needed, we performed one way sensitivity analyses by individually varying each input parameter across the ranges shown in the tables.

To help us gauge the overall impact of parameter uncertainty, we also performed a type of uncertainty analysis, known as two dimensional probabilistic sensitivity analysis, by creating probability distributions for nearly all parameters in the model. For estimates of administration costs and for cost of the vaccine itself, we applied triangular distributions with limits of 50% and 300%, and 50% and 200%, respectively. For all other costs, we used normal distributions with 95% confidence intervals equal to plus or minus 25% of the mean. We inserted three separate constants (each with a base value of 1.0) in our model, which, when varied, affected the calculated transition probabilities for *n*th infection, the probabilities that infection *n* would cause symptoms, and the probabilities that symptoms of infection *n*, if present, would be severe.

Table 4 | Expected clinical events and use of health services related to rotavirus infection in birth cohort of 100 000 Indian infants followed for five years under strategies of no vaccination and vaccination with RIX4414

	No vaccination	Vaccination	Change (%)
Clinical events per 100 000 children			
Any infection	278 672	253 657	-25 015 (-9.0)
Asymptomatic infections	181 164	185 092	3928 (2.2)
Symptomatic infections	97 508	68 565	-28 943 (-29.7)
Severe infections	18 260	11 279	-6981 (-38.2)
Deaths	398	235	-163 (-41.0)
Use of health services per 100 000 children			
Home treatment with oral rehydration solution	73 221	52 191	-21 030 (-28.7)
Outpatient visits	21 582	14 405	-7177 (-33.3)
Admissions to hospital	2367	1555	-812 (-34.3)

These three constants were varied over a normal distribution with 95% confidence limits of 0.5 and 1.5. For all other proportions and probabilities, we used β distributions with α and β parameters estimated from mean and standard error. We estimated standard errors based on the approximation that lower and upper limits used in one way sensitivity analysis represented 95% confidence limits, with ranges equal to approximately four times the standard error.^{56,57} One thousand probabilistically sampled parameter sets (a typical number in decision analyses⁵⁸⁻⁶¹) were each used to simulate a cohort of 100 000 individuals. We then calculated the proportion of these 1000 samplings that would have produced results considered cost effective.

RESULTS

Base case

The model predicted that, without vaccination, essentially all children would have had a first infection by 60 months of age (consistent with conventional wisdom^{8,13,62}), 98.6% would have had a second infection, and 94.4% would have had a third infection (fig 2). Table 4 shows the projected numbers of clinical events and use of health services per 100 000 children followed for five years under both strategies. Based on an actual Indian birth cohort size of about 25 million a year,⁶³ each year vaccination would be expected to prevent 1 745 000 severe episodes of gastroenteritis, 1 794 500 outpatient visits, 203 000 admissions to hospital, and 41 000 deaths among children younger than 5 years.

The additional direct medical cost incurred by moving from no vaccination to the vaccination strategy (net

of any savings from reduced expenditures for treatment) would be 432.4 rupees (about £5, €6, \$9) per person. On average, vaccination would be expected to save 0.05390 life years per person, yielding an incremental cost effectiveness ratio of 8023 rupees (or about £100, €113, \$164) per life years saved (table 5). The intervention would thus satisfy our cost effectiveness criterion of less than India's per capita gross domestic product (37 907 rupees in 2007⁶⁴) per life year saved. Taking the broader societal perspective, the incremental cost effectiveness ratio was 7984 rupees per life year saved. With DALYs averted as an alternative measure of effectiveness, the ratio was 6552 rupees per DALY averted.

Sensitivity analysis

In a sensitivity analysis, increasing the coverage level for the first and second doses of the vaccine by 10 percentage points increased the reduction in mortality due to vaccination from 41.1% to 47.6%, saving an additional 6500 lives annually population-wide. We also examined the impact of vaccination under a scenario of low efficacy in which each strain specific efficacy figure shown in table 2 was reduced by 15 percentage points. Even at this substantially reduced efficacy, vaccination could still be expected to save 26 750 lives in one year with an incremental cost effectiveness of 11 647 rupees per life year saved.

Figure 3 shows the individual parameters which, when varied across their full ranges, most affected the incremental cost effectiveness ratio from baseline. Increasing the probability that children with severe symptoms would present for outpatient treatment by 50% increased the ratio to 51 637 rupees per life year saved, an effect driven mainly by a 92% reduction in mortality that was independent of vaccination status. This was the only individual parameter capable of increasing the incremental cost effectiveness ratio above per capita gross domestic product. There is marked asymmetry of results for parameters which, when varied, would affect individuals in both the vaccination and no vaccination groups. In each of these cases, changes that lessen the morbidity or mortality of disease reduce the cost effectiveness of vaccination (resulting in higher incremental cost effectiveness ratios). When disease is less serious, the potential marginal health benefit of vaccination (the denominator of the incremental cost effectiveness ratio) becomes smaller. Meanwhile, marginal cost in the numerator tends to increase with less serious disease as savings on treatment costs due to vaccination become more modest.

We explored a scenario in which the overall infection rate, probability of symptoms given infection, and probability that any symptoms would be severe were simultaneously increased by 50%. In this scenario of higher disease burden, absolute mortality reduction per 100 000 due to vaccination rose from 164 to 310 lives, while the incremental cost effectiveness fell to 5007 rupees per life year saved.

Alternative discount rates of 0% for costs and 0% for health benefits yielded an incremental cost

Table 5 | Base case cost effectiveness results: strategy of no vaccination compared with strategy of vaccination with two doses of RIX4414

	Mean cost (2007 rupees)	Marginal cost	Mean years of life lost	Life years saved (LYS)	ICER* (rupees/LYS)
No vaccination	106.5	—	2.06627	—	—
Vaccination	538.9	432.4	2.01237	0.05390	8023

*Incremental cost effectiveness ratio (ICER) calculated as marginal cost in 2007 rupees divided by life years saved.

Fig 3 | Individual parameters with greatest influence on incremental cost effectiveness ratio, expressed in rupees per life year saved (LYS), in univariate sensitivity analysis. Solid vertical line represents base case incremental cost effectiveness ratio of 8023 rupees per life year saved

effectiveness ratio of 3608 rupees per life year saved, while rates of 3% for costs and 0% for benefits yielded a ratio of 3586 rupees per life year saved.

Figure 4 shows an acceptability curve summarising the results of our uncertainty analysis. The model was run 1000 times, each time with a different probabilistically sampled parameter set. In 94.7% of those runs, the cost effectiveness ratio for vaccination fell below per capita gross domestic product, our conservative criterion for cost effectiveness. In 97.8% of model runs, the ratio fell below three times per capita gross domestic product (the level below which interventions are considered “cost effective” by WHO guidelines⁵⁵).

DISCUSSION

The results of this study suggest that universal RIX4414 vaccination in India would save many thousands of lives annually across a wide range of scenarios. In the base case analysis, we projected that vaccination would annually prevent 1 745 000 severe episodes of gastroenteritis, 1 794 500 outpatient visits, 203 000 admissions to hospital, and 41 000 deaths among Indian children below the age of 5 at a cost of 8023 rupees (about £100, €113, \$165) per life year saved. The projected reduction in mortality was heavily influenced by changes in levels of vaccine coverage, vaccine efficacy, and probability that a severely ill child would receive outpatient care. While incremental cost effectiveness was sensitive to changes in probability of use of outpatient services for those with severe symptoms, parameters influencing disease severity, vaccine cost, case fatality rate, and vaccine efficacy, no scenario in our deterministic sensitivity analysis yielded an incremental cost effectiveness ratio greater than three times the per capita gross domestic product. Only one parameter, when varied to its upper limits, pushed the incremental cost effectiveness ratio above one times the per capita gross domestic product: the probability of outpatient care for the severely symptomatic of 0.863 (versus 0.575 in the base case). Underlying this large effect was the fact that improved access

to care greatly reduced baseline rotavirus mortality, diminishing the potential mortality benefit of vaccination. Uncertainty analysis suggested that, given the combined extent of uncertainty in all parameter estimates, vaccination would satisfy a conservative one times per capita gross domestic product criterion for cost effectiveness with 94.7% probability. Furthermore, it would satisfy WHO’s three times the per capita gross domestic product criterion with 97.8% probability.

Strengths of study

This study features several methodological strengths. The model simulates clinical events and use of health services in a temporally explicit fashion that incorporates the changing effects of each individual’s age, infection history, and vaccination history on infection risk and response to infection. Vaccine efficacy is adjusted to account for distributions of strains specific to India. Monthly probabilities of infection are based on hazard rates calculated from a meticulously executed birth cohort study, which captured even asymptomatic infections. Use of such complete epidemiological data in a model of rotavirus infection is important given the role of asymptomatic infections in reducing risk and severity of future infections. In addition, the study benefited from the availability of recent cost data.⁴⁷

We found no previously published analyses that examined the impact of rotavirus vaccination specifically in India. A study by Podewils et al published in 2005 examined the cost effectiveness of vaccination for low income Asian countries.²⁸ We consider, though, that these investigators might have substantially overestimated the incidence of admission to hospital, leading to significant overestimation of cost savings from vaccination. They applied a one year cumulative incidence of admission for rotavirus among children aged 0-60 months¹¹ to a hypothetical cohort of infants followed for five years by simply multiplying the incidence by five. If the closed group of children aged 0-60 months in the source study had been followed for subsequent years, however, much lower rates of

Fig 4 | Acceptability curve for strategy of vaccination with live attenuated human rotavirus vaccine (RIX4414) compared with no rotavirus vaccination. Curve represents probability that vaccination would be cost effective over range of threshold incremental cost effectiveness ratios (ICERs)

admission would probably have been observed, as suggested by the fact that 98% of admissions in the source study occurred in children younger than 24 months.¹¹

Kim et al recently published an analysis of rotavirus vaccination in Vietnam.³⁰ Though not individual based, their model shares some key features with ours, including acquired partial immunity from past infections and the possibility of multiple rotavirus infections. The authors also drew several epidemiological parameters from the Velazquez birth cohort study of Mexican infants.² They assumed that deaths related to rotavirus, admissions to hospital, and outpatient visits all decrease in proportion to one another under vaccination. This approach fails to take into account the effects of decreased severity of symptoms on relative rates of use of inpatient and outpatient services. Because we modelled the effects of vaccination on severity of symptoms and the effects of severity on probabilities of service use in specific settings, we could simulate the shift toward lower levels of care needed for children with rotavirus disease under vaccination (that is, larger decreases in admissions than in outpatient visits).

With their model Kim et al examined vaccination in a setting with a rate of rotavirus mortality substantially lower than that seen in India.³⁰ This limits the applicability of their findings for countries that, like India, have the highest rates of rotavirus mortality.^{14,22} Parameters specific to these other high mortality countries (vaccine coverage rates, rates of service use, costs, etc) would differ from those in India. The consistency of our model's conclusions over wide ranges of parameter inputs in sensitivity analysis suggests that vaccination would probably offer enormous public health benefit in many of these settings.

Irrespective of cost effectiveness, a public health intervention must also be affordable. Net of savings from reduced expenditures on subsidised treatment, we calculated that universal RIX4414 vaccination would cost the Indian Department of Health and Family Welfare 11.6bn rupees (about £140m, €160m, \$240m) annually or, for context, about 11.6% of that department's 2006-7 budget.⁶⁵ Whether this level of cost is acceptable is a decision to be made by country officials and the international organisations that would help finance mass vaccination. Fortunately, less expensive rotavirus vaccines might be just a few years away if the efforts of some Indian firms and officials in partnership with the National Institutes of Health, the Centers for Disease Control and Prevention, and the Program for Appropriate Technology in Health are successful. These agencies are supporting the development of candidate rotavirus vaccines based on native strains to be manufactured and used in some developing Asian countries, including India.^{19,24,25} Currently, the diphtheria-tetanus-pertussis and hepatitis B vaccines used in India are produced domestically for less than \$1 a dose.⁶⁶ Officials with a company hoping to manufacture India's first homegrown rotavirus vaccine have likewise set a goal of producing the agent for \$1 a dose.⁶⁷ According to our model, a universal rotavirus

vaccination programme with a per dose cost equivalent to \$1 would cost 1644 rupees (£20, €23, \$34) per life year saved, with a total annual cost equal to about 2.2% of the 2006-7 Indian Department of Health and Family Welfare's budget. This figure does not take into account possible benefits of improved efficacy provided by a vaccine derived from native strains.

We compared universal rotavirus vaccination to the status quo of no rotavirus vaccination. Future analyses should compare the cost effectiveness of rotavirus vaccination with possible strategies using other less expensive but underused interventions to reduce child mortality. One such intervention might be expansion of micronutrient supplementation and fortification programmes. In India, deficiencies of micronutrients are reportedly associated with more deaths than rotavirus, with around 330 000 child deaths each year attributed to vitamin A deficiency alone.⁶⁸ Despite this, supplementation and fortification programmes remain inadequate.^{68,69}

Limitations

Whenever possible, we based parameter estimates on data specific for India. Incidence and severity (but not service use or mortality) parameters in our model, however, were based on the results of a Mexican birth cohort study.² Evidence suggests that incidence rates of rotavirus infection are similar worldwide and across economic strata¹⁻⁷ and that survival is largely a function of access to medical care.^{11,38} It is reasonable to expect though that average symptom severity might be greater in poorer countries, where underlying health tends to be worse, compared with severity in an upper middle income⁷⁰ country like Mexico. In sensitivity analysis, we showed that any potential underestimation of disease burden would bias the analysis against the intervention. Vaccination would become twice as cost effective if infection rates, probability that infections were symptomatic, and probability that any symptoms were severe were all simultaneously increased by 50%. Less apparent is the direction of any mis-specification of severity dependent probabilities of service use. Because these types of data were not directly available in the published literature, we were forced to make inferences based partly on data specific to India³⁸ and partly on previous estimates of rotavirus related use of health services in inpatient and outpatient settings for developing countries in general.⁸ In particular, the model's conclusions were sensitive to variation in the probability that those with severe rotavirus disease would receive outpatient care. In the extreme, increasing this probability by 50% (from 0.575 to 0.863) would result in an incremental cost effectiveness ratio equivalent to about 1.4 times India's per capita gross domestic product, falling between the WHO's criteria for "very cost effective" (one times per capita gross domestic product) and "cost effective" (three times per capita gross domestic product) interventions.⁵⁵

Earlier live oral vaccines against rotavirus,⁷¹⁻⁷⁴ as well as those against cholera⁷⁵⁻⁷⁷ and polio,^{78,79} have

WHAT IS ALREADY KNOWN ON THIS TOPIC

Nearly a quarter of deaths from rotavirus gastroenteritis occur in India, a country with a high degree of rotavirus strain diversity, limited access to health care, and tightly constrained financial resources.

WHO has recently recommended rotavirus vaccination in developing countries of Asia and Africa

WHAT THIS STUDY ADDS

A model based on India specific inputs where possible, showed a 29.7% reduction in symptomatic episodes, 41.0% reduction in rotavirus mortality, 33.3% reduction in outpatient visits, and 34.3% reduction in hospital admissions with a programme of vaccination with RIX4414

A vaccination programme would satisfy standard criteria for cost effectiveness across a wide range of assumptions—including lower than expected vaccine efficacy—albeit at a substantial net programme cost

historically performed less well than expected in developing Asian and African countries. Some believe this might be because of differences in nutrition and co-infecting pathogens.^{14 19 24} Our model does not account for this directly. In addition to accounting for increased strain diversity, however, we performed a sensitivity analysis that showed that even with efficacy that was 15 percentage points lower against all strains, the vaccine could still save 26 750 Indian infants in a one year birth cohort and would remain similarly cost effective (11 647 rupees per life year saved).

Finally, as with previously published models of rotavirus vaccination, we did not take into account effects of herd immunity or declines in vaccine efficacy over time because of vaccination induced strain replacement.

Conclusion

Rotavirus vaccination with RIX4414 in India would prevent a substantial portion of rotavirus related morbidity, mortality, and use of health services at a cost per life year saved that would easily satisfy criteria for cost effectiveness. With WHO having recently extended their recommendation for rotavirus vaccination to developing Asian and African countries, implementation of mass vaccination programmes in these areas could begin soon, with benefits starting to accrue in a relatively short time. Even with steeply tiered pricing, though, the vaccine will probably be expensive by developing world standards. For this reason, we believe that any programme of vaccination with RIX4414 or other rotavirus vaccines with comparable cost and efficacy should be viewed as only a temporary solution until less expensive vaccines derived from native strains can be manufactured regionally. Rotavirus is only one member of a long list of killers in the developing world. Further analyses should compare vaccination with other, less expensive interventions such as expansion of micronutrient supplementation and fortification programmes to make certain that the most cost effective solutions do not go unexploited.

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