

# Literature Rotavirus vaccines

**Angel J, Franco MA, Greenberg HB. Rotavirus immune responses and correlates of protection. Curr Opin Virol. 2012 Aug;2(4):419-25. doi: 10.1016/j.coviro.2012.05.003. Epub 2012 Jun 5.**

Selected topics in the field of rotavirus immunity are reviewed focusing on recent developments that may improve efficacy and safety of current and future vaccines. Rotaviruses (RVs) have developed multiple mechanisms to evade interferon (IFN)-mediated innate immunity. Compared to more developed regions of the world, protection induced by natural infection and vaccination is reduced in developing countries where, among other factors, high viral challenge loads are common and where infants are infected at an early age. Studies in developing countries indicate that rotavirus-specific serum IgA levels are not an optimal correlate of protection following vaccination, and better correlates need to be identified. Protection against rotavirus following vaccination is substantially heterotypic; nonetheless, a role for homotypic immunity in selection of circulating postvaccination strains needs further study.

**Armah GE, Sow SO, Breiman RF, Dallas MJ, Tapia MD, Feikin DR, Binka FN, Steele AD, Laserson KF, Ansah NA, Levine MM, Lewis K, Coia ML, Attah-Poku M, Ojwando J, Rivers SB, Victor JC, Nyambane G, Hodgson A, Schödel F, Ciarlet M, Neuzil KM. 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. 2010 Aug 21;376(9741):606-14.**

Rotavirus gastroenteritis causes many deaths in infants in sub-Saharan Africa. Because rotavirus vaccines have proven effective in developed countries but had not been tested in developing countries, we assessed efficacy of a pentavalent rotavirus vaccine against severe disease in Ghana, Kenya, and Mali between April, 2007, and March, 2009.

**METHODS:** In our multicentre, double-blind, placebo-controlled trial, undertaken in rural areas of Ghana and Kenya and an urban area of Mali, we randomly assigned infants aged 4-12 weeks without symptoms of gastrointestinal disorders in a 1:1 ratio to receive three oral doses of pentavalent rotavirus vaccine 2 mL or placebo at around 6 weeks, 10 weeks, and 14 weeks of age. Infants with HIV infection were not excluded. Randomisation was done by computer-generated randomisation sequence in blocks of six. We obtained data for gastrointestinal symptoms from parents on presentation to health-care facilities and clinical data were obtained prospectively by clinicians. The primary endpoint was severe rotavirus gastroenteritis (Vesikari score  $\geq 11$ ), detected by enzyme immunoassay, arising 14 days or more after the third dose of placebo or vaccine to end of study (March 31, 2009; around 21 months of age). Analysis was per protocol; infants who received scheduled doses of vaccine or placebo without intervening laboratory-confirmed naturally occurring rotavirus disease earlier than 14 days after the third dose and had complete clinical and laboratory results were included in the analysis. This study is registered with ClinicalTrials.gov, number NCT00362648.

**FINDINGS:** 5468 infants were randomly assigned to receive pentavalent rotavirus vaccine (n=2733) or placebo (n=2735). 2357 infants assigned to vaccine and 2348 assigned to placebo

were included in the per-protocol analysis. 79 cases of severe rotavirus gastroenteritis were reported in 2610.6 person-years in the vaccine group, compared with 129 cases in 2585.9 person-years in the placebo group, resulting in a vaccine efficacy against severe rotavirus gastroenteritis of 39.3% (95% CI 19.1-54.7,  $p=0.0003$  for efficacy  $>0\%$ ). Median follow-up in both groups was 527 days starting 14 days after the third dose of vaccine or placebo was given. 42 (1.5%) of 2723 infants assigned to receive vaccine and 45 (1.7%) of 2724 infants assigned to receive placebo had a serious adverse event within 14 days of any dose. The most frequent serious adverse event was gastroenteritis (vaccine 17 [0.6%]; placebo 17 [0.6%]).

#### INTERPRETATION:

Pentavalent rotavirus vaccine is effective against severe rotavirus gastroenteritis in the first 2 years of life in African countries with high mortality in infants younger than 5 years. We support WHO's recommendation for adoption of rotavirus vaccine into national expanded programmes on immunisation in Africa.

**Banerjee I et al. Neonatal infection with G10P[11] rotavirus did not confer protection against subsequent rotavirus infection in a community cohort in Vellore, South India. *Journal of Infectious Diseases*, 2007;195:625-632.**

**BACKGROUND:** Various observational studies have suggested that neonatal rotavirus infection confers protection against diarrhea due to subsequent rotavirus infection. We examined the incidence of rotavirus infection and diarrhea during the first 2 years of life among children infected with the G10P[11] rotavirus strain during the neonatal period and those not infected with rotavirus.

**METHODS:** Children were recruited at birth and were followed up at least twice weekly. Stool samples, collected every 2 weeks for surveillance and at each episode of diarrhea, were screened by enzyme-linked immunosorbent assay and were genotyped by polymerase chain reaction.

**RESULTS:** Among 33 children infected neonatally with G10P[11] and 300 children not infected with rotavirus, there was no significant difference in the rates of rotavirus-positive diarrhea (rate ratio [RR], 1.05 [95% confidence interval [CI], 0.61-1.79]), moderate or severe rotavirus-positive diarrhea (RR, 1.42 [95% CI, 0.73-2.78]), or asymptomatic rotavirus shedding (RR, 1.25 [95% CI, 0.85-1.83]).

**CONCLUSION:** Neonatal G10P[11] infection with a strain resembling a vaccine candidate did not confer protection against subsequent rotavirus infection or diarrhea of any severity in this setting.

**Buttery JP, Danchin MH, Lee KJ, Carlin JB, McIntyre PB, Elliott EJ, Booy R, Bines JE; PAEDS/APSU Study Group. Intussusception following rotavirus vaccine administration: post-marketing surveillance in the National Immunization Program in Australia. *Vaccine*. 2011 Apr 5;29(16):3061-6.**

**INTRODUCTION:** In Australia, post-marketing surveillance for intussusception following vaccination commenced with funding of RotaTeq(®) and Rotarix(®) vaccines under the National Immunization Program (NIP) in July 2007.

**METHODS:** Two active surveillance mechanisms (hospital-based case ascertainment and monthly reports from paediatricians) identified intussusception cases between 1st July 2007 and 31st December 2008 in four states. Linkage to vaccination records identified cases occurring within 1-7 and 1-21 days of rotavirus vaccination. Expected cases within the post-vaccination windows were calculated by applying rates of intussusception from national hospitalisation data over 6 years (mid-2000 to mid-2006), by age and state, to numbers vaccinated (by dose) according to the Australian Childhood Immunization Register.

**RESULTS:** Combining exposure windows associated with all doses of rotavirus vaccine from 1 to 9 months of age, there was no evidence of an increased risk of intussusception following vaccination for either vaccine. However, in infants 1 to <3 months of age, there was suggestive evidence of excess intussusception cases 1-7 and 1-21 days following dose 1 (1-7 days: RotaTeq(®) relative risk (RR)=5.3, 95% confidence interval [CI] 1.1,15.4; Rotarix(®) RR 3.5, 95% CI 0.7,10.1; 1-21 days: RotaTeq(®) RR 3.5, 95% CI 1.3, 7.6; Rotarix(®)RR 1.5, 95% CI 0.4, 3.9). There was no evidence that clinical outcome of intussusception occurring within 21 days of rotavirus vaccination differed from that in cases occurring later post-vaccination.

**CONCLUSION:** Although we found no overall increase in intussusception following receipt of rotavirus vaccine, there was some evidence of an elevated risk following the first dose of both vaccines. Larger population-based studies using linked databases are required to provide more definitive evidence.

**Cardemil CV et al. Two Rotavirus Outbreaks Caused by Genotype G2P[4] at Large Retirement Communities: Cohort Studies. Ann Intern Med. 6 November 2012;157(9):621-631.**

**Background:** Outbreaks of rotavirus gastroenteritis in elderly adults are reported infrequently but are often caused by G2P[4] strains. In 2011, outbreaks were reported in 2 Illinois retirement facilities.

**Objective:** To implement control measures, determine the extent and severity of illness, and assess risk factors for disease among residents and employees.

**Design:** Cohort studies using surveys and medical chart abstraction.

**Setting:** Two large retirement facilities in Cook County, Illinois.

**Patients:** Residents and employees at both facilities and community residents with rotavirus disease.

**Measurements:** Attack rates, hospitalization rates, and rotavirus genotype.

**Results:** At facility A, 84 of 324 residents (26%) were identified with clinical or laboratory-confirmed rotavirus gastroenteritis (median age, 84 years) and 11 (13%) were hospitalized. The outbreak lasted 7 weeks. At facility B, 90 case patients among 855 residents (11%) were identified (median age, 88 years) and 19 (21%) were hospitalized. The facility B outbreak lasted 9.3 weeks. Ill employees were identified at both locations. In each facility, attack rates seemed to differ by residential setting, with the lowest rates among those in more separated settings or with high baseline level of infection control measures. The causative genotype for both outbreaks was G2P[4]. Some individuals shed virus detected by enzyme immunoassay or genotyping reverse transcription polymerase chain reaction for at least 35 days. G2P[4] was

also identified in 17 of 19 (89%) samples from the older adult community but only 15 of 40 (38%) pediatric samples.

Limitation: Medical or cognitive impairment among residents limited the success of some interviews.

Conclusion: Rotavirus outbreaks can occur among elderly adults in residential facilities and can result in considerable morbidity. Among older adults, G2P[4] may be of unique importance. Health professionals should consider rotavirus as a cause of acute gastroenteritis in adults.

**Centers for Disease Control and Prevention (CDC). Rotavirus surveillance--worldwide, 2001-2008. MMWR Morb Mortal Wkly Rep. 2008 Nov 21;57(46):1255-7.**

Rotavirus infection is the leading cause of severe acute diarrhea among young children worldwide. An estimated 527,000 children aged <5 years die from rotavirus diarrhea each year, with >85% of these deaths occurring in low-income countries of Africa and Asia. Two licensed rotavirus vaccines have shown efficacy of 85%-98% against severe rotavirus diarrhea in trials conducted in the Americas and Europe, and they have been introduced into routine immunization programs in 11 countries in these regions and in Australia. Additional trials of these vaccines are ongoing to assess efficacy in low-income countries of Asia and Africa, where vaccine performance might be affected by factors such as concurrent enteric infections, greater prevalence of malnutrition, and a greater prevalence of unusual rotavirus strains. Results of these additional trials are expected within the next 1-2 years. To collect epidemiologic and burden-of-disease data that could form the basis of vaccination policy worldwide, beginning in 2001, the World Health Organization (WHO), in collaboration with partners, established networks of hospital-based sentinel surveillance sites for detection of rotavirus diarrhea and characterization of rotavirus strains. This report presents an analysis of results from the WHO surveillance networks for 2001-2008, which indicated that approximately 40% of diarrhea hospitalizations among children aged <5 years worldwide were attributed to rotavirus infection. The most common rotavirus strains found were G1, G2, G3, G4, and G9, and the distribution of strains varied markedly across regions. These data demonstrate the substantial burden of rotavirus diarrhea worldwide and highlight the potential health impact of vaccination.

**Cherian T, Wang S, Mantel C. Rotavirus vaccines in developing countries: the potential impact, implementation challenges, and remaining questions. Vaccine. 2012 Apr 27;30 Suppl 1:A3-6.**

Diarrhoeal disease is one of the commonest causes of death in children, especially in developing countries in Africa and Asia. Rotavirus has been consistently identified as the commonest pathogen associated with severe diarrhoea. Hence, the availability of vaccines against this organism provides the opportunity to reduce child mortality. Data from efficacy trials in developing countries in Africa and Asia showed that the vaccine efficacy was lower than that observed in other countries. Nevertheless, the vaccines are expected to be of significant benefit in high mortality countries in these regions. While the reports published in this supplement add to our understanding about the performance of these vaccines in developing countries in these regions, questions remain over the overall impact of these vaccines when used in national programmes of developing countries in Africa and Asia, the

optimal vaccination schedules and the impact of age restrictions for vaccine use on immunization coverage. Additional research is required to improve understanding on the performance of these vaccines in developing countries in Africa and Asia and measures that may improve performance. Data that will assist in the definition of the optimal immunization schedule and possibly allow relaxation of the age restrictions for vaccine use may help in enhancing the impact of the vaccines in these countries. Finally, disease surveillance and studies are required to document the impact of vaccination and monitor changes in disease epidemiology.

**Clark HF et al. Rotavirus vaccines. In: Plotkin S, Orenstein W, Offit P, eds. Vaccines, 5th ed. Philadelphia, Saunders, 2008:715-734. (No summary. New edition 2012)**

**Cunliffe NA, Ngwira BM, Dove W, Thindwa BD, Turner AM, Broadhead RL, Molyneux ME, Hart CA. Epidemiology of rotavirus infection in children in Blantyre, Malawi, 1997-2007. J Infect Dis. 2010 Sep 1;202 Suppl:S168-74.**

Acute gastroenteritis caused by rotavirus infection is an important cause of morbidity and mortality among infants and young children in Africa. From 1997 through 2007, we enrolled 3740 children <5 years of age with acute gastroenteritis who received hospital care at the Queen Elizabeth Central Hospital in Blantyre, Malawi. Group A rotavirus was detected in fecal specimens by enzyme immunoassay. Rotavirus strains were characterized for VP7 (G) and VP4 (P) types with use of reverse-transcription polymerase chain reaction. Overall, rotavirus was detected in one-third of children. The median age of children with rotavirus gastroenteritis was 7.8 months, compared with 10.9 months for those without rotavirus in stool specimens ( $P > .001$ ). Rotavirus circulated throughout the year, with the detection proportion greatest during the dry season (from May through October). A total of 15 single rotavirus strain types were detected during the study period, with genotypes P[8]G1, P[6]G8, P[4]G8, P[6]G1, P[8]G3, and P[6]G9 comprising 83% of all strains characterized. Serotype G12 was detected for the first time in Blantyre during the final 2 years of study. Zoonotic transmission and viral reassortment contributed to the rich diversity of strains identified. Current rotavirus vaccines have the potential to greatly reduce the rotavirus disease burden in Malawi, but they will be required to protect against a broad range of rotavirus serotypes in a young population with year-round rotavirus exposure.

**Cunliffe NA, Gondwe JS, Kirkwood CD, Graham SM, Nhlane NM, Thindwa BD, Dove W, Broadhead RL, Molyneux ME, Hart CA. Effect of concomitant HIV infection on presentation and outcome of rotavirus gastroenteritis in Malawian children. Lancet. 2001 Aug 18;358(9281):550-5.**

**BACKGROUND:** Rotaviruses represent important causes of severe diarrhoea in early childhood. We examined the effect of HIV infection on the presentation and outcome of rotavirus gastroenteritis in Malawian children.

**METHODS:** Children younger than 5 years who were treated for acute gastroenteritis at the Queen Elizabeth Central Hospital in Blantyre from July, 1997, to June, 1999, were enrolled. Children with rotavirus diarrhoea, with and without HIV infection, were followed up for up to 4 weeks after hospital discharge. Rotavirus disease severity (assessed with a 20-point score),

duration of rotavirus shedding, and seroresponse to rotavirus were compared between HIV-infected and HIV-uninfected children.

**FINDINGS:** 786 inpatients (median age 8 months, 271 [34%] of whom were HIV-1-infected) and 400 outpatients (median age 9 months, 65 [16%] of whom were HIV-infected) were enrolled. Rotavirus was detected less frequently among HIV-infected children (102 of 336 [30%]) than among HIV-uninfected children (348 of 850 [41%], (relative risk 0.71 [95% CI 0.53-0.87],  $p=0.0007$ ). There were no differences in rotavirus disease severity for hospitalised children with and without HIV infection, but HIV-infected children were more likely to die during follow-up (11/50 [22%]) than HIV-uninfected children (0/61,  $p<0.0001$ ). Of 29 HIV-infected and 45 HIV-uninfected children who completed follow-up, six (21%) HIV-infected children shed rotavirus, compared with two (4%) HIV-uninfected children (4.66 [1.01-21.51],  $p=0.05$ ), but shedding was not associated with diarrhoea. Three-quarters of children exhibited a four-fold rise of serum IgG or IgA to rotavirus, which did not vary by HIV status.

**INTERPRETATION:** Malawian children with concomitant HIV infection resolved acute rotavirus infections. Rotavirus vaccine safety and immunogenicity in HIV-infected infants should now be determined.

**Dennehy PH, Vesikari T, Matson DO, Itzler RF, Dallas MJ, Goveia MG, DiNubile MJ, Heaton PM, Ciarlet M. Efficacy of the pentavalent rotavirus vaccine, RotaTeq® (RV5), between doses of a 3-dose series and with less than 3 doses (incomplete regimen). Hum Vaccin. 2011 May;7(5):563-8.**

Post-hoc analyses of the Rotavirus Efficacy and Safety Trial (REST) were conducted to determine whether the pentavalent rotavirus vaccine (RV5) confers early protection against rotavirus gastroenteritis (RVGE) before completion of the 3-dose regimen. To evaluate the efficacy of RV5 between doses in reducing the rates of RVGE-related hospitalizations and emergency department (ED) visits in infants who ultimately received all 3 doses of RV5/placebo, events occurring from 2 weeks after the first and second doses to receipt of the subsequent dose (Analysis A) and events occurring from 2 weeks after the first and second doses to 2 weeks after the subsequent dose (Analysis B) were analyzed. In Analysis A, RV5 reduced the rates of combined hospitalizations and ED visits for G1-G4 RVGE or RVGE regardless of serotype between doses 1 and 2 by 100% (95% confidence interval [CI]: 72-100%) or 82% (95% CI: 39-97%), respectively, and between doses 2 and 3, RV5 reduced the rates of combined hospitalizations and ED visits for G1-G4 RVGE or RVGE regardless of serotype by 91% (95% CI: 63-99%) or 84% (95% CI: 54-96%), respectively. Similar rate reductions were observed in Analysis B. These data suggest that RV5 provides a high level of protection between doses against hospitalizations and ED visits for RVGE starting as early as 14 days after the first dose.

**do Carmo GM, Yen C, Cortes J, Siqueira AA, de Oliveira WK, Cortez-Escalante JJ, Lopman B, Flannery B, de Oliveira LH, Carmo EH, Patel M. Decline in diarrhea mortality and admissions after routine childhood rotavirus immunization in Brazil: a time-series analysis. PLoS Med. 2011 Apr;8(4):e1001024.**

**BACKGROUND:** In 2006, Brazil began routine immunization of infants <15 wk of age with a single-strain rotavirus vaccine. We evaluated whether the rotavirus vaccination program was associated with declines in childhood diarrhea deaths and hospital admissions by monitoring disease trends before and after vaccine introduction in all five regions of Brazil with varying disease burden and distinct socioeconomic and health indicators.

**METHODS AND FINDINGS:** National data were analyzed with an interrupted time-series analysis that used diarrhea-related mortality or hospitalization rates as the main outcomes. Monthly mortality and admission rates estimated for the years after rotavirus vaccination (2007-2009) were compared with expected rates calculated from pre-vaccine years (2002-2005), adjusting for secular and seasonal trends. During the three years following rotavirus vaccination in Brazil, rates for diarrhea-related mortality and admissions among children <5 y of age were 22% (95% confidence interval 6%-44%) and 17% (95% confidence interval 5%-27%) lower than expected, respectively. A cumulative total of ~1,500 fewer diarrhea deaths and 130,000 fewer admissions were observed among children <5 y during the three years after rotavirus vaccination. The largest reductions in deaths (22%-28%) and admissions (21%-25%) were among children younger than 2 y, who had the highest rates of vaccination. In contrast, lower reductions in deaths (4%) and admissions (7%) were noted among children two years of age and older, who were not age-eligible for vaccination during the study period.

**CONCLUSIONS:** After the introduction of rotavirus vaccination for infants, significant declines for three full years were observed in under-5-y diarrhea-related mortality and hospital admissions for diarrhea in Brazil. The largest reductions in diarrhea-related mortality and hospital admissions for diarrhea were among children younger than 2 y, who were eligible for vaccination as infants, which suggests that the reduced diarrhea burden in this age group was associated with introduction of the rotavirus vaccine. These real-world data are consistent with evidence obtained from clinical trials and strengthen the evidence base for the introduction of rotavirus vaccination as an effective measure for controlling severe and fatal childhood diarrhea.

**Feikin DR, Laserson KF, Ojwando J, Nyambane G, Ssempijja V, Audi A, Nyakundi D, Oyieko J, Dallas MJ, Ciarlet M, Neuzil KM, Breiman RF. Efficacy of pentavalent rotavirus vaccine in a high HIV prevalence population in Kenya. Vaccine. 2012 Apr 27;30 Suppl 1:A52-60.**

Rotavirus gastroenteritis (RVGE) is a leading cause of death in African children. The efficacy of pentavalent rotavirus vaccine (PRV) against severe RVGE evaluated in Ghana, Kenya, and Mali in a randomized, double-blind, placebo-controlled trial, showed a combined regional efficacy of 39.3% (95% confidence interval [CI]: 19.1,54.7) in nearly 2 years of follow-up. This report concentrates on the Kenya findings.

**METHODS:** Infants received 3 doses of PRV/placebo at approximately 6-, 10-, and 14-weeks of age. HIV testing was offered to all participants. Data on illness symptoms and signs were collected upon presentation to healthcare facilities, where stools were collected, and analyzed by rotavirus-specific enzyme-linked immunosorbent assay. The primary endpoint was severe RVGE (Vesikari score  $\geq 11$ ), occurring  $\geq 14$  days following the third dose. At monthly home visits, symptoms of illnesses during the past 2 weeks were solicited and limited physical exams were performed; dehydration was defined by WHO's Integrated Management of Childhood Illness.

**FINDINGS:** Vaccine efficacy (VE) against severe RVGE through nearly 2 years of follow-up among 1308 Kenyan children was 63.9% (95% CI: -5.9,89.8). Through the first year of life, VE against severe RVGE was 83.4% (95% CI: 25.5,98.2). From home visits, VE against all-cause gastroenteritis with severe dehydration was 34.4% (95% CI: 5.3,54.6) through the first year and 29.7% (95% CI: 2.5,49.3) through the entire follow-up period. The reduction in incidence of gastroenteritis with severe dehydration in the community during the first year of

life (19.0 cases/100 person-years) was almost six times greater than the reduction in severe RVGE presenting to the clinic (3.3/100 person-years). Oral rehydration solution use was lower among PRV recipients (VE 23.1%, 95% CI: 8.8,35.1). An estimated 41% of gastroenteritis with severe dehydration in the first year reported at home was rotavirus-related.

**CONCLUSIONS:** PRV significantly reduced severe RVGE in Kenya. The impact of PRV might be greatest in rural Africa in protecting the many children who develop severe gastroenteritis and cannot access health facilities.

**Fischer TK, Valentiner-Branth P, Steinsland H, Perch M, Santos G, Aaby P, Mølbak K, Sommerfelt H. Protective immunity after natural rotavirus infection: a community cohort study of newborn children in Guinea-Bissau, West Africa. J Infect Dis. 2002 Sep 1;186(5):593-7.**

To study the natural history of rotavirus infection and to determine the protection it confers against reinfection and diarrhea, 200 newborns in Guinea-Bissau were prospectively followed for up to 2 years. Rotavirus was detected in stool specimens collected weekly. By age 2 years, the incidence of primary rotavirus infection was 74%. In the first 3 months of life, 17% of the infections were diarrhea associated, compared with 60% at 9-11 months; after age 18 months, all infections were asymptomatic. A primary infection conferred 52% (95% confidence interval [CI], 16% to 73%) and 70% (95% CI, 29% to 87%) protection against subsequent rotavirus infection and rotavirus diarrhea, respectively. The protection was 66% (95% CI, 24% to 85%) against reinfection within the same epidemic, compared with 34% (95% CI, -29% to 67%) against reinfection in any subsequent epidemic. The high level of protection against symptomatic rotavirus infection provides an important incentive for development of a rotavirus

**Giaquinto C, Dominiak-Felden G, Van Damme P, Myint TT, Maldonado YA, Spoulou V, Mast TC, Staat MA. Summary of effectiveness and impact of rotavirus vaccination with the oral pentavalent rotavirus vaccine: a systematic review of the experience in industrialized countries. Hum Vaccin. 2011 Jul;7(7):734-48. doi: 10.4161/hv.7.7.15511.**

The pentavalent rotavirus (RV) vaccine RotaTeq™ has been available in industrialized countries since 2006. Several studies have been conducted to evaluate the benefit of RV vaccination under routine conditions of use. A systematic review of all publicly available data from RotaTeq™ vaccine-effectiveness and vaccination-impact studies in the USA, Europe and Australia between 2006 and February 2010 was undertaken. Depending on the population studied, effectiveness of up to 100% (95% confidence interval 85-100%) associated with decreased hospitalizations for RV gastroenteritis (RVGE) was seen. Vaccination-impact studies demonstrated that the burden of RVGE has been reduced significantly since the introduction of RV vaccination. Evidence included reductions in healthcare utilization due to RVGE (hospitalizations and emergency-department visits reduced by up to 90%), reductions in the magnitude and duration of the RV season as assessed by laboratory testing for RV, and the possible induction of herd immunity.



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**Gilliland SM et al. Investigation of porcine circovirus contamination in human vaccines. *Biologicals*, 2012, 40:270-277.**

DNA from porcine circovirus type 1 (PCV1) and 2 (PCV2) has recently been detected in two vaccines against rotaviral gastroenteritis from manufacturers A and B. We investigated if PCV1 sequences are present in other viral vaccines. We screened seeds, bulks and final vaccine preparations from ten manufacturers using qRT-PCR. We detected  $3.8 \times 10^3$  to  $1.9 \times 10^7$  PCV1 DNA copies/milliliter in live poliovirus seeds for inactivated polio vaccine (IPV) from manufacturer A, however, following inactivation and purification, the finished IPV was PCV1-negative. PCV1 DNA was not detectable in live polio preparations from other vaccine producers. There was no detectable PCV1 DNA in the measles, mumps, rubella and influenza vaccines analysed including material supplied by manufacturer A. We confirmed that the PCV1 genome in the rotavirus vaccine from manufacturer A is near full-length. It contains two mutations in the PCV *cap* gene, which may result from viral adaptation to Vero cells. Bulks of this vaccine contained  $9.8 \times 10^{10}$  to  $1.8 \times 10^{11}$  PCV1 DNA copies/millilitre and between  $4.1 \times 10^7$  and  $5.5 \times 10^8$  DNA copies were in the final doses. We found traces of PCV1 and PCV2 DNA in the rotavirus vaccine from manufacturer B. This highlights the issue of vaccine contamination and may impact on vaccine quality control.

**Gladstone BP et al. Protective effect of natural rotavirus infection in an Indian birth cohort. *New England Journal of Medicine*, 2011;365:337-346.**

**Background:** More than 500,000 deaths are attributed to rotavirus gastroenteritis annually worldwide, with the highest mortality in India. Two successive, naturally occurring rotavirus infections have been shown to confer complete protection against moderate or severe gastroenteritis during subsequent infections in a birth cohort in Mexico. We studied the protective effect of rotavirus infection on subsequent infection and disease in a birth cohort in India (where the efficacy of oral vaccines in general has been lower than expected).

**Methods:** We recruited children at birth in urban slums in Vellore; they were followed for 3 years after birth, with home visits twice weekly. Stool samples were collected every 2 weeks, as well as on alternate days during diarrheal episodes, and were tested by means of enzyme-linked immunosorbent assay and polymerase-chain-reaction assay. Serum samples were obtained every 6 months and evaluated for seroconversion, defined as an increase in the IgG antibody level by a factor of 4 or in the IgA antibody level by a factor of 3.

**Results:** Of 452 recruited children, 373 completed 3 years of follow-up. Rotavirus infection generally occurred early in life, with 56% of children infected by 6 months of age. Levels of reinfection were high, with only approximately 30% of all infections identified being primary. Protection against moderate or severe disease increased with the order of infection but was only 79% after three infections. With G1P[8], the most common viral strain, there was no evidence of homotypic protection.

**Conclusions:** Early infection and frequent reinfection in a locale with high viral diversity resulted in lower protection than has been reported elsewhere, providing a possible explanation why rotavirus vaccines have had lower-than-expected efficacy in Asia and Africa.

**GlaxoSmithKline Biologicals, Rixensart, Belgium:**  
[http://us.gsk.com/products/assets/us\\_rotarix.pdf](http://us.gsk.com/products/assets/us_rotarix.pdf) (No summary)

**Goveia MG, DiNubile MJ, Dallas MJ, Heaton PM, Kuter BJ; REST Study Team.**  
**Efficacy of pentavalent human-bovine (WC3) reassortant rotavirus vaccine based on breastfeeding frequency. *Pediatr Infect Dis J.* 2008 Jul;27(7):656-8.**

The efficacy of a live, oral, pentavalent rotavirus vaccine against G1-4 rotavirus gastroenteritis (RVGE) was retrospectively assessed based on breastfeeding frequency among 5098 infants in a placebo-controlled trial. The efficacy against any RVGE severity for infants never breastfed, sometimes breastfed, or exclusively breastfed was 68.3%, 82.2%, and 68.0%, respectively. The efficacy against severe RVGE was 100%, 95.4%, and 100%, respectively. Breastfeeding did not seem to adversely impact the efficacy of pentavalent rotavirus vaccine.

**Groome MJ, Madhi SA. Five-year cohort study on the burden of hospitalisation for acute diarrhoeal disease in African HIV-infected and HIV-uninfected children: potential benefits of rotavirus vaccine. *Vaccine.* 2012 Apr 27;30 Suppl 1:A173-8. doi: 10.1016/j.vaccine.2011.08.004.**

**INTRODUCTION:** Diarrhoea remains an important cause of death in children under five years of age, including in areas with high prevalence of HIV infection. Rotavirus contributes significantly to childhood diarrhoea in South Africa but data on the burden of rotavirus disease in HIV-infected children are limited.

**METHODS:** This secondary data analysis, involving a cohort of 39,879 children enrolled into a pneumococcal conjugate vaccine efficacy trial, evaluated the incidence of hospitalisation for acute gastroenteritis in HIV-infected and HIV-uninfected children under five years of age from Soweto, South Africa. The data were used to evaluate the potential burden of hospitalisation that would be preventable with rotavirus vaccine.

**RESULTS:** Acute gastroenteritis (AGE) was identified as a leading cause of hospitalisation in the cohort and was associated with 21% of all hospitalisations. Twenty-six percent of the AGE hospitalisations occurred in HIV-infected children. The incidence of AGE was greatest in the under-6 months age group and 90% of cases occurred within the first two years of life. The overall incidence of AGE was 5.4 fold (CI(95%) 4.9, 6.0) higher in HIV-infected compared to HIV-uninfected children. In addition, the estimates of rotavirus incidence were 2.3 fold (CI(95%) 1.8, 2.9) higher in HIV-infected compared to HIV-uninfected children. HIV-infected children were 1.8 fold (CI(95%) 1.4, 2.4) more likely to have prolonged hospitalisation and the case fatality rate was 4.0 (CI(95%) 2.0, 7.8) fold higher in HIV-infected compared to HIV-uninfected children.

**CONCLUSION:** Despite rotavirus reportedly being less frequently identified in hospitalised HIV-infected children, the absolute burden of rotavirus-associated hospitalisation is likely to be greater compared to HIV-uninfected children. The introduction of rotavirus vaccine into

the national immunisation program in South Africa is likely to benefit HIV-infected and HIV-uninfected children and reduce the overall burden of AGE hospitalisation in our childhood population.

**Hu L, Crawford SE, Hyser JM, Estes MK, Prasad BV. Rotavirus non-structural proteins: structure and function. Curr Opin Virol. 2012 Aug;2(4):380-8.**

The replication of rotavirus is a complex process that is orchestrated by an exquisite interplay between the rotavirus non-structural and structural proteins. Subsequent to particle entry and genome transcription, the non-structural proteins coordinate and regulate viral mRNA translation and the formation of electron-dense viroplasms that serve as exclusive compartments for genome replication, genome encapsidation and capsid assembly. In addition, non-structural proteins are involved in antagonizing the antiviral host response and in subverting important cellular processes to enable successful virus replication. Although far from complete, new structural studies, together with functional studies, provide substantial insight into how the non-structural proteins coordinate rotavirus replication. This brief review highlights our current knowledge of the structure-function relationships of the rotavirus non-structural proteins, as well as fascinating questions that remain to be understood.

**Kawamura N, Tokoeda Y, Oshima M, Okahata H, Tsutsumi H, Van Doorn LJ, Muto H, Smolenov I, Suryakiran PV, Han HH. Efficacy, safety and immunogenicity of RIX4414 in Japanese infants during the first two years of life. Vaccine. 2011 Aug 26;29(37):6335-41.**

A phase III, randomized, double-blind study evaluated the efficacy, reactogenicity, safety and immunogenicity of a human rotavirus vaccine, RIX4414 in Japanese infants aged 6-14 weeks when administered as two doses (0, 1-month schedule). Efficacy against any and severe rotavirus gastroenteritis leading to medical intervention caused by circulating wild-type rotavirus from two weeks post-Dose 2 until two years of age was 79.3% (95% CI: 60.5-89.8%) and 91.6% (95% CI: 62.4-99.1%), respectively. Solicited, unsolicited symptoms and serious adverse events were reported at a similar frequency in both groups. Serum anti-rotavirus antibody seroconversion rate one-month post-Dose 2 was 85.3% (95% CI: 68.9-95%) in RIX4414 group. RIX4414 was efficacious, well-tolerated and immunogenic in Japanese infants and introduction of vaccination could help in reducing the disease burden.

**Kiulia NM, Nyaundi JK, Peenze I, Nyachio A, Musoke RN, Steele AD, Mwenda JM. Rotavirus infections among HIV-infected children in Nairobi, Kenya. J Trop Pediatr. 2009 Oct;55(5):318-23.**

Human rotaviruses have emerged as a leading cause of acute diarrhea in children <5 years of age worldwide. Although there are previous reports relating to various aspects of rotaviruses, there is limited data on the involvement of rotavirus infection in HIV-infected children. We therefore evaluated the importance of rotavirus infections in HIV-related diarrhea in Kenyan children. Fecal samples were collected from a total of 207 children during the period February

1999 to June 2000 and screened for HRV antigen by enzyme-linked immunosorbent assay (ELISA). Positive samples were analyzed by VP6 subgroup specificity assay, by polyacrylamide gel electrophoresis (PAGE) and reverse transcriptase/polymerase chain reaction (RT-PCR). Fourteen percent (29/207) of the samples were positive. HIV-seropositive children with diarrhea were more likely than their counterparts without diarrhea to have rotaviruses [23.3% (10/43) versus 2.9% (2/70);  $p = 0.0001$ ]. Rotavirus strain G3P[6] was predominant. These results indicate that rotavirus is an important viral etiological agent causing diarrhea in HIV-seropositive children.

**Laserson KF, Nyakundi D, Feikin DR, Nyambane G, Cook E, Oyieko J, Ojwando J, Rivers SB, Ciarlet M, Neuzil KM, Breiman RF. Safety of the pentavalent rotavirus vaccine (PRV), RotaTeq(®), in Kenya, including among HIV-infected and HIV-exposed infants. Vaccine. 2012 Apr 27;30 Suppl 1:A61-70.**

Two multicenter Phase III trials were conducted in five countries from March 2007 to March 2009 to evaluate the safety and efficacy of the pentavalent rotavirus vaccine (PRV), RotaTeq(®), in Africa and Asia. In this report, we evaluate the safety of this vaccine, including among HIV-infected and HIV-exposed infants, in Kenya. 1308 Infants were randomized 1:1 to receive 3 doses of PRV/placebo at approximately 6, 10, and 14 weeks of age. HIV counseling and testing were offered to all participants. A positive PCR result indicated HIV infection; the presence of HIV antibody in PCR-negative children indicated HIV exposure without HIV infection. All serious adverse events (SAE) within 14 days of any dose, and vaccine-related SAEs, intussusception, and deaths occurring at any time during the study, were reported ("SAE surveillance"). In addition, 297 participants were followed for 42 days after any dose for any adverse event (AE), regardless of severity ("intensive safety surveillance"). The safety evaluation was stratified by HIV status. SAEs were reported in 20/649 vaccine recipients (3.1%) and 21/643 placebo recipients (3.3%) within 14 days following vaccination ( $p = 0.9$ ). The most common SAE in the vaccinated group was pneumonia (1.7%). No individual SAE was significantly more common among vaccine vs. placebo recipients. Seventy-two deaths were reported, 38 (5.9%) and 34 (5.3%) among vaccine and placebo recipients, respectively ( $p = 0.66$ ). No cases of intussusception were reported. During intensive safety surveillance, 137/147 (93.2%) vaccine recipients and 147/150 (98.0%) placebo recipients experienced one or more AEs (risk ratio = 0.95; 95% CI: 0.91-1.0;  $p = 0.05$ ). 88.5% of the infants were tested for HIV infection; 21/581 (3.6%) children in the vaccine group and 17/577 (2.9%) in the placebo group were HIV-infected. Among the 37 HIV-infected infants with full safety follow-up, 5/21 (23.8%) vaccine recipients and 2/16 (12.5%) placebo recipients reported an SAE ( $p = 0.67$ ). In total, 12 deaths occurred among identified HIV-infected infants: 8 (38%) receiving vaccine vs. 4 (23.5%) receiving placebo (RR = 1.6, 95% CI: 0.59-4.5). Among the 21 HIV-infected infants in the vaccine group, 2 of 8 deaths were gastroenteritis-related; among the 17 HIV-infected infants in the placebo group, 3 of 4 deaths were gastroenteritis-related. There were no significant differences in serious or non-serious AEs, including vaccine-related SAEs, between the 88 HIV-exposed vaccine recipients vs. the 89 HIV-exposed placebo recipients. PRV appears to be a safe intervention against rotavirus gastroenteritis among infants in Kenya. AEs, including serious AEs, were not associated with receipt of vaccine. Further, SAEs were not significantly more common among HIV-infected or HIV-exposed participants; however, the low number of HIV-infected infants did not provide sufficient power to fully assess safety in HIV-infected vaccine recipients.

**Lazzerini M et al. Editorial Group: Cochrane Infectious Diseases Group. Oral zinc for treating diarrhoea in children Published Online: 13 JUN 012. Assessed as up-to-date: 20 FEB 2012. DOI: 10.1002/14651858.CD005436.pub3**

In developing countries, millions of children suffer from severe diarrhoea every year. This is due to infection and malnutrition, and many die from dehydration due to the diarrhoea. Giving fluids by mouth (using an oral rehydration solution) has been shown to save children's lives, but it seems to have no effect on the length of time the children suffer with diarrhoea. Children in developing countries are often zinc deficient. This systematic review of 24 trials involving more than 9000 children shows that zinc supplementation may reduce the duration of diarrhoea in children aged six months or more.

**Liakopoulou E, Mutton K, Carrington D, Robinson S, Steward CG, Goulden NJ, Cornish JM, Marks DI. Rotavirus as a significant cause of prolonged diarrhoeal illness and morbidity following allogeneic bone marrow transplantation. Bone Marrow Transplant. 2005 Oct;36(8):691-4.**

Infective diarrhoea is common among allogeneic stem cell transplant (SCT) recipients, frequently caused by viruses and may be difficult to differentiate from acute graft-versus-host disease (GVHD). Viral pathogens may directly or indirectly impact upon transplant-related mortality. Rotavirus is one of the most common causes of diarrhoea worldwide, but one of the least studied causes of diarrhoea post SCT. In this retrospective study we describe 21 cases of confirmed rotavirus infection in allogeneic SCT recipients. Most of these cases may occur in clusters during the winter and spring period. Symptoms of rotaviral infection were diarrhoea (95%), vomiting (62%), abdominal pain (38%), weight loss and loss of appetite in 38 and 29% of the cases, respectively. Possible extraintestinal manifestations of rotavirus infection were observed. The duration of the symptoms in this series ranged from 4 days to 4 months with median of 15 days. Patients with rotavirus infection were invariably lymphopenic and/or on immunosuppression for GVHD. Of the patients diagnosed with rotavirus, 86% required hospitalisation. In 57% of the cases, other viral pathogens were isolated near to the rotavirus infection period. Rotavirus infection is an important cause of prolonged diarrhoea post SCT, causing significant morbidity and frequently requiring hospitalisation.

**Linhares AC 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 Apr 5;371(9619):1181-1189.**

**BACKGROUND:** Peak incidence of rotavirus gastroenteritis is seen in infants between 6 and 24 months of age. We therefore aimed to assess the 2-year efficacy and safety of an oral live attenuated human rotavirus vaccine for prevention of severe gastroenteritis in infants.

**METHODS:** 15 183 healthy infants aged 6-13 weeks from ten Latin American countries randomly assigned in a 1 to 1 ratio to receive two oral doses of RIX4414 or placebo at about 2 and 4 months of age in a double-blind, placebo-controlled phase III study were followed up until about 2 years of age. Primary endpoint was vaccine efficacy from 2 weeks after dose two

until 1 year of age. Treatment allocation was concealed from investigators and parents of participating infants. Efficacy follow-up for gastroenteritis episodes was undertaken from 2 weeks after dose two until about 2 years of age. Analysis was according to protocol. This study is registered with ClinicalTrials.gov, number NCT00140673 (eTrack444563-023).

**FINDINGS:** 897 infants were excluded from the according-to-protocol analysis. Fewer cases ( $p < 0.0001$ ) of severe rotavirus gastroenteritis were recorded for the combined 2-year period in the RIX4414 group (32 [0.4%] of 7205; 95% CI 0.3-0.6) than in the placebo group (161 [2.3%] of 7081; 1.9-2.6), resulting in a vaccine efficacy of 80.5% (71.3-87.1) to 82.1% (64.6-91.9) against wild-type G1, 77.5% (64.7-86.2) against pooled non-G1 strains, and 80.5% (67.9-88.8) against pooled non-G1 P[8] strains. Vaccine efficacy for hospital admission for rotavirus gastroenteritis was 83.0% (73.1-89.7) and for admission for diarrhoea of any cause was 39.3% (29.1-48.1). No cases of intussusception were reported during the second year of follow-up.

**INTERPRETATION:** Two doses of RIX4414 were effective against severe rotavirus gastroenteritis during the first 2 years of life in a Latin American setting. Inclusion of RIX4414 in routine paediatric immunisations should reduce the burden of rotavirus gastroenteritis worldwide.

**Loughlin J, Mast TC, Doherty MC, Wang FT, Wong J, Seeger JD. Postmarketing evaluation of the short-term safety of the pentavalent rotavirus vaccine. *Pediatr Infect Dis J*. 2012 Mar;31(3):292-6.**

**BACKGROUND:** A pentavalent rotavirus vaccine (RV5) demonstrated efficacy and safety in a large clinical trial before US licensure in 2006. The primary objective of this observational study was to assess the occurrence of intussusception (IS) among infants who received RV5 in routine use. Secondary objectives assessed the occurrence of Kawasaki disease (KD) and general safety.

**METHODS:** We identified and followed infants with a health insurance claim for RV5 during the first 2 years of RV5 availability. Concurrent and historical cohorts receiving diphtheria-tetanus-acellular pertussis (DTaP) vaccine were used as comparators; the historical DTaP cohort informed sequential monitoring boundaries for IS and KD. Medical records from potential IS and KD cases were reviewed to confirm outcomes. General safety was evaluated across a wide range of outcomes using prespecified criteria. Incidence rates for outcomes along with relative risks and 95% confidence intervals (CIs) were estimated.

**RESULTS:** The 85,397 RV5 and 62,820 DTaP recipients contributed 17,433 and 12,339 person-years, resulting in 6 and 5 confirmed cases of IS, respectively, within 30 days following any dose. The relative risk of IS was 0.8 (95% confidence interval: 0.22-3.52). The number of IS or KD cases did not cross the monitoring boundaries. The general safety evaluation did not identify any specific diagnoses or patterns of diagnoses that might suggest other safety concerns.

**CONCLUSION:** RV5 was not associated with an increased risk of IS, KD, or any other recognized health outcome.

**Madhi SA, Kirsten M, Louw C, Bos P, Aspinall S, Bouckennooghe A, Neuzil KM, Steele AD. Efficacy and immunogenicity of two or three dose rotavirus-vaccine regimen in South African children over two consecutive rotavirus-seasons: a randomized, double-blind, placebo-controlled trial. Vaccine. 2012 Apr 27;30 Suppl 1:A44-51.**

**BACKGROUND:** Human rotavirus vaccine (HRV; i.e., Rotarix) reduced the incidence of severe rotavirus gastroenteritis (RVGE) by 77% (95% Confidence interval: 56-88%) during the first year of life in South Africa. Persistence of HRV-derived protection against RVGE during subsequent rotavirus seasons, although evident in industrialized settings, remains to be established in African settings. This study reports on the efficacy of HRV against severe RVGE over two consecutive rotavirus seasons in South African children.

**METHODS:** A prospective, double-blind, placebo controlled multi-centered trial in South Africa and Malawi randomly assigned infants in a 1:1:1 ratio to receive either two (10 and 14 weeks; HRV\_2D) or three (6, 10 and 14 weeks; HRV\_3D) doses of HRV or placebo. The primary analysis involved pooling of HRV\_2D and HRV\_3D arms. Episodes of gastroenteritis caused by wild-type rotavirus were identified through active follow-up surveillance and graded by the Vesikari scale.

**RESULTS:** 1339 infants (447 in the HRV\_2D group, 447 in the HRV\_3D group and 445 in the placebo group) were enrolled in Year 2 of the study, including 1035 (77.3%) who were followed up over two consecutive rotavirus seasons (i.e., Cohort 2 subjects). Rotarix was associated with ongoing protection against severe RVGE, preventing 2.5 episodes per 100 vaccinated children over two consecutive rotavirus seasons; vaccine efficacy: 59% (95% Confidence interval: 1-83%). An exploratory analysis indicated better immunogenicity (among Cohort 1 subjects) and a higher point-efficacy estimate over two seasons in the HRV\_3D compared to HRV\_2D arms of the study in Cohort 2 subjects.

**CONCLUSION:** Rotarix is associated with significant reductions in severe gastroenteritis episodes through 2 years of life among South African children. Further research is needed to determine the optimal dosing schedule of Rotarix in providing long-term protection against rotavirus illness in African children.

**Madhi SA, Cunliffe NA, Steele D, Witte D, Kirsten M, Louw C, Ngwira B, Victor JC, Gillard PH, Chevart BB, Han HH, Neuzil KM. Effect of human rotavirus vaccine on severe diarrhea in African infants. New England Journal of Medicine, 2010, 362:289-298.**

**BACKGROUND:** Rotavirus is the most common cause of severe gastroenteritis among young children worldwide. Data are needed to assess the efficacy of the rotavirus vaccine in African children.

**METHODS:** We conducted a randomized, placebo-controlled, multicenter trial in South Africa (3166 infants; 64.1% of the total) and Malawi (1773 infants; 35.9% of the total) to evaluate the efficacy of a live, oral rotavirus vaccine in preventing severe rotavirus gastroenteritis. Healthy infants were randomly assigned in a 1:1:1 ratio to receive two doses of vaccine (in addition to one dose of placebo) or three doses of vaccine--the pooled vaccine

group--or three doses of placebo at 6, 10, and 14 weeks of age. Episodes of gastroenteritis caused by wild-type rotavirus during the first year of life were assessed through active follow-up surveillance and were graded with the use of the Vesikari scale.

**RESULTS:** A total of 4939 infants were enrolled and randomly assigned to one of the three groups; 1647 infants received two doses of the vaccine, 1651 infants received three doses of the vaccine, and 1641 received placebo. Of the 4417 infants included in the per-protocol efficacy analysis, severe rotavirus gastroenteritis occurred in 4.9% of the infants in the placebo group and in 1.9% of those in the pooled vaccine group (vaccine efficacy, 61.2%; 95% confidence interval, 44.0 to 73.2). Vaccine efficacy was lower in Malawi than in South Africa (49.4% vs. 76.9%); however, the number of episodes of severe rotavirus gastroenteritis that were prevented was greater in Malawi than in South Africa (6.7 vs. 4.2 cases prevented per 100 infants vaccinated per year). Efficacy against all-cause severe gastroenteritis was 30.2%. At least one serious adverse event was reported in 9.7% of the infants in the pooled vaccine group and in 11.5% of the infants in the placebo group.

**CONCLUSIONS:** Human rotavirus vaccine significantly reduced the incidence of severe rotavirus gastroenteritis among African infants during the first year of life.

**McClenahan SD, Krause PR, Uhlenhaut C. Molecular and infectivity studies of porcine circovirus in vaccines. Vaccine. 2011 Jun 24;29(29-30):4745-53.**

This report describes FDA's laboratory response to the 2010 reports that porcine circovirus type 1 (PCV-1) DNA was present in U.S.-licensed rotavirus vaccines and in cells used to produce inactivated poliovirus vaccines. In the present study, Rotarix® (GlaxoSmithKline, Rixensart, Belgium) was found to contain full-length PCV-1 genomes that are particle-associated, and cell culture assays in swine testis (ST) and PCV-free porcine kidney (PK-15) cells confirmed that PCV-1 sequences in this vaccine represent infectious virus. RotaTeq® (Merck and Co., West Point, PA, USA) contained small PCV-1 and PCV-2 genome fragments, but did not contain detectable larger portions of (or full-length) PCV genomes, and cell culture assays did not amplify PCV from this vaccine. Inactivated poliovirus vaccine bulks (GlaxoSmithKline) were also negative for the presence of PCV by cell culture infectivity assay. In these vaccines, molecular characterization of PCV nucleic acids was useful for predicting the results of cell culture assays.

**Merck Sharp & Dohme Corp., USA (No summary)**

**[http://www.merck.com/product/usa/pi\\_circulars/r/rotateq/rotateq\\_pi.pdf](http://www.merck.com/product/usa/pi_circulars/r/rotateq/rotateq_pi.pdf)**

**Narváez CF, Feng N, Vásquez C, Sen A, Angel J, Greenberg HB, Franco MA. Human Rotavirus-Specific IgM Memory B Cells Have Differential Cloning Efficiencies and Switch Capacities and Play a Role in Antiviral Immunity In Vivo. J Virol. 2012 Oct;86(19):10829-40.**

Protective immunity to rotavirus (RV) is primarily mediated by antibodies produced by RV-specific memory B cells (RV-mBc). Of note, most of these cells express IgM, but the function of this subset is poorly understood. Here, using limiting dilution assays of highly sort-purified human IgM(+) mBc, we found that 62% and 21% of total (non-antigen-specific) IgM(+) and RV-IgM(+) mBc, respectively, switched in vitro to IgG production after polyclonal



stimulation. Moreover, in these assays, the median cloning efficiencies of total IgM(+) (17%) and RV-IgM(+) (7%) mBc were lower than those of the corresponding switched (IgG(+) IgA(+)) total (34%) and RV-mBc (17%), leading to an underestimate of their actual frequency. In order to evaluate the in vivo role of IgM(+) RV-mBc in antiviral immunity, NOD/Shi-scid interleukin-2 receptor-deficient (IL-2R $\gamma$ (null)) immunodeficient mice were adoptively transferred highly purified human IgM(+) mBc and infected with virulent murine rotavirus. These mice developed high titers of serum human RV-IgM and IgG and had significantly lower levels than control mice of both antigenemia and viremia. Finally, we determined that human RV-IgM(+) mBc are phenotypically diverse and significantly enriched in the IgM(hi) IgD(low) subset. Thus, RV-IgM(+) mBc are heterogeneous, occur more frequently than estimated by traditional limiting dilution analysis, have the capacity to switch Ig class in vitro as well as in vivo, and can mediate systemic antiviral immunity.

**Pang X, Cao M, Zhang M, Lee B. Increased sensitivity for various rotavirus genotypes in stool specimens by amending three mismatched nucleotides in the forward primer of a real-time RT-PCR assay. J Virol Methods. 2011 Mar;172(1-2):85-7.**

The real-time TaqMan RT-PCR assay (Pang et al., 2004) did not detect 14 clinical samples with rotavirus G2 genotype. Three to five nucleotides (nt) were found to be mismatched between the published forward primer when compared to G2P[4], G2P[8], G3P[4], G9P[4], G8 and G12 sequences. An additional forward primer was designed and included in a modified assay to test the 14 clinical samples and 12 samples with known rotavirus G and P genotypes. The modified assay has improved significantly the sensitivity for specific rotavirus strains without affecting the detection of other genotypes, creating a molecular assay with broad detection of various genotypes of group A rotaviruses.

**Parashar UD, Hummelman EG, Bresee JS, Miller MA, Glass RI. Global illness and deaths caused by rotavirus disease in children. Emerg Infect Dis. 2003 May;9(5):565-72.**

To estimate the global illness and deaths caused by rotavirus disease, we reviewed studies published from 1986 to 2000 on deaths caused by diarrhea and on rotavirus infections in children. We assessed rotavirus-associated illness in three clinical settings (mild cases requiring home care alone, moderate cases requiring a clinic visit, and severe cases requiring hospitalization) and death rates in countries in different World Bank income groups. Each year, rotavirus causes approximately 111 million episodes of gastroenteritis requiring only home care, 25 million clinic visits, 2 million hospitalizations, and 352,000-592,000 deaths (median, 440,000 deaths) in children <5 years of age. By age 5, nearly every child will have an episode of rotavirus gastroenteritis, 1 in 5 will visit a clinic, 1 in 65 will be hospitalized, and approximately 1 in 293 will die. Children in the poorest countries account for 82% of rotavirus deaths. The tremendous incidence of rotavirus disease underscores the urgent need for interventions, such as vaccines, particularly to prevent childhood deaths in developing nations.

**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 Jul;12(7):561-70. doi: 10.1016/S1473-3099(12)70029-4.**

Rotavirus is the most common cause of fatal and severe childhood diarrhoea worldwide. Two new rotavirus vaccines have shown efficacy against severe rotavirus disease in large clinical trials. Between 2006 and 2010, 27 countries introduced rotavirus vaccination into national immunisation programmes and, subsequently, the burden of severe rotavirus disease in these countries has decreased substantially in both vaccinated and unvaccinated children. Rotavirus vaccination has led to large, sustained declines in childhood deaths from diarrhoea in Brazil and Mexico, which supports estimates that rotavirus was the leading cause of diarrhoeal deaths in these countries. Studies after licensing have provided new insights into these vaccines, such as the duration of protection, relative effectiveness in poor populations, and strain evolution after vaccine introduction. The challenge for policy makers worldwide is to analyse the effect of vaccination in early adopter countries and to assess whether the benefits outweigh the costs and encourage wider dissemination of these vaccines.

**Patel M, Pedreira C, De Oliveira LH, Umaña J, Tate J, Lopman B, Sanchez E, Reyes M, Mercado J, Gonzalez A, Perez MC, Balmaceda A, Andrus J, Parashar U. Duration of protection of pentavalent rotavirus vaccination in nicaragua. Pediatrics. 2012 Aug;130(2):e365-72.**

**OBJECTIVE:** To evaluate the duration of protection of pentavaent rotavirus vaccine (RV5) against rotavirus hospitalizations in Nicaragua, a developing country in Central America.

**METHODS:** We conducted a case-control study at 4 hospitals from 2007 through 2010, including 1016 children hospitalized with laboratory-confirmed rotavirus diarrhea, 4930 controls with nonrotavirus diarrhea (ie, "test-negative"), and 5627 controls without diarrhea. All cases and controls were aged  $\geq 6$  months and born after August 2006. Outcomes included odds of antecedent vaccination between case-patients and controls, and effectiveness of vaccination ( $1 - \text{adjusted odds ratio [OR]} \times 100$ ). Duration of protection was assessed by comparing effectiveness among children aged  $< 1$  year compared with  $\geq 1$  year.

**RESULTS:** Indicators of socioeconomic conditions and nonrotavirus vaccination (oral polio vaccine and diphtheria/tetanus/pertussis/hepatitis A/hepatitis B) for test-negative controls were more comparable to the rotavirus case-patients than nondiarrhea controls. RV5 vaccination was associated with a significantly lower risk of rotavirus hospitalization by using test-negative controls (OR: 0.55; 95% confidence interval [CI]: 0.41-0.74) and nondiarrhea controls (OR: 0.30; 95% CI: 0.22-0.40). Risk of rotavirus hospitalization was twofold lower among RV5 vaccinated children aged  $< 1$  year (OR: 0.36; 95% CI: 0.22-0.57) compared with RV5 vaccinated children aged  $\geq 1$  year (OR: 0.70; 95% CI: 0.47-1.05).

**CONCLUSIONS:** RV5 provided good protection against severe rotavirus disease in Nicaragua during the first year of life, when most severe and fatal rotavirus disease in developing countries occurs. However, the decline in protection with age warrants monitoring of disease among older children and consideration of a booster dose evaluation at the end of infancy.

**Patel MM et al. Intussusception risk and health benefits of rotavirus vaccination in Mexico and Brazil. N Engl J Med. 2011 Jun 16;364(24):2283-92.**

**BACKGROUND:** Because postlicensure surveillance determined that a previous rotavirus vaccine, RotaShield, caused intussusception in 1 of every 10,000 recipients, we assessed the association of the new monovalent rotavirus vaccine (RV1) with intussusception after routine immunization of infants in Mexico and Brazil.

**METHODS:** We used case-series and case-control methods to assess the association between RV1 and intussusception. Infants with intussusception were identified through active surveillance at 69 hospitals (16 in Mexico and 53 in Brazil), and age-matched infants from the same neighborhood were enrolled as controls. Vaccination dates were verified by a review of vaccination cards or clinic records.

**RESULTS:** We enrolled 615 case patients (285 in Mexico and 330 in Brazil) and 2050 controls. An increased risk of intussusception 1 to 7 days after the first dose of RV1 was identified among infants in Mexico with the use of both the case-series method (incidence ratio, 5.3; 95% confidence interval [CI], 3.0 to 9.3) and the case-control method (odds ratio, 5.8; 95% CI, 2.6 to 13.0). No significant risk was found after the first dose among infants in Brazil, but an increased risk, albeit smaller than that seen after the first dose in Mexico--an increase by a factor of 1.9 to 2.6 - was seen 1 to 7 days after the second dose. A combined annual excess of 96 cases of intussusception in Mexico (approximately 1 per 51,000 infants) and in Brazil (approximately 1 per 68,000 infants) and of 5 deaths due to intussusception was attributable to RV1. However, RV1 prevented approximately 80,000 hospitalizations and 1300 deaths from diarrhea each year in these two countries.

**CONCLUSIONS:** RV1 was associated with a short-term risk of intussusception in approximately 1 of every 51,000 to 68,000 vaccinated infants. The absolute number of deaths and hospitalizations averted because of vaccination far exceeded the number of intussusception cases that may have been associated with vaccination. (Funded in part by the GAVI Alliance and the U.S. Department of Health and Human Services.).

**Patel MM, Parashar UD. Assessing the effectiveness and public health impact of rotavirus vaccines after introduction in immunization programs. J Infect Dis. 2009 Nov 1;200 Suppl 1:S291-9.**

Two new vaccines against severe rotavirus gastroenteritis that have high efficacy in middle- and high-income countries have recently been licensed in many countries worldwide. Clinical trials in low-income countries in Africa and Asia are ongoing. Experience gained through studies of natural rotavirus infection and the clinical trials for the current and previous rotavirus vaccines indicate that, as countries begin to introduce these newly approved vaccines into routine childhood immunization programs, monitoring their performance in real world settings should be a high priority. Key epidemiological considerations in the postlicensure period include (1) how the vaccine will perform against severe rotavirus disease under routine public health use; (2) how routine vaccination will impact the epidemiology of disease with regard to the burden of severe disease and death, age distribution of cases, seasonality, and serotype distribution; (3) whether vaccination will have a sufficient impact on transmission to reduce disease burden in unvaccinated age groups; and (4) whether vaccine

will confer protection through the first 3 years of life, when most severe disease and mortality associated with rotavirus occur. Monitoring of impact with focus on these public health considerations will allow parents, health care providers, and decision makers to appreciate the health benefits of vaccination in reducing the burden of severe rotavirus disease. It will also allow assessment of the effectiveness of rotavirus vaccines in programmatic use and the need for modifying vaccination schedules or vaccine formulations to enhance the performance of immunization. In this article, we review data for the protective efficacy of the 2 new rotavirus vaccines, with emphasis on issues particularly important for consideration as these vaccines are introduced in routine infant immunization programs.

**Phua KB, Lim FS, Lau YL, Nelson EA, Huang LM, Quak SH, Lee BW, van Doorn LJ, Teoh YL, Tang H, Suryakiran PV, Smolenov IV, Bock HL, Han HH. Rotavirus vaccine RIX4414 efficacy sustained during the third year of life: a randomized clinical trial in an Asian population. Vaccine. 2012 Jun 22;30(30):4552-7.**

RIX4414 (Rotarix™), has shown high efficacy during the first 2-years of life. A 2-year randomized, double-blind, placebo-controlled trial in Singapore, Hong Kong, and Taiwan was extended for another year. Infants (6-17 weeks) received 2-doses (1-2 months apart) of RIX4414 (n=5359) or placebo (n=5349). During the third-year follow-up, 4359 (RIX4414) and 4328 (placebo) infants were monitored. 64 (1.2%) and 2 (0.04%) infants in the placebo and RIX4414 groups, respectively, reported severe rotavirus-gastroenteritis (RVGE), resulting in a vaccine efficacy of 96.9% (95% CI [88.3-99.6]). Efficacy was 100% (67.5-100) in the third-year. RIX4414 was efficacious against G1 (100.0% [84.8-100]) and pooled non-G1 RV types (94.9% [80.2-99.4]). This study shows that the vaccine is highly efficacious, regardless of circulating RV-types, up to the first 3 years of life in affluent Asian urban populations.

**Phua KB et al. Safety and efficacy of human rotavirus vaccine during the first 2 years of life in Asian infants: randomised, double-blind, controlled study. Vaccine. 2009 Oct 9;27(43):5936-41.**

This study evaluates the safety and efficacy against severe rotavirus gastroenteritis of the oral live attenuated human rotavirus vaccine RIX4414 (Rotarix) during the first 2 years of life in Asian infants from high-income countries. Healthy infants were enrolled to receive 2 doses of RIX4414 (N=5,359) or placebo (N=5,349). From 2 weeks post-dose 2 to 2 years of age, vaccine efficacy was 96.1% (95%CI:85.1%; 99.5%) against severe rotavirus gastroenteritis, 100% (95%CI:80.8%; 100%) against wild-type G1P[8] and 93.6% (95%CI:74.7%; 99.3%) against circulating non-G1 rotavirus types. No intussusception cases were reported within 31 days post-vaccination. RIX4414 shows a good safety profile and offers high protection during the first 2 years of life with potentially significant public health impact in this population.

**Postma MJ, Jit M, Rozenbaum MH, Standaert B, Tu HA, Hutubessy RC. Comparative review of three cost-effectiveness models for rotavirus vaccines in national immunization programs; a generic approach applied to various regions in the world. BMC Med. 2011 Jul 8;9:84.**

**BACKGROUND:** This study aims to critically review available cost-effectiveness models for rotavirus vaccination, compare their designs using a standardized approach and compare similarities and differences in cost-effectiveness outcomes using a uniform set of input parameters.

**METHODS:** We identified various models used to estimate the cost-effectiveness of rotavirus vaccination. From these, results using a standardized dataset for four regions in the world could be obtained for three specific applications.

**RESULTS:** Despite differences in the approaches and individual constituting elements including costs, QALYs Quality Adjusted Life Years and deaths, cost-effectiveness results of the models were quite similar. Differences between the models on the individual components of cost-effectiveness could be related to some specific features of the respective models. Sensitivity analysis revealed that cost-effectiveness of rotavirus vaccination is highly sensitive to vaccine prices, rotavirus-associated mortality and discount rates, in particular that for QALYs.

**CONCLUSIONS:** The comparative approach followed here is helpful in understanding the various models selected and will thus benefit (low-income) countries in designing their own cost-effectiveness analyses using new or adapted existing models. Potential users of the models in low and middle income countries need to consider results from existing studies and reviews. There will be a need for contextualization including the use of country specific data inputs. However, given that the underlying biological and epidemiological mechanisms do not change between countries, users are likely to be able to adapt existing model designs rather than developing completely new approaches. Also, the communication established between the individual researchers involved in the three models is helpful in the further development of these individual models. Therefore, we recommend that this kind of comparative study be extended to other areas of vaccination and even other infectious disease interventions.

**Richardson V, Hernandez-Pichardo J, Quintanar-Solares M, Esparza-Aguilar M, Johnson B, Gomez-Altamirano CM, Parashar U, Patel M. Effect of rotavirus vaccination on death from childhood diarrhea in Mexico. N Engl J Med. 2010 Jan 28;362(4):299-305.**

**BACKGROUND:** A phased introduction of a monovalent rotavirus vaccine occurred in Mexico from February 2006 through May 2007. We assessed the effect of vaccination on deaths from diarrhea in Mexican children in 2008 and 2009.

**METHODS:** We obtained data on deaths from diarrhea, regardless of cause, from January 2003 through May 2009 in Mexican children under 5 years of age. We compared diarrhea-related mortality in 2008 and during the 2008 and 2009 rotavirus seasons with the mortality at baseline (2003-2006), before the introduction of the rotavirus vaccine. Vaccine coverage was estimated from administrative data.

**RESULTS:** By December 2007, an estimated 74% of children who were 11 months of age or younger had received one dose of rotavirus vaccine. In 2008, there were 1118 diarrhea-related deaths among children younger than 5 years of age, a reduction of 675 from the annual median of 1793 deaths during the 2003-2006 period. Diarrhea-related mortality fell from an

annual median of 18.1 deaths per 100,000 children at baseline to 11.8 per 100,000 children in 2008 (rate reduction, 35%; 95% confidence interval [CI], 29 to 39;  $P<0.001$ ). Among infants who were 11 months of age or younger, diarrhea-related mortality fell from 61.5 deaths per 100,000 children at baseline to 36.0 per 100,000 children in 2008 (rate reduction, 41%; 95% CI, 36 to 47;  $P<0.001$ ). As compared with baseline, diarrhea-related mortality was 29% lower for children between the ages of 12 and 23 months, few of whom were age-eligible for vaccination. Mortality among unvaccinated children between the ages of 24 and 59 months was not significantly reduced. The reduction in the number of diarrhea-related deaths persisted through two full rotavirus seasons (2008 and 2009).

**CONCLUSIONS:** After the introduction of a rotavirus vaccine, a significant decline in diarrhea-related deaths among Mexican children was observed, suggesting a potential benefit from rotavirus vaccination.

**Ruiz-Palacios GM et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. N Engl J Med. 2006 Jan 5;354(1):11-22.**

**BACKGROUND:** The safety and efficacy of an attenuated G1P[8] human rotavirus (HRV) vaccine were tested in a randomized, double-blind, phase 3 trial.

**METHODS:** We studied 63,225 healthy infants from 11 Latin American countries and Finland who received two oral doses of either the HRV vaccine (31,673 infants) or placebo (31,552 infants) at approximately two months and four months of age. Severe gastroenteritis episodes were identified by active surveillance. The severity of disease was graded with the use of the 20-point Vesikari scale. Vaccine efficacy was evaluated in a subgroup of 20,169 infants (10,159 vaccinees and 10,010 placebo recipients).

**RESULTS:** The efficacy of the vaccine against severe rotavirus gastroenteritis and against rotavirus-associated hospitalization was 85 percent ( $P<0.001$  for the comparison with placebo) and reached 100 percent against more severe rotavirus gastroenteritis. Hospitalization for diarrhea of any cause was reduced by 42 percent (95 percent confidence interval, 29 to 53 percent;  $P<0.001$ ). During the 31-day window after each dose, six vaccine recipients and seven placebo recipients had definite intussusception (difference in risk, -0.32 per 10,000 infants; 95 percent confidence interval, -2.91 to 2.18;  $P=0.78$ ).

**CONCLUSIONS:** Two oral doses of the live attenuated G1P[8] HRV vaccine were highly efficacious in protecting infants against severe rotavirus gastroenteritis, significantly reduced the rate of severe gastroenteritis from any cause, and were not associated with an increased risk of intussusception.

**Sanderson C et al. Global review of rotavirus morbidity and mortality data by age and WHO region. Report to WHO/IVR 2011. (No summary)**

**Saulsbury FT, Winkelstein JA, Yolken RH. Chronic rotavirus infection in immunodeficiency. J Pediatr. 1980 Jul;97(1):61-5.**

The characteristics of rotavirus infection in 23 children with a variety of primary immunodeficiency diseases were studied. Stools and sera were tested for rotavirus by means of the enzyme-linked immunosorbent assay and the enzyme-linked fluorescent assay, respectively. Four immunodeficient patients had diarrhea during the study period and all had rotavirus infection; rotavirus was not detected in the stools of the 19 asymptomatic immunodeficient patients. Forty-six control children with diarrhea were tested and 22 had rotavirus infection; rotavirus was not detected in 39 asymptomatic control children. One immunodeficient patient with X-linked agammaglobulinemia and one with severe combined immunodeficiency had chronic, symptomatic rotavirus infection with rotavirus excretion lasting more than six weeks. The other two immunodeficient patients and eight control children eliminated the rotavirus from their stools in periods ranging from two to 12 days. Rotavirus antigen was detected in the sera of three of the four immunodeficient patients; none of the 14 control infants tested had rotavirus antigen detected in their sera. This study indicates that rotavirus may produce a chronic infection in immunodeficient children.

**Shui IM, Baggs J, Patel M, Parashar UD, Rett M, Belongia EA, Hambidge SJ, Glanz JM, Klein NP, Weintraub E. Risk of intussusception following administration of a pentavalent rotavirus vaccine in US infants. JAMA. 2012 Feb 8;307(6):598-604.**

**CONTEXT:** Current rotavirus vaccines were not associated with intussusception in large prelicensure trials. However, recent postlicensure data from international settings suggest the possibility of a low-level elevated risk, primarily in the first week after the first vaccine dose.

**OBJECTIVE:** To examine the risk of intussusception following pentavalent rotavirus vaccine (RV5) in US infants.

**DESIGN, SETTING, AND PATIENTS:** This cohort study included infants 4 to 34 weeks of age, enrolled in the Vaccine Safety Datalink (VSD) who received RV5 from May 2006-February 2010. We calculated standardized incidence ratios (SIRs), relative risks (RRs), and 95% confidence intervals for the association between intussusception and RV5 by comparing the rates of intussusception in infants who had received RV5 with the rates of intussusception in infants who received other recommended vaccines without concomitant RV5 during the concurrent period and with the expected number of intussusception visits based on background rates assessed prior to US licensure of the RV5 (2001-2005).

**MAIN OUTCOME MEASURE:** Intussusception occurring in the 1- to 7-day and 1- to 30-day risk windows following RV5 vaccination.

**RESULTS:** During the study period, 786,725 total RV5 doses, which included 309,844 first doses, were administered. We did not observe a statistically significant increased risk of intussusception with RV5 for either comparison group following any dose in either the 1- to 7-day or 1- to 30-day risk window. For the 1- to 30-day window following all RV5 doses, we observed 21 cases of intussusception compared with 20.9 expected cases (SIR, 1.01; 95% CI, 0.62-1.54); following dose 1, we observed 7 cases compared with 5.7 expected cases (SIR, 1.23; 95% CI, 0.5-2.54). For the 1- to 7-day window following all RV5 doses, we observed 4 cases compared with 4.3 expected cases (SIR, 0.92; 95% CI, 0.25-2.36); for dose 1, we observed 1 case compared with 0.8 expected case (SIR, 1.21; 95% CI, 0.03-6.75). The upper

95% CI limit of the SIR (6.75) from the historical comparison translates to an upper limit for the attributable risk of 1 intussusception case per 65,287 RV5 dose-1 recipients.

**CONCLUSION:** Among US infants aged 4 to 34 weeks who received RV5, the risk of intussusception was not increased compared with infants who did not receive the rotavirus vaccine.

**Soares-Weiser K, Maclehose H, Bergman H, Ben-Aharon I, Nagpal S, Goldberg E, Pitan F, Cunliffe N. Vaccines for preventing rotavirus diarrhoea: vaccines in use. Cochrane Database Syst Rev. 2012 Nov 14;11:CD008521. doi: 10.1002/14651858.CD008521.pub3.**

**BACKGROUND:** Rotavirus results in more diarrhoea-related deaths in children less than five years of age than any other single agent in countries with high childhood mortality. It is also a common cause of diarrhoea-related hospital admissions in countries with low childhood mortality. Currently licensed rotavirus vaccines include a monovalent rotavirus vaccine (RV1; Rotarix, GlaxoSmithKline Biologicals) and a pentavalent rotavirus vaccine (RV5; RotaTeq, Merck & Co., Inc.). Lanzhou lamb rotavirus vaccine (LLR; Lanzhou Institute of Biomedical Products) is used in China only.

**OBJECTIVES:** To evaluate rotavirus vaccines approved for use (RV1, RV5, and LLR) for preventing rotavirus diarrhoea.

**SEARCH METHODS:** We searched MEDLINE (via PubMed) (1966 to May 2012), the Cochrane Infectious Diseases Group Specialized Register (10 May 2012), CENTRAL (published in The Cochrane Library 2012, Issue 5), EMBASE (1974 to 10 May 2012), LILACS (1982 to 10 May 2012), and BIOSIS (1926 to 10 May 2012). We also searched the ICTRP (10 May 2012), www.ClinicalTrials.gov (28 May 2012) and checked reference lists of identified studies.

**SELECTION CRITERIA:** We selected randomized controlled trials (RCTs) in children comparing rotavirus vaccines approved for use with placebo, no intervention, or another vaccine.

**DATA COLLECTION AND ANALYSIS:** Two authors independently assessed trial eligibility, extracted data, and assessed risk of bias. We combined dichotomous data using the risk ratio (RR) and 95% confidence intervals (CI). We stratified the analysis by child mortality, and used GRADE to evaluate evidence quality.

**MAIN RESULTS:** Forty-one trials met the inclusion criteria and enrolled a total of 186,263 participants. Twenty-nine trials (101,671 participants) assessed RV1, and 12 trials (84,592 participants) evaluated RV5. We did not find any trials assessing LLR. RV1 Children aged less than one year: In countries with low-mortality rates, RV1 prevents 86% of severe rotavirus diarrhoea cases (RR 0.14, 95% CI 0.07 to 0.26; 40,631 participants, six trials; high-quality evidence), and, based on one large multicentre trial in Latin America and Finland, probably prevents 40% of severe all-cause diarrhoea episodes (rate ratio 0.60, 95% CI 0.50 to 0.72; 17,867 participants, one trial; moderate-quality evidence). In countries with high-mortality rates, RV1 probably prevents 63% of severe rotavirus diarrhoea cases (RR 0.37, 95% CI 0.18 to 0.75; 5414 participants, two trials; moderate-quality evidence), and, based on one trial in Malawi and South Africa, 34% of severe all-cause diarrhoea cases (RR 0.66, 95% CI 0.44 to 0.98; 4939 participants, one trial; moderate-quality evidence). Children aged up to two years:



In countries with low-mortality rates, RV1 prevents 85% of severe rotavirus diarrhoea cases (RR 0.15, 95% CI 0.12 to 0.20; 32,854 participants, eight trials; high-quality evidence), and probably 37% of severe all-cause diarrhoea episodes (rate ratio 0.63, 95% CI 0.56 to 0.71; 39,091 participants, two trials; moderate-quality evidence). In countries with high-mortality rates, based on one trial in Malawi and South Africa, RV1 probably prevents 42% of severe rotavirus diarrhoea cases (RR 0.58, 95% CI 0.42 to 0.79; 2764 participants, one trial; moderate-quality evidence), and 18% of severe all-cause diarrhoea cases (RR 0.82, 95% CI 0.71 to 0.95; 2764 participants, one trial; moderate-quality evidence). RV5 Children aged less than one year: In countries with low-mortality rates, RV5 probably prevents 87% of severe rotavirus diarrhoea cases (RR 0.13, 95% CI 0.04 to 0.45; 2344 participants, three trials; moderate-quality evidence), and, based on one trial in Finland, may prevent 72% of severe all-cause diarrhoea cases (RR 0.28, 95% CI 0.16 to 0.48; 1029 participants, one trial; low-quality evidence). In countries with high-mortality rates, RV5 prevents 57% of severe rotavirus diarrhoea (RR 0.43, 95% CI 0.29 to 0.62; 5916 participants, two trials; high-quality evidence), but there was insufficient data to assess the effect on severe all-cause diarrhoea. Children aged up to two years: Four studies provided data for severe rotavirus and all-cause diarrhoea in countries with low-mortality rates. Three trials reported on severe rotavirus diarrhoea cases and found that RV5 probably prevents 82% (RR 0.18, 95% CI 0.07 to 0.50; 3190 participants, three trials; moderate-quality evidence), and another trial in Finland reported on severe all-cause diarrhoea cases and found that RV5 may prevent 96% (RR 0.04, 95% CI 0.00 to 0.70; 1029 participants, one trial; low-quality evidence). In high-mortality countries, RV5 prevents 41% of severe rotavirus diarrhoea cases (RR 0.59, 95% CI 0.43 to 0.82; 5885 participants, two trials; high-quality evidence), and 15% of severe all-cause diarrhoea cases (RR 0.85, 95% CI 0.75 to 0.98; 5977 participants, two trials; high-quality evidence). There was no evidence of a vaccine effect on mortality (181,009 participants, 34 trials; low-quality evidence), although the trials were not powered to detect an effect on this end point. Serious adverse events were reported in 4565 out of 99,438 children vaccinated with RV1 and in 1884 out of 78,226 children vaccinated with RV5. Fifty-eight cases of intussusception were reported in 97,246 children after RV1 vaccination, and 34 cases in 81,459 children after RV5 vaccination. No significant difference was found between children receiving RV1 or RV5 and placebo in the number of serious adverse events, and intussusception in particular.

**AUTHORS' CONCLUSIONS:** RV1 and RV5 prevent episodes of rotavirus diarrhoea. The vaccine efficacy is lower in high-mortality countries; however, due to the higher burden of disease, the absolute benefit is higher in these settings. No increased risk of serious adverse events including intussusception was detected, but post-introduction surveillance studies are required to detect rare events associated with vaccination.

**Soares-Weiser K et al (b). Rotavirus vaccine schedules: a systematic review of safety and efficacy from RCTs and observational studies of childhood schedules using RV1 and RV5 vaccines- Report to WHO/IVR 2012. (No summary)**

**Steele AD, Madhi SA, Louw CE, Bos P, Tumbo JM, Werner CM, Bicer C, De Vos B, Delem A, Han HH. Safety, Reactogenicity, and Immunogenicity of Human Rotavirus**

**Vaccine RIX4414 in Human Immunodeficiency Virus-positive Infants in South Africa. *Pediatr Infect Dis J.* 2011 Feb;30(2):125-30.**

**BACKGROUND:** rotavirus and human immunodeficiency virus (HIV) infections are a cause of great public health concern in developing countries. The current study evaluated the safety, reactogenicity, and immunogenicity of RIX4414 vaccine in asymptomatic or mildly symptomatic (clinical stages I and II according to WHO classification) HIV-infected South African infants.

**METHODS:** a total of 100 HIV-positive infants aged 6 to 10 weeks enrolled in this double-blind, 1:1 randomized, placebo-controlled study were allocated into 2 groups to receive 3 doses of RIX4414 vaccine/placebo according to a 0-, 1-, and 2-month schedule. Routine vaccines were concomitantly administered. Solicited and unsolicited symptoms were recorded for 15 and 31 days after each dose, respectively. Serious adverse events were recorded throughout the study period. Serum antirotavirus IgA concentrations (enzyme-linked immunosorbent assay, cut-off  $\geq 20$  U/mL) and the immunodeficiency status were determined at screening and 2 months post-Dose 3. Stool samples were analyzed for rotavirus using enzyme-linked immunosorbent assay at predetermined points and during diarrhea episodes.

**RESULTS:** all symptoms (solicited and unsolicited) occurred at a similar frequency in both groups. Six fatal serious adverse events in RIX4414 and 9 in placebo groups were reported. At 2 months post-Dose 3, the seroconversion rates were 57.1% (95% CI: 34-78.2) in RIX4414 and 18.2% (95% CI: 5.2-40.3) in the placebo group. The mean absolute CD4 cell count, CD4 percentage, and HIV-1 viral load were comparable in both groups at screening and 2 months post-Dose 3. Rotavirus shedding peaked at Day 7 after Dose 1 of RIX4414 with prolonged shedding was observed in 1 infant only.

**CONCLUSIONS:** Three doses of RIX4414 vaccine was tolerated well by the South African HIV-positive infants. A satisfactory immune response was mounted without aggravating their immunologic or HIV condition.

**Steele AD, Reynders J, Scholtz F, Bos P, de Beer MC, Tumbo J, Van der Merwe CF, Delem A, De Vos B. Comparison of 2 different regimens for reactogenicity, safety, and immunogenicity of the live attenuated oral rotavirus vaccine RIX4414 coadministered with oral polio vaccine in South African infants. *J Infect Dis.* 2010 Sep 1;202 Suppl:S93-100.**

A phase II, randomized, double-blind, placebo-controlled study was conducted in South Africa during 2003-2004 to evaluate the safety, reactogenicity, and immunogenicity of 2 regimens of the live attenuated oral human rotavirus vaccine RIX4414 when coadministered with the Expanded Program on Immunization childhood vaccines, including oral polio vaccine.

**METHODS:** Healthy infants were randomized (2:2:1) to receive either 2 doses of RIX4414 ( $n = 190$ ; at 10 and 14 weeks, with placebo at 6 weeks), 3 doses of RIX4414 ( $n = 189$ ; at 6, 10, and 14 weeks), or 3 doses of placebo ( $n = 96$ ), all with concomitant routine vaccinations. The antirotavirus IgA seroconversion rate was assessed using enzyme-linked immunosorbent assay at 2 months after the last dose of RIX4414 or placebo. Antipolio types 1, 2, and 3

antibodies were measured using a virus neutralization assay. Solicited symptoms were recorded for 15 days after each dose.

**RESULTS:** The antirotavirus IgA seroconversion rates were similar in the RIX4414 2- and 3-dose groups (44.3% and 44.4%, respectively;  $P = .544$ , by 1-sided Fisher exact test) and antirotavirus IgA geometric mean concentrations were also comparable. Seroprotection rates for antipolio types 1, 2, and 3 antibodies were high (93%-100%) and were not significantly different among groups. Solicited symptoms reported within 15 days after vaccination were similar in all groups.

**CONCLUSIONS:** The immune seroconversion response to the RIX4414 vaccine with 3 doses was not superior to the 2-dose regimen. There was no interference by either regimen with antibody response to oral polio vaccine, and RIX4414 was well tolerated when given with routine vaccinations.

**Steele AD, Cunliffe N, Tumbo J, Madhi SA, De Vos B, Bouckennooghe A. A review of rotavirus infection in and vaccination of human immunodeficiency virus-infected children. J Infect Dis. 2009 Nov 1;200 Suppl 1:S57-62.**

Diarrhea caused by infection with rotavirus annually results in an estimated 611,000 deaths among infants and young children <5 years of age worldwide, and these deaths primarily occur in developing countries. Infection with human immunodeficiency virus (HIV) is also common among young children in many developing countries, particularly in sub-Saharan Africa and Asia. The need for a vaccine to reduce the number of deaths caused by rotavirus infection among children in developing countries is substantial, but current rotavirus vaccines comprise live attenuated oral viruses, the behaviors of which are unknown in HIV-infected children. Therefore, we reviewed available data on natural rotavirus infection in HIV-infected children and examined unpublished data on a small group of HIV-infected infants in South Africa who were given a live rotavirus vaccine. Together, these data suggest that vaccination programs against rotavirus infection could include HIV-infected populations. However, studies addressing the safety, reactogenicity, and immunogenicity of rotavirus vaccines in an HIV-infected population are urgently needed.

**van Hoek AJ, Ngama M, Ismail A, Chuma J, Cheburet S, Mutonga D, Kamau T, Nokes DJ. A Cost Effectiveness and Capacity Analysis for the Introduction of Universal Rotavirus Vaccination in Kenya: Comparison between Rotarix and RotaTeq Vaccines. PLoS One. 2012;7(10):e47511. doi: 10.1371/journal.pone.0047511. Epub 2012 Oct 24.**

**BACKGROUND:** Diarrhoea is an important cause of death in the developing world, and rotavirus is the single most important cause of diarrhoea associated mortality. Two vaccines (Rotarix and RotaTeq) are available to prevent rotavirus disease. This analysis was undertaken to aid the decision in Kenya as to which vaccine to choose when introducing rotavirus vaccination.

**METHODS:** Cost-effectiveness modelling, using national and sentinel surveillance data, and an impact assessment on the cold chain.

**RESULTS:** The median estimated incidence of rotavirus disease in Kenya was 3015 outpatient visits, 279 hospitalisations and 65 deaths per 100,000 children under five years of age per year. Cumulated over the first five years of life vaccination was predicted to prevent 34% of the outpatient visits, 31% of the hospitalizations and 42% of the deaths. The estimated prevented costs accumulated over five years totalled US\$1,782,761 (direct and indirect costs) with an associated 48,585 DALYs. From a societal perspective Rotarix had a cost-effectiveness ratio of US\$142 per DALY (US\$5 for the full course of two doses) and RotaTeq US\$288 per DALY (\$10.5 for the full course of three doses). RotaTeq will have a bigger impact on the cold chain compared to Rotarix.

**CONCLUSION:** Vaccination against rotavirus disease is cost-effective for Kenya irrespective of the vaccine. Of the two vaccines Rotarix was the preferred choice due to a better cost-effectiveness ratio, the presence of a vaccine vial monitor, the requirement of fewer doses and less storage space, and proven thermo-stability.

**Velázquez FR, Colindres RE, Grajales C, Hernández MT, Mercadillo MG, Torres FJ, Cervantes-Apolinar M, DeAntonio-Suarez R, Ortega-Barria E, Blum M, Breuer T, Verstraeten T. Postmarketing surveillance of intussusception following mass introduction of the attenuated human rotavirus vaccine in Mexico. *Pediatr Infect Dis J*. 2012 Jul;31(7):736-44.**

**BACKGROUND:** Mexico initiated mass vaccination with the attenuated human rotavirus vaccine (Rotarix) in 2006. This postlicensure study aimed to assess any potential temporal association between vaccination and intussusception in Mexican infants.

**METHODS:** Prospective, active surveillance for intussusception among infants aged less than 1 year was conducted in 221 hospitals across Mexico from the Mexican Institute of Social Security between January 2008 and October 2010. The temporal association between vaccination and intussusception was assessed by self-controlled case-series analysis.

**RESULTS:** Of the 753 episodes of intussusception reported in 750 infants, 701 were in vaccinated infants (34.5% post-dose 1, 65.5% post-dose 2). The relative incidence of intussusception within 31 days of vaccination was 1.75 (95.5% confidence interval [CI]: 1.24-2.48; P=0.001) post-dose 1 and 1.06 (95.5% CI: 0.75-1.48; P=0.75) post-dose 2. The relative incidence of intussusception within 7 days of vaccination was 6.49 post-dose 1 (95.5% CI: 4.17-10.09; P<0.001) and 1.29 post-dose 2 (95.5% CI: 0.80-2.11; P=0.29). Clustering of intussusception within 7 days of vaccination was observed post-dose 1. An attributable risk of

**CONCLUSION:** This is the largest surveillance study for intussusception after rotavirus vaccination to date. A temporal increase in the risk for intussusception was seen within 7 days of administration of the first vaccine dose. It is still uncertain whether rotavirus vaccination has any impact on the overall incidence of intussusception. This finding has to be put in perspective with the well-documented substantial benefits of rotavirus vaccination.

**Velázquez FR, Matson DO, Calva JJ, Guerrero L, Morrow AL, Carter-Campbell S, Glass RI, Estes MK, Pickering LK, Ruiz-Palacios GM. Rotavirus infections in infants as protection against subsequent infections. N Engl J Med. 1996 Oct 3;335(14):1022-8.**

**BACKGROUND:** Rotavirus is the leading cause of severe diarrhea in infants. To provide a base line for assessing the efficacy of rotavirus vaccines, we evaluated the protection that is conferred by natural rotavirus infection.

**METHODS:** We monitored 200 Mexican infants from birth to two years of age by weekly home visits and stool collections. A physician assessed the severity of any episodes of diarrhea and collected additional stool specimens for testing by enzyme immunoassay and typing of strains. Serum collected during the first week of life and every four months thereafter was tested for antirotavirus IgA and IgG.

**RESULTS:** A total of 316 rotavirus infections were detected on the basis of the fecal excretion of virus (56 percent) or a serologic response (77 percent), of which 52 percent were first and 48 percent repeated infections. Children with one, two, or three previous infections had progressively lower risks of both subsequent rotavirus infection (adjusted relative risk, 0.62, 0.40, and 0.34, respectively) and diarrhea (adjusted relative risk, 0.23, 0.17, and 0.08) than children who had no previous infections. No child had moderate-to-severe diarrhea after two infections, whether symptomatic or asymptomatic. Subsequent infections were significantly less severe than first infections ( $P=0.024$ ), and second infections were more likely to be caused by another G type ( $P=0.054$ ).

**CONCLUSION:** In infants, natural rotavirus infection confers protection against subsequent infection. This protection increases with each new infection and reduces the severity of the diarrhea. 3 to 4 additional cases of intussusception per 100,000 vaccinated infants was estimated.

**Vesikari T, Karvonen A, Ferrante SA, Ciarlet M. Efficacy of the pentavalent rotavirus vaccine, RotaTeq®, in Finnish infants up to 3 years of age: the Finnish Extension Study. Pediatr. 2010 Nov;169(11):1379-86. doi: 10.1007/s00431-010-1242-3.**

Rotavirus Efficacy and Safety Trial (REST) enrolled nearly 70,000 infants, of whom more than 23,000 were from Finland. REST determined the efficacy of the pentavalent rotavirus vaccine (RV5) against rotavirus-related hospitalisations and emergency department (ED) visits in the first year after vaccination. Finnish infants initially in REST transitioned into the Finnish Extension Study (FES), where they were followed for rotavirus-related hospitalisations and ED visits through their second year of life and beyond. FES identified 150 (31%) additional rotavirus gastroenteritis (RVGE) cases beyond those identified in REST in the Finnish participants. Overall, RV5 reduced RVGE hospitalisations and ED visits, regardless of the rotavirus serotype, by 93.8% (95% confidence interval [CI]: 90.8-95.9%) for up to 3.1 years following the last vaccine dose. Vaccine efficacy against combined hospitalisations and ED visits between ages 4 months to 11 months, 12 months to 23 months, and 24 months to 35 months was 93.9% (95% CI: 89.1-96.9%), 94.4% (95% CI: 90.2-97.0%), and 85.9% (95% CI: 51.6-97.2%), respectively. The reduction of hospitalisations and ED visits due to any acute gastroenteritis, rotavirus or not, was 62.4% (95% CI: 57.6-66.6%) over the entire follow-up period. The results from FES confirm that RV5 induces high and sustained protection against rotavirus-related hospitalisations and ED visits, and has a very

substantial impact on all gastroenteritis-related hospitalisations and ED visits into the third year of life in Finnish children.

**Vesikari T, Karvonen A, Prymula R, Schuster V, Tejedor JC, Cohen R, Meurice F, Han HH, Damaso S, Bouckennooghe A. Efficacy of human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in European infants: randomised, double-blind controlled study. Lancet. 2007 Nov 24;370(9601):1757-63**

**BACKGROUND:** We aimed to assess the efficacy of the oral live attenuated human rotavirus vaccine Rotarix (RIX4414) for prevention of rotavirus gastroenteritis in European infants during their first 2 years of life.

**METHODS:** 3994 study participants were enrolled from six countries and were randomly assigned two oral doses of either RIX4414 (n=2646) or placebo (n=1348), which were coadministered with the first two doses of specific childhood vaccinations. Follow-up for gastroenteritis episodes was undertaken from 2 weeks post-dose two through the two consecutive rotavirus seasons following vaccinations (combined efficacy follow-up period; mean duration 17 months [SD 1.6]). Our primary endpoint was vaccine efficacy against rotavirus gastroenteritis of any severity during the first efficacy follow-up period (2 weeks post-dose two to the end of the first rotavirus season). Stool specimens obtained during gastroenteritis episodes were tested for rotavirus by ELISA and typed by RT-PCR. Episodes scoring 11 or greater on the 20-point Vesikari scale were classified as severe. Analysis was according to protocol. This study is registered with ClinicalTrials.gov, number NCT00140686 (eTrack102247).

**FINDINGS:** 120 infants were excluded from the according-to-protocol analysis. During the first efficacy follow-up period (mean duration 5.7 months [SD 1.2]), 24 of 2572 infants allocated RIX4414 versus 94 of 1302 given placebo had rotavirus gastroenteritis episodes of any severity, resulting in a vaccine efficacy of 87.1% (95% CI 79.6-92.1;  $p<0.0001$ ). For the combined efficacy follow-up period, vaccine efficacy against severe rotavirus gastroenteritis was 90.4% (85.1-94.1;  $p<0.0001$ ), for admission owing to rotavirus gastroenteritis 96.0% (83.8-99.5;  $p<0.0001$ ), and for rotavirus-related medical attention 83.8% (76.8-88.9;  $p<0.0001$ ), and significant protection against severe rotavirus gastroenteritis by circulating G1, G2, G3, G4, and G9 rotavirus types was shown.

**INTERPRETATION:** In a European setting, two doses of RIX4414 coadministered with childhood vaccines provided high protection against any and severe rotavirus gastroenteritis, with an overall reduction of admissions for gastroenteritis over two consecutive rotavirus epidemic seasons.

**Vesikari T et al. Safety and efficacy of pentavalent human-bovine (WC3) reassortant rotavirus vaccine in preventing rotavirus gastroenteritis and reducing associated health care resource utilization. The New England Journal of Medicine, 2006,354:23–33.**

**BACKGROUND:** Rotavirus is a leading cause of childhood gastroenteritis and death worldwide.

**METHODS:** We studied healthy infants approximately 6 to 12 weeks old who were randomly assigned to receive three oral doses of live pentavalent human-bovine (WC3 strain) reassortant rotavirus vaccine containing human serotypes G1, G2, G3, G4, and P[8] or placebo at 4-to-10-week intervals in a blinded fashion. Active surveillance was used to identify subjects with serious adverse and other events.

**RESULTS:** The 34,035 infants in the vaccine group and 34,003 in the placebo group were monitored for serious adverse events. Intussusception occurred in 12 vaccine recipients and

15 placebo recipients within one year after the first dose including six vaccine recipients and five placebo recipients within 42 days after any dose (relative risk, 1.6; 95 percent confidence interval, 0.4 to 6.4). The vaccine reduced hospitalizations and emergency department visits related to G1-G4 rotavirus gastroenteritis occurring 14 or more days after the third dose by 94.5 percent (95 percent confidence interval, 91.2 to 96.6 percent). In a nested substudy, efficacy against any G1-G4 rotavirus gastroenteritis through the first full rotavirus season after vaccination was 74.0 percent (95 percent confidence interval, 66.8 to 79.9 percent); efficacy against severe gastroenteritis was 98.0 percent (95 percent confidence interval, 88.3 to 100 percent). The vaccine reduced clinic visits for G1-G4 rotavirus gastroenteritis by 86.0 percent (95 percent confidence interval, 73.9 to 92.5 percent).

**CONCLUSIONS:** This vaccine was efficacious in preventing rotavirus gastroenteritis, decreasing severe disease and health care contacts. The risk of intussusception was similar in vaccine and placebo recipients.

**Vesikari T, Karvonen AV, Majuri J, Zeng SQ, Pang XL, Kohberger R, Forrest BD, Hoshino Y, Chanock RM, Kapikian AZ. Safety, efficacy, and immunogenicity of 2 doses of bovine-human (UK) and rhesus-rhesus-human rotavirus reassortant tetravalent vaccines in Finnish children. J Infect Dis. 2006 Aug 1;194(3):370-6.**

**BACKGROUND:** Live oral rhesus-rhesus-human rotavirus reassortant tetravalent (RRV-TV) vaccine was efficacious against rotavirus gastroenteritis but was withdrawn because of a rare association with intussusception. A corresponding tetravalent (types G1, G2, G3, and G4) reassortant vaccine based on bovine-human (UK) rotavirus reassortant tetravalent (BRV-TV) vaccine was developed concurrently.

**METHODS:** Before the withdrawal of RRV-TV vaccine, parallel placebo-controlled trials of BRV-TV vaccine (observer blinded) versus RRV-TV vaccine (double blinded) with a 2 : 1 ratio of vaccine : placebo were conducted in Finland in a total of 510 infants. Two doses of study vaccine or placebo were administered at ages 3 and 5 months.

**RESULTS:** The first dose of RRV-TV vaccine was followed by a significant excess rate of febrile reactions (36%), whereas the rate of fever after the administration of BRV-TV vaccine did not differ significantly from that in the placebo group. Neither vaccine induced diarrhea. A seroresponse was detected in 97% of BRV-TV vaccine recipients and 94% of RRV-TV vaccine recipients. Both vaccines were equally effective, with 68%-69% efficacy against any and 88%-100% efficacy against severe rotavirus gastroenteritis during the first epidemic season.

**CONCLUSIONS:** BRV-TV vaccine is a promising new candidate rotavirus vaccine, with low reactogenicity and high efficacy. Two doses of BRV-TV or RRV-TV vaccine are sufficient for the induction of protection against severe rotavirus disease.

**Wang FT, Mast TC, Glass RJ, Loughlin J, Seeger JD. Effectiveness of an Incomplete RotaTeq® (RV5) Vaccination Regimen in Preventing Rotavirus Gastroenteritis in the United States. Pediatr Infect Dis J. 2012 Sep 25.**

**BACKGROUND:** Effectiveness of the pentavalent rotavirus vaccine (RV5) after administration of the complete (3 dose) regimen has been demonstrated in a real-world setting. This study assessed the effectiveness of RV5 following partial completion of the 3-dose regimen. **METHODS:** Using a large national health insurance claims database, 2 cohorts of infants (those who received RV5 and a concurrent group who received diphtheria-tetanus-acellular pertussis (DTaP), but not RV5) were followed through the 2007 and 2008 rotavirus

seasons (January 1 to May 31) to identify cases of rotavirus gastroenteritis and all-cause gastroenteritis resulting in medical care encounters. Vaccine effectiveness following the first and the second RV5 doses was estimated by quantifying reductions in hospitalizations, emergency department and physician office visits. RESULTS: A first RV5 dose was received by 42,306 infants while 28,417 infants in the concurrent comparison group received a first DTaP dose; 43,704 infants received a second RV5 dose and 31,810 infants received a second DTaP dose. One dose of RV5 was associated with an 88% effectiveness against rotavirus gastroenteritis hospitalizations and ED visits and 44% effectiveness against all-cause gastroenteritis hospitalizations and ED visits. A two-dose regimen of RV5 was associated with 94% effectiveness against rotavirus gastroenteritis hospitalizations and ED visits and 40% effectiveness against all-cause gastroenteritis hospitalizations and ED visits. CONCLUSION: The RV5 vaccine exhibits effectiveness against rotavirus gastroenteritis even before completing the full 3 dose regimen. These results are of particular relevance when considering the benefits of a partially-completed rotavirus vaccine series.

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