BMJ

BMJ 2013;346:f3726 doi: 10.1136/bmj.f3726 (Published 19 June 2013)

RESEARCH

Effectiveness of monovalent rotavirus vaccine in Bolivia: case-control study

Manish M Patel *epidemiologist*[1], Maritza Patzi *epidemiologist*[2], Desiree Pastor *epidemiologist*[3], Aleida Nina *microbiologist*[4], Yelin Roca *microbiologist*[5], Leovigildo Alvarez *microbiologist*[6], Volga Iniguez *research microbiologist*[7], Rosario Rivera *microbiologist*[7], Ka Ian Tam *microbiologist*[1], Osbourne Quaye *microbiologist*[1], Michael Bowen *research microbiologist*[1], Umesh Parashar *epidemiologist*[1], Lucia Helena De Oliveira *epidemiologist*[8]

[1]Viral Gastroenteritis Team, DVD, NCIRD, MS-A34, Centers for Disease Control and Prevention, 1600 Clifton Road, NE, Atlanta, GA 30333, USA; [2]Ministerio de Salud, La Paz, Bolivia; [3]PanAmerican Health Organization, La Paz, Bolivia; [4]Laboratorio de Virologia, INLASA, Ministerio de Salud y Deportes, La Paz, Bolivia; [5]National Reference Laboratory, CENETROP, Santa Cruz, Bolivia; [6]Laboratorio de Virologia, Cochababma, Bolivia; [7]Instituto de Biologia Molecular y Biotecnologia, Universidad Mayor de San Andres, La Paz, Bolivia; [8]PanAmerican Health Organization, Washington DC, USA

Abstract

Objective To evaluate the effectiveness of two doses of a monovalent rotavirus vaccine (RV1) against hospital admission for rotavirus in Bolivia.

Design Case-control study.

Setting Six hospitals in Bolivia, between March 2010 and June 2011.

Participants 400 hospital admissions for rotavirus, 1200 non-diarrhea hospital controls, and 718 rotavirus negative hospital controls.

Main outcome measures Odds of antecedent vaccination between case patients and controls; effectiveness of vaccination ((1–adjusted odds ratio)×100), adjusted for age and other confounders; and stratified effectiveness by dose, disease severity, age group, and serotype.

Results In comparison with non-diarrhea controls, case patients were more likely to be male and attend day care but less likely to have chronic underlying illness, higher level maternal education, and telephones and computers in their home. Rotavirus negative controls were somewhat more similar to case patients but also were more likely to be male and attend day care and less likely to have higher level maternal education and computers in their homes. The adjusted effectiveness of RV1 against hospital admission for rotavirus was 69% (95% confidence interval 54% to 79%) with rotavirus negative controls and 77% (65% to 84%) with non-diarrhea controls. The effectiveness of one dose of RV1 was 36% and 56%, respectively. With both control groups, protection was sustained through two years of life, with similar efficacy against hospital admission among children under 1 year (64% and 77%) and over 1 year of age (72% and 76%). RV1 provided significant protection against diverse serotypes, partially and fully heterotypic to the G1P[8] vaccine. Effectiveness using the two control groups was 80% and 85% against G9P[8], 74% and 93%% against G3P[8], 59% and 69% against G2P[4], and 80% and 87% against G9P[6] strains.

Conclusion The monovalent rotavirus vaccine conferred high protection against hospital admission for diarrhea due to rotavirus in Bolivian children. Protection was sustained through two years of life against diverse serotypes different from the vaccine strain.

Introduction

The World Health Organization recommends two live attenuated oral rotavirus vaccines, a monovalent RIX4144 strain human vaccine (RV1, Rotarix, GlaxoSmithKline Biologicals) and a pentavalent bovine-human WC3 reassortant vaccine (RV5, RotaTeq, Merck Vaccines, Whitehouse Station, NJ), for all children worldwide to help to control the large burden of deaths and hospital admissions due to rotavirus.[1] An outstanding question for the global community is whether oral rotavirus vaccines will work well under routine conditions of public health programs, particularly in countries with high mortality where they potentially offer the greatest life saving benefits. Rotavirus vaccines have performed well in middle and high income settings, where efficacy has ranged from 77% to 98%.[2-5] In contrast, the efficacy of these vaccines in controlled clinical trial conditions was lower in low income settings in Asia and Africa, ranging from 18% to 64%.[6 7] Although the reasons for the lower performance of live, oral vaccines in developing countries are not fully understood, it is likely attributable to host or environmental factors that impair a robust immune response such as competing enteric pathogens, micronutrient malnutrition, breast milk interference, or circulating maternal antibodies.[8]

Correspondence to: M Patel Aul3@CDC.GOV

Full realization of the life saving potential of rotavirus vaccines hinges on identifying modifiable factors associated with their lower performance in high mortality settings.

Some 45 middle and high income countries, including 14 in Latin America, have introduced a rotavirus vaccine in the past seven years and consequently have experienced dramatic reductions in the burden of severe rotavirus disease, including indirect benefits to children who remained unvaccinated.[9] Data have been limited on the performance of rotavirus vaccines under ordinary conditions of a public health program in high mortality settings. A published study from Nicaragua showed that the effectiveness of the RV5 vaccine was similar (about 50%) to that seen in the clinical trials from low income settings in Africa and Asia.[10] No data are available for the effectiveness of the RV1 vaccine in routine programmatic use in countries with high childhood mortality, as classified by WHO.[11] Effectiveness data are particularly needed to gain a better understanding of the benefit-risk balance because of the recent safety concerns of a low level risk of intussusception associated with RV1 in Mexico and Brazil.[12] Thus, our primary objective was to evaluate the effectiveness of two doses of RV1 against hospital admissions for rotavirus in Bolivia, the first GAVI eligible country worldwide to introduce RV1 vaccine.

Methods

Study design and setting

Bolivia is a lower-middle income country in South America with an annual birth cohort of about 263 000 and a gross national income of $1699 (£1092; €1284) per capita in 2009.[13] The Bolivian Ministry of Health added RV1 to the routine childhood immunization schedule in August 2008, recommending two doses of RV1 for all children in Bolivia at 2 and 4 months of age. From March 2010 to June 2011 we did a case-control evaluation at six hospitals in four of the largest cities in Bolivia (La Paz, El Alto, Cochabamba, and Santa Cruz) to assess the effectiveness of RV1 against hospital admissions for rotavirus. These hospitals are ministry hospitals that were selected on the basis of WHO guidelines for rotavirus surveillance that recommend selecting hospitals that admit more than 250 children for gastroenteritis each year.[14] These six hospitals were estimated to have 19% of all hospital admissions for diarrhea among children before the introduction of vaccine.

Participants: cases

We defined cases as children admitted to the hospital overnight for treatment of acute diarrhea, defined as at least three loose stools in a 24 hour period. Inclusion criteria were onset of diarrhea less than 14 days before the hospital visit; a rotavirus positive stool sample during the first 48 hours of admission (to avoid nosocomial infection); and eligibility to receive at least one dose of RV1, defined as being born after June 1, 2008 and being at least 8 weeks of age when admitted to hospital. We excluded cases when we were unable to contact a parent or care-taker to obtain consent, identify three hospital controls, or verify vaccination status through parental card or vaccination registry. To identify case patients, we did active hospital based surveillance 24 hours a day in the emergency department and inpatient wards. Bulk stool specimens were collected within 48 hours of admission. Specimens were stored at 2-8°C before transfer to the national laboratory on a weekly basis during the first nine months of the study and to a local laboratory during the last six months of the study. Rotavirus testing was done with a commercially available enzyme immunoassay (ProSpecT ELISA, Oxoid, UK). Specimens were stored frozen at −70°C until they were shipped to the Centers for Disease Control and Prevention, Atlanta, GA, USA for genotyping analysis. Genotyping was done on samples with sufficient stools, as described by Hull et al.[15]

Participants: controls

We assessed effectiveness by using two groups of controls: children admitted to hospital for conditions other than diarrhea (that is, hospital controls) and children with rotavirus negative diarrhea (that is, test negative controls). For non-diarrhea hospital controls, inclusion criteria were seeking care in the emergency department or being admitted to the same hospital as the case for an acute illness unrelated to diarrhea or a vaccine preventable condition (measles, mumps, rubella, diphtheria, pertussis, tetanus, tuberculosis, hepatitis B); being born within 30 days of the case's date of birth; and being eligible to receive at least one dose of RV1, defined as being born after June 1, 2008 and being at least 8 weeks of age when admitted to hospital. We excluded controls when we were unable to contact a parent or care-taker to obtain consent, identify three hospital controls for each case, or verify vaccination status through parental card or vaccination registry. After a rotavirus case was identified, we routinely queried emergency department and hospital admission logs daily during the subsequent two weeks to identify three consecutive hospital controls. All efforts were made to capture the child during the hospital visit to avoid logistical challenges of home visits and potential loss to follow-up. We also sought to assess vaccine effectiveness by using children with rotavirus negative diarrhea as controls (test negative controls). Test negative controls were those children who were enrolled during the surveillance for rotavirus diarrhea but tested negative for rotavirus by enzyme immunoassay.

Variables

We conducted face to face interviews with parents of case patients and hospital controls during the hospital visit. After written informed consent had been given, we obtained information on vaccination history, demographics, socioeconomic factors, history of breast feeding, and medical history. For cases, we also gathered information on clinical characteristics, treatment, and course of illness. We selected variables on the basis of recommendations from a WHO guideline document on studies of the effectiveness of rotavirus vaccines.[16] The primary objective of the study was to assess differences in antecedent exposure to the full series (two doses versus zero) among cases compared with non-diarrhea controls and compared with test negative controls.

Data sources

We obtained vaccination history from the parent and considered it confirmed if the parent showed a vaccination card with the date of vaccination, the type of vaccine used, and the name of the child. If parents reported any vaccination but did not possess a card, we obtained confirmation by review of vaccine cards at the clinic where the child was reportedly vaccinated. We identified vaccination records at the clinic on the basis of the participant's name, sex, and date of birth. We obtained a photocopy of the vaccination record for cases and controls, and, after data entry into an electronic database, we verified all RV1 vaccination dates against this record.

Sample size for vaccine effectiveness

Using a precision based approach,[17] we estimated that we needed a total of 170 case patients to compute a vaccine effectiveness

of 60% with a confidence limit width of 30%, using a matched design with a control to case ratio of three to one and vaccine coverage of 50%. We enrolled a total of 400 case patients to allow for subgroup analyses including effectiveness of partial vaccination, strain specific effectiveness, and effectiveness stratified by age. Because we did not specifically calculate sample sizes for the subgroup analyses (strain specific and age stratified vaccine effectiveness), we did a post hoc power analysis and present vaccine effectiveness results when expected power using χ^2 exceeded 80% at a significance level of 0.05 given the observed number of cases and controls for each of the secondary outcomes.

Efforts to minimize bias

To minimize bias associated with differential surveillance and diagnosis, we used a standard WHO recommended case definition for severe gastroenteritis at all surveillance sites and laboratory confirmed diagnosis of rotavirus with a validated enzyme immunoassay with high sensitivity and specificity. For non-diarrhea controls, we excluded children with diseases not preventable by rotavirus vaccine because they would be less likely to receive rotavirus vaccine than the source population from which the cases arose. Information bias was minimized by blinding coordinators who verified vaccination records from knowledge of case or control status and the study hypothesis. Efforts to determine vaccine status were similar between cases and controls.

Statistical methods

Our primary aim was to calculate the vaccine effectiveness of two doses of RV1 against hospital admission for rotavirus. To assess for a potential gradient in protection by severity, we analyzed for vaccine effectiveness against rotavirus diarrhea with a clinical severity score of at least 11 and at least 15 on a 20 point Vesikari scoring scale that was used in the RV1 clinical trials.[4]

We firstly did bivariate analyses to assess for differences in indicators of socioeconomic condition between rotavirus case patients and the two groups of controls to identify potential confounders or biases for the association between RV1 vaccination and rotavirus disease. We used the Wilcoxon rank sum test or χ^2 test to assess differences.

We constructed two separate logistic regression models for non-diarrhea and test negative controls to calculate odds ratios with associated 95% confidence intervals.[18] For both models, we considered cases and controls to be vaccinated with the respective number of doses (one or two) if the most recent dose was administered 14 days before the case patient's hospital visit (the reference date). Children who received two doses did not contribute to the one dose vaccine effectiveness analysis, and children who received one dose of vaccine did not contribute to the two dose vaccine effectiveness analysis. For non-diarrhea controls, we used a conditional logistic regression model to estimate the crude odds ratio, because these controls were matched to case-patients by hospital and date of birth (±30 days). To estimate a crude odds ratio with test negative controls comparable to the crude odds ratio for non-diarrhea controls generated through a matched analysis, we used an unconditional logistic regression that included hospital, age (in months), and month/year of birth in the base model, because test negative controls were unmatched with regard to age and hospital during the design phase of the study. For both control groups, we then assessed for confounding by using multivariate modeling. To the base models, we included all additional variables with P<0.20 in the bivariate analyses. We then used a hierarchical backward elimination approach to select the variables in the final model individually, excluding those variables at a significance level of P>0.05.[19] For substantive reasons, we retained age in months, month/year of birth, and hospital for test negative controls. To assess for potential clustering by hospital, we included hospital as a random effect in the regression models, but it did not alter the model outcomes.

We did subgroup analyses to assess protection from partial dose vaccination (that is, one dose of RV1), strain specific protection, and protection among children 6-11 months of age compared with those aged 12 months or over. We assessed for interaction by age (6-11 months versus >11 months of age) and the prevalent strains by including an interaction term for age and vaccination and for strain type and vaccination in the model.

Finally, to assess the potential for bias in our estimates of effectiveness, we did a "bias indicator" analysis to examine whether two doses of RV1 provided protection against cases of diarrhea that tested negative for rotavirus with non-diarrhea controls, under the hypothesis that significant vaccine effectiveness against test negative diarrhea would be due to residual confounding in the non-diarrhea controls. For this analysis, we compared vaccination rates among rotavirus negative diarrhea cases and non-diarrhea controls and adjusted for age, hospital, and month/year of birth by using unconditional logistic regression.

We estimated the adjusted odds ratio by using the exponential of the coefficient for the vaccination variable in the model. We calculated the 95% confidence interval for the adjusted odds ratio by using the standard error of the coefficient,[18] and we subsequently calculated vaccine effectiveness as (1−adjusted odds ratio)×100%. Statistical significance was designated as P<0.05. We used SAS statistical software (version 9.2) for analyses.

Results

Participants

We approached a total of 451 case patients, 1247 non-diarrhea controls, and 817 test negative controls. Of these, we excluded 51 (11%), 47 (4%), and 99 (12%), respectively, and the final analysis included 400 case patients, 1200 non-diarrhea controls, and 718 test negative controls (fig 1⇓). In comparison with non-diarrhea controls, case patients were more likely to be male and attend day care but less likely to have chronic underlying illness, higher level maternal education, and telephones and computers in their home (table 1⇓). Test-negative controls were somewhat more similar to case-patients but also were more likely to be male and attend day care and less likely to have higher level maternal education and computers in their homes.

Vaccine records were confirmed for all participants in the analysis. Adherence to the age recommendations was good; only 10% of the children were vaccinated outside the recommended age windows of 2 and 4 months of age (fig 2⇓).

Vaccine effectiveness estimates

We identified no difference greater than 10% between the crude and adjusted estimates of vaccine effectiveness for either the primary or secondary analyses in the study (tables 2⇓, 3⇓, and 4⇓). The adjusted vaccine effectiveness of a full series of two doses of RV1 against hospital admission for rotavirus was 77% (95% confidence interval 65% to 84%) with non-diarrhea controls and 69% (54% to 79%) with test negative controls (table 2⇓). One dose of RV1 also provided significant protection

of 56% (32% to 72%) with non-diarrhea controls and 36% (0% to 59%) with test negative controls.

Of the 400 case patients admitted to hospital for rotavirus diarrhea, 373 (93%) had rotavirus diarrhea with a Vesikari score of 11 or greater and 191 (48%) had a Vesikari score of 15 or greater. Protection was similar against each of the severity outcomes in the study. With non-diarrhea controls, RV1 provided protection of 76% (64% to 84%) for a Vesikari score of 11 or above and 74% (54% to 85%) against a score of at least 15. When we used test negative controls, vaccine effectiveness was 69% (53% to 79%) for Vesikari score of 11 or above and 62% (37% to 88%) for a severity score of at least 15 (table 2⇓).

Of the 400 cases, 295 had sufficient stool samples for genotyping. Commonly detected strains included G9P[8] (n=107; 36%), G2P[4] (74; 25%), G3P[8] (52; 18%), and G9P[6] (23; 8%). Others were non-typeable (24; 8%) or other sparsely detected strains (15; 5%). Vaccine effectiveness ranged from 59% to 93% against four different strains, without any significant interaction by type of strain (P=0.70). With non-diarrhea controls, strain specific effectiveness was 85% (69% to 93%) and 93% (70% to 98%) against the partially heterotypic G9P[8] and G3P[8] strains and 69% (14% to 89%) and 87% (19% to 98%) against the fully heterotypic G2P[4] and G9P[6] strains (table 3⇓). With test negative controls, strain specific effectiveness was 80% (60% to 90%) and 74% (22% to 91%) against the partially heterotypic G9P[8] and G3P[8] strains and 59% (7% to 78%) and 80% (37% to 94%) against the fully heterotypic G2P[4] and G9P[6] strains.

We found no significant difference in effectiveness of RV1 against hospital admission for rotavirus between the two age groups when using non-diarrhea controls (P=0.42) or test negative controls (P=0.35) (table 4⇓). For non-diarrhea controls, vaccine effectiveness was 77% (51% to 89%) for children aged 6-11 months compared with76% (59% to 86%) for those aged 12 months or over. For test negative controls, vaccine effectiveness was 64% (34% to 80%) for children aged 6-11 months compared with 72% (52% to 86%) for those aged 12 months or over. Similarly, effectiveness was high for both age groups when we restricted the analysis to hospital admissions with severity scores of 11 or greater and to admissions related to the most prevalent strain, G9P[8].

In the bias indicator analysis, RV1 did not confer protection against non-rotavirus diarrhea cases in comparison with non-diarrhea controls for one dose (9%, −33% to 37%) or two doses (9%, −27% to 24%) of RV1.

Discussion

Using two different sources of controls, we have shown that RV1 vaccination under routine conditions of a public health program in a GAVI eligible country with high child mortality conferred protection of about 54% to 84% (lowest and highest upper and lower confidence limits of all two dose vaccine effectiveness estimates) against hospital admission for rotavirus. Given the national rotavirus vaccine coverage of 80% in 2011 (increased from 65% in 2009 and 76% in 2010),[20] we would expect that vaccination is preventing some 43% to 67% of the national burden of hospital admissions for rotavirus in Bolivia. These are particularly encouraging findings given that the efficacy of rotavirus vaccines has ranged from 18% to 64% in clinical trials from other similar high mortality settings.[3 6 7] We also assessed for duration of protection and noted that effectiveness was sustained through two years of life, the age period within which most of the hospital admissions for rotavirus occur in low and lower-middle income settings.[21-23] In addition, one dose of RV1 provided nearly 40-50% protection against hospital admission for rotavirus in Bolivia, a finding that was not assessed in the clinical trials. This early effect of vaccine on rotavirus diarrhea has important implications for countries where the burden of severe disease, particularly deaths, occurs before the full series is administered or where children may not return for their full series. Lastly, vaccine effectiveness was high against the range of circulating rotavirus strains during this evaluation, including against fully heterotypic G2P[4] and G9P[6] strains. Taken together, these results show the powerful effect of vaccination on improving child health in Bolivia and offer substantial encouragement for decision makers in low and lower-middle income countries considering introduction of vaccine to curb the burden of severe and fatal rotavirus disease.

Comparison with other studies

In Bolivia, RV1 provided higher protection (~71-77%) against outcomes of similar severity than RV5 provided in the low income setting of Nicaragua (50%).[10] In fact, effectiveness for RV1 in Bolivia was similar to that for RV1 in El Salvador (76%),[24] a slightly more developed lower-middle income country in Central America, and comparable to RV1 efficacy for first two years of life in the large clinical trial from 10 Latin American countries (80%).[2] In this trial, the efficacy of RV1 in Nicaragua was 78% (18 to 96) through two years of life.[25] The differing efficacy by vaccine type might reflect a chance occurrence, as data on effectiveness of RV5 in Latin America are available only from a single country.[10] Furthermore, in clinical trials, the efficacy of RV1 in the first year of life in Malawi (49%) was comparable to that of RV5 in low and lower-middle income countries in Africa (48%) and Asia (39%).[6 7 26] The possibility of inter-study differences in case severity might also explain some of the variation in vaccine effectiveness; however, all studies applied comparable WHO recommended case definitions and Vesikari severity scores, which should have minimized this effect. As rotavirus vaccines are introduced in additional low and lower-middle income countries in Africa and Asia, further assessments of effectiveness of both RV1 and RV5 in these settings to compare the performance of the two vaccines will be important.

In clinical trials from Africa and in some post-licensure studies from low socioeconomic settings, protection from both RV5 and RV1 seemed to be lower among children older than 1 year compared with those aged under 1.[6 24 27 28] We did not see this phenomenon in Bolivia, which is consistent with the sustained effectiveness of 79-83% seen through two years of life in the large RV1 clinical trial in high and middle income countries from Latin America.[2] In addition, two studies in impoverished populations in Brazil and Australia have suggested that RV1 (G1P[8]) effectiveness against fully heterotypic strains (such as G2P[4]) might diminish more rapidly than that against homotypic strains, but confidence bounds were too wide for a meaningful conclusion.[29 30] In Bolivia, we saw sustained protection against partially heterotypic G9P[8] strains, which is consistent with findings from the large Latin America pre-licensure RV1 trial, but we also did not have sufficient power to assess duration of protection against fully heterotypic G2P[4] strains. Although these findings are encouraging, our data should be interpreted with some caution as the study was not specifically designed to evaluate effectiveness among specific age groups. Such questions could be better assessed as the vaccine program matures and additional older children are vaccinated.

Strengths and limitations of study

Some limitations must be considered. Estimates of vaccine protection obtained through observational studies hinge upon differences in exposure to vaccination between cases and controls and thus are subject to biases relating to recording and ascertainment of exposure. The availability of documentation of vaccination status differed between case patients (93%), test negative controls (88%), and non-diarrhea controls (98%) in our study and might have biased our estimates of effectiveness to some extent. The control population might be enriched with non-vaccinees if controls with missing vaccine history were more likely to be vaccinated than were cases with missing history, which might have increased our estimates of effectiveness. If controls with missing vaccine history had lower vaccination rates than cases with missing history, effectiveness estimates might be biased towards null. In addition, each of the control groups might have its own specific biases. For example, a false positive enzyme immunoassay result for rotavirus could lead to misclassification of a test negative control as a case. If the vaccine offers any protection, this would enrich the case population with vaccinees thus falsely lowering estimates of effectiveness. However, test negative controls have previously proved to be good controls in studies of rotavirus vaccine effectiveness when compared with community or non-diarrhea controls,[29 31-33] and the similarity in estimates of effectiveness with both control groups in our study provides further reassurance.

Although some differences in demographics and socioeconomic indicators existed between the cases, non-diarrhea controls, and test negative controls, we did not identify any substantial differences between the crude and adjusted estimates of vaccine effectiveness. However, some residual unmeasured confounding could still be present. Bias related to health seeking behavior is possible, but the test negative diarrhea controls are likely to have similar healthcare seeking patterns as rotavirus diarrhea cases and thus to be less prone to this potential bias than are non-diarrhea controls. In addition, our bias indicator analysis did not identify any significant bias with the non-diarrhea controls. Lastly, if fecal shedding of RV1 leads to horizontal transmission of vaccine virus and resultant immune response in unvaccinated contacts of vaccine recipients, as was shown in a clinical trial in the Dominican Republic, this might decrease the attack rates of disease in unvaccinated children and decrease estimates of RV1 effectiveness as measured through observational studies.[34]

Conclusions and policy implications

In conclusion, our study provides evidence for protection by RV1 vaccination against hospital admissions for rotavirus and severe rotavirus disease caused by four different rotavirus strains during the first two years of life in a low income setting in Latin America. Attainment of significant protection from one dose of RV1 also is encouraging for target populations in low and lower-middle income settings, who can develop severe and fatal rotavirus disease during the first few months of life. Further research is needed to refine our understanding of the heterogeneous immune response to rotavirus vaccines in low socioeconomic settings. Potential strategies to improve vaccine efficacy that warrant investigation may include altering the age at rotavirus immunization to avoid the negative influence of circulating maternal antibodies, decoupling rotavirus vaccines and oral polio vaccine, and adding additional doses in the routine schedule or as a booster with the measles dose at the end of infancy. Although understanding the reasons for lower efficacy is important, it should not hinder use of currently available rotavirus vaccines. Our study provides compelling data favoring broader use of rotavirus vaccine in low income settings to reduce the burden of severe and fatal rotavirus disease among children.

We thank the sentinel hospital rotavirus surveillance team in Bolivia for their efforts in the enrollment of the participants for the rotavirus vaccine effectiveness evaluation.

Contributors: MMP, UP, DP, VI, and LHDO created and designed the study. DP, MP, AN, RR, and YR collected the data. AN, YR, VI, RR, KIT, OQ, and MP did the specimen analysis. MMP did the data analysis. MP, DP, VI, MB, UP, and LHDO interpreted the data. MMP drafted the report. DP, MP, AN, YR, VI, RR, KIT, OQ, MB, UP, and LHDO critically revised the report.

Funding: Support for this project was provided by the Program for Appropriate Technology in Health (PATH) through funding from the Global Alliance for Vaccines and Immunisation (GAVI). The views expressed by the authors do not necessarily reflect the views of GAVI or PATH. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: support for this project was provided by PATH through funding from GAVI; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: This case-control evaluation was approved by human subjects' offices at the Centers for Disease Control and Prevention, the Pan American Health Organization, and the Bolivian National Bioethics Committee. Surveillance coordinators obtained informed consent from parents or legal guardian of the child.

Data sharing: No additional data available.

1 World Health Organization. Rotavirus vaccines: an update. *Wkly Epidemiol Rec* 2009;84:533-40.
2 Linhares AC, Velazquez FR, Perez-Schael I, Saez-Llorens X, Abate H, Espinoza F, et al. Efficacy and safety of an oral live attenuated human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in Latin American infants: a randomised, double-blind, placebo-controlled phase III study. *Lancet* 2008;371:1181-9.
3 Madhi SA, Cunliffe NA, Steele D, Witte D, Kirsten M, Louw C, et al. Effect of human rotavirus vaccine on severe diarrhea in African infants. *N Engl J Med* 2010;362:289-98.
4 Ruiz-Palacios GM, Perez-Schael I, Velazquez 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;354:11-22.
5 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;354:23-33.
6 Armah GE, Sow SO, Breiman RF, Dallas MJ, Tapia MD, Feikin DR, et al. Efficacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in sub-Saharan Africa: a randomised, double-blind, placebo-controlled trial. *Lancet* 2011;376:606-14.
7 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* 2011;376:615-23.
8 Patel M, Shane AL, Parashar UD, Jiang B, Gentsch JR, Glass RI. Oral rotavirus vaccines: how well will they work where they are needed most? *J Infect Dis* 2009;200(suppl 1):S39-48.
9 Patel MM, Glass R, Desai R, Tate JE, Parashar UD. Fulfilling the promise of rotavirus vaccines: how far have we come since licensure? *Lancet Infect Dis* 2012;12:561-70.
10 Patel M, Pedreira C, De Oliveira LH, Tate J, Orozco M, Mercado J, et al. Association between pentavalent rotavirus vaccine and severe rotavirus diarrhea among children in Nicaragua. *JAMA* 2009;301:2243-51.
11 World Health Organization. World health report. WHO, 2003:182-4 (available at www.who.int/whr/2003/en/member_states_182-184_en.pdf).
12 Patel MM, Lopez-Collada VR, Bulhoes MM, De Oliveira LH, Bautista Marquez A, Flannery B, et al. Intussusception risk and health benefits of rotavirus vaccination in Mexico and Brazil. *N Engl J Med* 2011;364:2283-92.
13 United Nations Children's Fund. Annual number of births. 2012. http://data.un.org/Data.aspx?d=SOWC&f=inID%3A75.
14 World Health Organization. Generic protocols for (i) hospital-based surveillance to estimate the burden of rotavirus gastroenteritis in children and (ii) a community-based survey on utilization of health care services for gastroenteritis in children. WHO, 2002 (available at http://whqlibdoc.who.int/hq/2002/WHO_V&B_02.15.pdf).
15 Hull JJ, Teel EN, Kerin TK, Freeman MM, Esona MD, Gentsch JR, et al. United States rotavirus strain surveillance from 2005 to 2008: genotype prevalence before and after vaccine introduction. *Pediatr Infect Dis J* 2011;30(1 suppl):S42-7.
16 World Health Organization. Generic protocol for monitoring impact of rotavirus vaccination on rotavirus disease burden and viral strains. WHO, 2009 (available at www.who.int/nuvi/rotavirus/WHO_IVB_08.16_eng.pdf).

What is already known on this topic

Early studies have shown that the monovalent rotavirus vaccine has had a substantial effect on reducing severe childhood diarrhea after routine introduction in middle and high income settings

However, the efficacy of rotavirus vaccine is lower in low income settings with the highest childhood mortality due to diarrhea

In recently published clinical trials of rotavirus vaccines in Africa, waning of efficacy was also noted among children older than 1 year, and concerns exist about protection against strains heterotypic to the vaccine component

What this study adds

These data offer the first evidence of homotypic and heterotypic protection by the monovalent rotavirus vaccine against severe rotavirus disease after routine use in a high mortality setting

The vaccine provided good protection among children under 1 year of age who bear the largest portion of the severe and fatal childhood rotavirus disease

Protection was sustained during the second year of life, a finding that the clinical trials were not powered to evaluate

17 Satten GA, Kupper LL. Sample size determination for pair-matched case-control studies where the goal is interval estimation of the odds ratio. *J Clin Epidemiol* 1990;43:55-9.
18 Hosmer DW, Lemeshow S. Applied logistic regression. 2nd ed. Wiley, 2000.
19 Kleinbaum DG, Klein M, Pryor ER. Modeling strategy for assessing interaction and confounding. In: Logistic regression: a self-learning text. 2nd ed. Springer, 2002.
20 World Health Organization. WHO-UNICEF estimates of Rota_last coverage. 2012. http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tswucoveragerota_last.html.
21 Bahl R, Ray P, Subodh S, Shambharkar P, Saxena M, Parashar U, et al. Incidence of severe rotavirus diarrhea in New Delhi, India, and G and P types of the infecting rotavirus strains. *J Infect Dis* 2005;192(suppl 1):S114-9.
22 Bresee JS, Hummelman E, Nelson EA, Glass RI. Rotavirus in Asia: the value of surveillance for informing decisions about the introduction of new vaccines. *J Infect Dis* 2005;192(suppl 1):S1-5.
23 Cunliffe NA, Kilgore PE, Bresee JS, Steele AD, Luo N, Hart CA, et al. Epidemiology of rotavirus diarrhoea in Africa: a review to assess the need for rotavirus immunization. *Bull World Health Organ* 1998;76:525-37.
24 De Palma O, Cruz L, Ramos H, de Baires A, Villatoro N, Pastor D, et al. Effectiveness of rotavirus vaccination against childhood diarrhoea in El Salvador: case-control study. *BMJ* 2010;340:c2825.
25 Ruiz-Palacios GM, Rivera L, Saez-Llorens X, Vergara R, Cheuvart B, Bouckenooghe A, Linhares A, et al. RIX4414 (Rotarix) has demonstrated efficacy during the first 2 years of life in infants from 11 Latin American Countries (abstract). Presented at the 10th International Rotavirus Symposium, 19-21 September 2012, Bangkok, Thailand.
26 Madhi S, Lerumo T, Louw C, Kirsten M, Neuzil K, Steele D, et al. Efficacy of human rotavirus vaccine RIX4414(RotarixTM) in South African infants during the first year of life—an interim report [abstract]. Presented at the 8th International Rotavirus Syposium, June 3, 2008: Istanbul, Turkey.
27 Cunliffe NA, Witte D, Ngwira BM, Todd S, Bostock NJ, Turner AM, et al. Efficacy of human rotavirus vaccine against severe gastroenteritis in Malawian children in the first two years of life: a randomized, double-blind, placebo controlled trial. *Vaccine* 2012;30(suppl 1):A36-43.
28 Patel M, Pedreira C, De Oliveira LH, Umana J, Tate J, Lopman B, et al. Duration of protection of pentavalent rotavirus vaccination in Nicaragua. *Pediatrics* 2012;130:e365-72.
29 Correia JB, Patel MM, Nakagomi O, Montenegro FM, Germano EM, Correia NB, et al. Effectiveness of monovalent rotavirus vaccine (Rotarix) against severe diarrhea caused by serotypically unrelated G2P[4] strains in Brazil. *J Infect Dis* 2010;201:363-9.
30 Snelling TL, Andrews RM, Kirkwood CD, Culvenor S, Carapetis JR. Case-control evaluation of the effectiveness of the G1P[8] human rotavirus vaccine during an outbreak of rotavirus G2P[4] infection in central Australia. *Clin Infect Dis* 2011;52:191-9.
31 Boom JA, Tate JE, Sahni LC, Rench MA, Hull JJ, Gentsch JR, et al. Effectiveness of pentavalent rotavirus vaccine in a large urban population in the United States. *Pediatrics* 2010;125:e199-207.
32 Boom JA, Tate JE, Sahni LC, Rench MA, Quaye O, Mijatovic-Rustempasic S, et al. Sustained protection from pentavalent rotavirus vaccination during the second year of life at a large, urban United States pediatric hospital. *Pediatr Infect Dis J* 2010;29:1133-5.
33 Staat MA, Payne DC, Donauer S, Weinberg GA, Edwards KM, Szilagyi PG, et al. Effectiveness of pentavalent rotavirus vaccine against severe disease. *Pediatrics* 2011;128:e267-75.
34 Rivera L, Pena LM, Stainier I, Gillard P, Cheuvart B, Smolenov I, et al. Horizontal transmission of a human rotavirus vaccine strain—a randomized, placebo-controlled study in twins. *Vaccine* 2011;29:9508-13.

Accepted: 28 May 2013

Cite this as: *BMJ* 2013;346:f3726

Tables

Table 1| Comparison of characteristics of case patients with rotavirus diarrhea, controls with non-rotavirus diarrhea, and controls with non-diarrheal illness, March 2010 to June 2011. Values are numbers (percentages) unless stated otherwise

Characteristic	Cases (rotavirus positive*) (n=400)	Controls			
		Rotavirus negative† (n=718)	P value	Non-diarrhea‡ (n=1200)	P value
Median (range) age, months	12 (1-35)	12 (2-32)	0.26§	12 (1-36)	0.27§
Male sex	260 (65)	400 (56)	0.002	642 (54)	<0.001
Chronic underlying illness	21 (5)	39 (5)	0.89	118 (10)	0.01
History of breast feeding	371 (93)	674 (94)	0.69	1161 (97)	0.002
Day care attendance	61 (15)	57 (8)	<0.001	117 (10)	0.009
Low birth weight (<2500 g)	34/367 (9)	83/680 (12)	0.15	113/1135 (10)	0.7
Maternal education:			0.01		<0.001
None	7/398 (2)	14/712 (2)		20/1194 (2)	
Primary school	119/398 (30)	230/712 (32)		279/1194 (23)	
Secondary school	210/398 (53)	311/712 (44)		591/1194 (50)	
Tertiary school	62/398 (16)	157/712 (22)		304/1194 (25)	
Median (range) No of children in home	2 (1-18)	2 (1-20)	0.12§	2 (1-10)	<0.001§
Median (range) No of people in home	4.5 (1-16)	4.0 (1-20)	0.86§	4 (1-20)	0.47§
Socioeconomic parameters:					
Median (range) No of rooms in home	3 (1-11)	3 (1-11)	0.03§	4 (1-11)	<0.001§
Electricity in home	392 (98)	707 (98)	0.56	1176 (98)	0.92
Own motorized vehicle	99 (25)	177 (25)	0.97	343 (29)	0.14
Telephone in home	85 (21)	171 (24)	0.33	353 (29)	0.002
Computer in home	59 (15)	141 (20)	0.04	284 (24)	<0.001

*Patients admitted to hospital or emergency department with acute gastroenteritis who had enzyme immunoassay stool testing positive for rotavirus.

†Patients admitted to hospital or emergency department with acute gastroenteritis who had enzyme immunoassay stool testing negative for rotavirus.

‡Non-diarrhea hospital controls were matched by age (±30 days) and hospital.

§P value for Wilcoxon rank sum test.

Table 2| Effectiveness of rotavirus vaccine against rotavirus disease by severity, Bolivia

	One dose vaccinees*			Two dose vaccinees*		
		Vaccine effectiveness, % (95% CI)			Vaccine effectiveness, % (95% CI)	
Group	No/total (%)	Crude	Adjusted	No/total (%)	Crude	Adjusted
Rotavirus disease requiring hospital admission						
Cases	100/192 (52)	—	—	208/300 (69)	—	—
Non-diarrhea controls†	226/343 (66)	57 (35 to 71)	56 (32 to 72)	857/974 (88)	80 (70 to 86)	77 (65 to 84)
Test negative controls‡	131/208 (63)	39 (8 to 60)	36 (0 to 59)	510/587 (87)	70 (56 to 79)	69 (54 to 79)
Severe rotavirus disease (Vesikari severity score ≥11)						
Cases	92/177 (52)	—	—	196/281 (70)	—	—
Non-diarrhea controls†	207/316 (66)	55 (30 to 70)	54 (28 to 70)	803/912 (88)	79 (68 to 85)	76 (64 to 84)
Test negative controls‡	131/208 (63)	42 (11 to 62)	34 (–5 to 69)	510/587 (87)	70 (55 to 79)	69 (53 to 79)
Very severe rotavirus disease (Vesikari score ≥15)						
Cases	53/91 (58)	—	—	100/138 (72)	—	—
Non-diarrhea controls†	112/166 (67)	40 (–1 to 68)	40 (–9 to 66)	407/461 (88)	77 (60 to 87)	74 (54 to 85)
Test negative controls‡	131/208 (63)	24 (–27 to 55)	6 (–63 to 78)	510/587 (87)	66 (44 to 79)	62 (37 to 88)

*Cases and controls were considered vaccinated with respective number of doses (one or two) if most recent dose was administered ≥14 days before date of case's hospital visit.

†Because non-diarrhea controls were matched on age and hospital, conditional logistic regression was used to compute odds ratio for vaccination (one or two doses) versus no vaccination; crude vaccine effectiveness includes only vaccination in model; adjusted vaccine effectiveness for model with hospital admission includes sex, number of children and rooms in home, and computer; model for Vesikari ≥11 includes sex and number of children and rooms in home; model for Vesikari ≥15 includes sex and number of rooms in home.

‡Unconditional logistic regression was used to compute odds ratio for vaccination (one or two doses) versus no vaccination among cases and test negative controls; crude vaccine effectiveness adjusts only for age in months, month/year of birth, and hospital; adjusted vaccine effectiveness for model with hospital admission includes age in months, month/year of birth, hospital, sex, number of children and rooms in home, and computer; model for Vesikari ≥11 includes age in months, month/year of birth, hospital, sex, and number of children and rooms in home; model for Vesikari ≥15 includes age in months, month/year of birth, hospital, sex, and number of rooms in home.

Table 3| Strain specific effectiveness of two doses of rotavirus vaccine* against hospital admission with rotavirus, Bolivia

Group	No/total (%)	Vaccine effectiveness (95% CI)	
		Crude	Adjusted
G9P[8] hospital admission			
Cases	52/77 (68)		
Non-diarrhea controls†	233/253 (92)	86 (71 to 93)	85 (69 to 93)
Test negative controls‡	510/586 (87)	80 (64 to 89)	80 (60 to 90)
G3P[8] hospital admission			
Cases	30/42 (71)		
Non-diarrhea controls†	126/130 (97)	92 (70 to 98)	93 (70 to 98)
Test negative controls‡	510/586 (87)	72 (23 to 89)	74 (22 to 91)
G2P[4] hospital admission			
Cases	45/56 (80)		
Non-diarrhea controls†	163/180 (91)	68 (16 to 88)	69 (14 to 89)
Test negative controls‡	510/586 (87)	60 (14 to 81)	59 (7 to 78)
G9P[6] hospital admission			
Cases	7/14 (50)		
Non-diarrhea controls†	31/43 (72)	88 (25 to 98)	87 (19 to 98)
Test negative controls‡	510/586 (87)	77 (33 to 93)	80 (37 to 94)

*Cases and controls were considered vaccinated with two doses if the most recent dose was administered ≥14 days before date of case's hospital visit.
†For non-diarrheal controls, crude vaccine effectiveness includes only vaccination in model; adjusted vaccine effectiveness for model with G9P[8] includes sex; model for G3P[8] includes number of children rooms in home; model for G2P[4] includes number of children in home and maternal education; model for G9P[6] includes only vaccination.
‡For test negative controls, crude vaccine effectiveness adjusts only for hospital, age in months, and month/year of birth; adjusted vaccine effectiveness for G9P[8] includes hospital, age in months, month/year of birth, and sex; G3P[8] includes hospital, age in months, month/year of birth, sex, and maternal education; G2P[4] includes hospital, age in months, month/year of birth, and number of children in home; G9P[6] includes hospital, age in months, and month/year of birth.

Table 4 Effectiveness (% (95% CI)) of full series of rotavirus vaccine* against rotavirus disease stratified by age, Bolivia

	Non-diarrhea controls†		Test negative controls‡	
Subgroups	**Crude**	**Adjusted**	**Crude**	**Adjusted**
Rotavirus hospital admission				
All ages	80 (70 to 86)	77 (65 to 84)	70 (53 to 80)	69 (54 to 79)
Age 6-11 months	79 (57 to 90)	77 (51 to 89)	65 (38 to 80)	64 (34 to 80)
Age ≥12 months	78 (62 to 87)	76 (59 to 86)	76 (62 to 87)	72 (52 to 86)
Vesikari score ≥11 (severe diarrhea)				
All ages	79 (68 to 85)	76 (64 to 84)	70 (56 to 79)	69 (53 to 79)
Age 6-11 months	79 (58 to 89)	78 55 to 91)	66 (39 to 81)	66 (34 to 82)
Age ≥12 months	78 (63 to 87)	76 (59 to 86)	77 (62 to 87)	72 (51 to 86)
G9P[8] hospital admission				
All ages	86 (71 to 93)	85 (69 to 93)	80 (64 to 89)	80 (60 to 90)
Age 6-11 months	89 (65 to 97)	90 (65 to 97)	81 (51 to 92)	82 (59 to 92)
Age ≥12 months	83 (59 to 93)	82 (47 to 94)	78 (73 to 95)	78 (46 to 91)

*Cases and controls were considered vaccinated with respective number of doses (one, two, or three) if most recent dose was administered ≥14 days before date of case's hospital visit.

†Because non-diarrhea controls were matched on age and hospital, conditional logistic regression was used to compute odds ratio for vaccination versus no vaccination; crude vaccine effectiveness includes only vaccination in model; adjusted vaccine effectiveness for model with hospital admission includes sex, day care, and computer for 6-11 months and sex, number of children, and rooms for ≥12 months; model for Vesikari ≥11 includes sex, day care, and telephone for 6-11 months and sex and number of children and rooms for ≥12 months; model for Vesikari ≥15 includes none for 6-11 months and sex and number of rooms for ≥12 months.

‡Unconditional logistic regression was used to compute odds ratio for vaccination versus no vaccination among cases and test negative controls; crude vaccine effectiveness adjusts only for month/year of birth and hospital; adjusted vaccine effectiveness for model with hospital admission and Vesikari ≥11 includes month/year of birth, hospital, sex, and day care for 6-11 months and month/year of birth, hospital, and day care for ≥12 months; adjusted model for G9P[8] includes month/year of birth and hospital for 6-11 and ≥12 months.

Figures

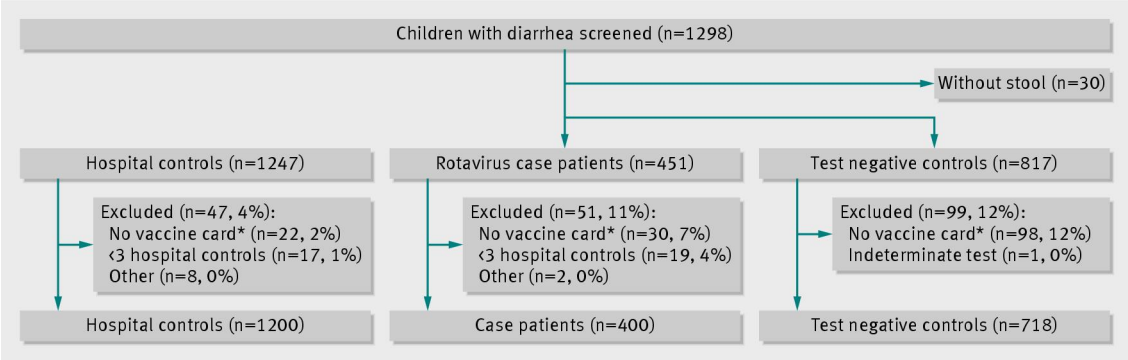

Fig 1 Flow chart depicting enrollment of rotavirus case patients, non-diarrhea controls, and test negative controls. *Children with or without verbal history of vaccination and for whom no records were found in vaccination clinics

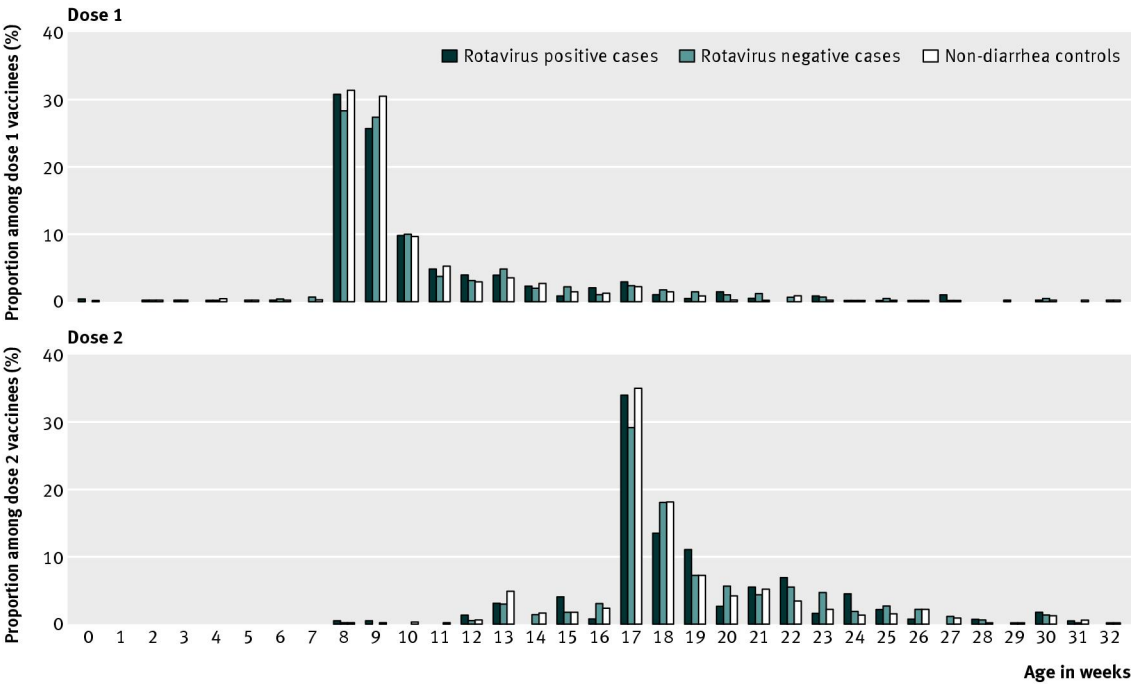

Fig 2 Age at rotavirus vaccine administration among rotavirus positive cases, rotavirus negative controls, and non-diarrhea controls