

Rotavirus vaccines

Selected references

Epidemiology, agent, disease, and immune response

Epidemiology

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.

Parashar UD, Gibson CJ, Bresee JS, Glass RI. Rotavirus and Severe Childhood Diarrhea. *Emerg Infect Dis* 2006 Febr; 12(2): 304-306

Studies published between 1986 and 1999 indicated that rotavirus causes ≈22% (range 17%–28%) of childhood diarrhea hospitalizations. From 2000 to 2004, this proportion increased to 39% (range 29%–45%). Application of this proportion to the recent World Health Organization estimates of diarrhea-related childhood deaths gave an estimated 611,000 (range 454,000–705,000) rotavirus-related deaths

Black RE, Merson MH, Rahman AS, Yunus M, Alim AR, Huq I, Yolken RH, Curlin GT. A two-year study of bacterial, viral, and parasitic agents associated with diarrhea in rural Bangladesh. *J Infect Dis.* 1980 Nov;142(5):660-4

Enteric pathogens associated with diarrhea were studied for two years at a diarrhea treatment center in rural Bangladesh. Enterotoxigenic *Escherichia coli* (ETEC) was the most frequently identified pathogen for patients of all ages. Rotavirus and ETEC were isolated from approximately 50% and approximately 25%, respectively, of patients less than two years of age. A bacterial or viral pathogen was identified for 70% of these young children and for 56% of all patients with diarrhea. Most ETEC isolates were obtained in the hot dry months of March and April and the hot wet months of August and September. Rotavirus identification peaked in the cool dry months of December and January, but infected patients were found year-round. The low case-fatality rates for patients with watery diarrhea and substantial dehydration further document the usefulness of treating patients with diarrhea with either a glucose- or sucrose-base electrolyte solution such as those used in this treatment center.

Cunliffe NA, Kilgore PE, Bresee JS, Steele AD, Luo N, Hart CA, Glass RI. Epidemiology of rotavirus diarrhoea in Africa: a review to assess the need for rotavirus immunization. Bull World Health Organ. 1998;76(5):525-37.

Rapid progress towards the development of rotavirus vaccines has prompted a reassessment of the disease burden of rotavirus diarrhoea in developing countries and the possible impact of these vaccines in reducing diarrhoeal morbidity and mortality among infants and young children. We examined the epidemiology and disease burden of rotavirus diarrhoea among hospitalized and clinic patients in African countries through a review of 43 published studies of the etiology of diarrhoea. The studies were carried out from 1975 through 1992, and only those in which a sample of more than 100 patients with diarrhoea were specifically screened for rotavirus by using an established diagnostic test were included. Rotavirus was detected in a median of 24% of children hospitalized for diarrhoea and in 23% who were treated as outpatients; 38% of the hospitalized patients with rotavirus were < 6 months and 81% were < 1 year of age. Rotavirus was detected year-round in nearly every country and generally exhibited distinct seasonal peaks during the dry months. In 5 countries where rotavirus strains had been G-typed, 74% of strains were of one of the four common serotypes (G1 to G4), G1 was the predominant serotype, and 26% were non-typeable. This cumulative experience from 15 African countries suggests that rotavirus is the most important cause of severe diarrhoea in African children and that most strains in circulation today belong to common G types that are included in reassortant vaccines. Wherever large numbers of cases of rotavirus diarrhoea occur early in infancy, immunization at birth may protect the children before their first symptomatic infection.

Soriano-Gabarro M, Mrukowicz J, Vesikari T, Verstraeten T. Burden of rotavirus disease in European Union countries. Pediatr Infect Dis J. 2006 Jan;25(1 Suppl):S7-S11.

Two new rotavirus vaccines are expected to be introduced in the European Union (EU) in coming years. A human rotavirus vaccine has already been licensed in several countries worldwide, and a pentavalent bovine vaccine has been submitted for licensure in the United States and the EU. Few data exist on the burden of rotavirus disease and its associated costs within the EU. To estimate the burden of rotavirus disease in the EU, we adapted a model based on the approach developed by the Centers for Disease Control and Prevention to the European situation and applied it to recent population and mortality data from European countries. Country-specific estimates were added to obtain a global estimate of rotavirus episodes treated at home, clinic visits, hospitalization and death. We estimate that 3.6 million episodes of rotavirus disease occur annually among the 23.6 million children younger than 5 years of age in the EU. Every year, rotavirus accounts for 231 deaths, >87,000 hospitalizations and almost 700,000 outpatient visits. Rotavirus disease constitutes a large public health burden in the EU. Except for deaths, the burden of disease is not dissimilar to that in the developing world. Country-specific studies are required to more accurately understand the burden of disease caused by rotavirus. With the introduction of new rotavirus vaccines in sight, rotavirus gastroenteritis may be regarded as the single most frequent vaccine-preventable disease among children in the EU.

Banerjee I, Ramani S, Primrose B, Moses P, Iturriza-Gomara M, Gray JJ, Jaffar S, Monica B, Muliylil JP, Brown DW, Estes MK, Kang G. Comparative study of the epidemiology of rotavirus in children from a community-based birth cohort and a hospital in South India. J Clin Microbiol. 2006 Jul;44(7):2468-74.

Rotavirus gastroenteritis is the major cause of severe dehydrating diarrhea in children worldwide. This study compares rotavirus diarrhea in 351 children in a community-based cohort and 343 children admitted to a hospital during the same period. Clinical information and fecal specimens were obtained during diarrheal episodes. Fecal samples were screened for VP6 antigen, and the positive samples were G and P typed by reverse transcription-PCR. Rotavirus was detected in 82/1,152 (7.1%) episodes of diarrhea in the community and 94/343 (27.4%) cases in the hospital. The median age of affected children (7.5 versus 10.5 months) and the mean severity of symptoms (Vesikari score, 7.6+/-3.4 versus 11+/-2.5) were lower in the community. A larger proportion of children in the community were breast-fed than were children admitted to the hospital (73% versus 34.8%). In the community, the genotypes identified in symptomatic patients, in order of frequency, were G1 (36.5%), G10 (17.1%), G2 (15.9%), and G9 (7.3%) and mixed infections (7.3%). The most common G-P combinations were G1P[8], G2P[4], G1P[4], and G10P[11]. The distribution of G types from hospitalized children was G1 (46.8%), G9 (19.1%), G2 (8.5%), G10 (1.1%), and 4.3% mixed infections. The most common G-P combinations were G1P[8] and G9P[8]. This study documents significant genetic heterogeneity of rotaviruses in the community and the hospital. G10P[11] strains resembling a vaccine candidate strain caused disease in the community, indicating the need for careful epidemiological studies as well as safety studies for the vaccine candidates.

Kane EM, Turcios RM, Arvay ML, Garcia S, Bresee JS, Glass RI. The epidemiology of rotavirus diarrhea in Latin America. Anticipating rotavirus vaccines. *Rev Panam Salud Publica*. 2004 Dec;16(6):371-7.

OBJECTIVE: To assess the disease burden and characterize the epidemiology of rotavirus diarrhea in Latin America. **METHODS:** We conducted a literature review of studies of children < 5 years of age who were hospitalized or seen as outpatients for diarrhea and for whom rotavirus was sought as the etiologic agent of the diarrhea. This review included inpatient and outpatient studies published since 1998 that included at least 100 children and reported surveillance activities lasting at least 12 consecutive months. **RESULTS:** A total of 18 inpatient and 10 outpatient studies met the criteria for inclusion in this review. Rotavirus was detected in a median of 31% of inpatients (range, 16%-52%) and 30.5% of outpatients (range, 4%-42%). The median detection rate was higher in studies that used an enzyme-linked immunosorbent assay (ELISA) (inpatients 38%, outpatients 33%) versus less sensitive methods of detection. The age distribution of rotavirus disease varied among countries, with 65%-85% of children hospitalized in the first year of life. Most countries had rotavirus admissions year round, and rotavirus generally exhibited a winter seasonal peak in both temperate and tropical climates. **CONCLUSIONS:** The heavy burden of disease attributable to rotavirus in Latin America suggests that vaccines currently being tested could have considerable impact in preventing hospitalizations, clinic visits, and deaths. The findings of the young age distribution of patients highlight the importance of early immunization for the success of a vaccine program. The data suggest that future surveillance for rotavirus diarrhea in Latin America should use a standardized surveillance protocol with an ELISA for detection. Data from surveillance studies will be critical to monitor the impact of the future introduction of vaccines

Bresee J, Fang ZY, Wang B, Nelson EA, Tam J, Soenarto Y, Wilopo SA, Kilgore P, Kim JS, Kang JO, Lan WS, Gaik CL, Moe K, Chen KT, Jiraphongsa C, Ponguswanna Y, Nguyen VM, Phan VT, Le TL, Hummelman E, Gentsch JR, Glass R; Asian Rotavirus

Surveillance Network. First report from the Asian Rotavirus Surveillance Network. *Emerg Infect Dis.* 2004 Jun;10(6):988-95.

Rotavirus remains the most common cause of severe, dehydrating diarrhea among children worldwide. Several rotavirus vaccines are under development. Decisions about new vaccine introduction will require reliable data on disease impact. The Asian Rotavirus Surveillance Network, begun in 2000 to facilitate collection of these data, is a regional collaboration of 36 hospitals in nine countries or areas that conduct surveillance for rotavirus hospitalizations using a uniform World Health Organization protocol. We summarize the Network's organization and experience from August 2001 through July 2002. During this period, 45% of acute diarrheal hospitalizations among children 0-5 years were attributable to rotavirus, higher than previous estimates. Rotavirus was detected in all sites year-round. This network is a novel, regional approach to surveillance for vaccine-preventable diseases. Such a network should provide increased visibility and advocacy, enable more efficient data collection, facilitate training, and serve as the paradigm for rotavirus surveillance activities in other regions.

Agent

Montenegro FM, Correia JB, Rodrigues Falbo A, Dove W, Nakagomi T, Nakagomi O, Cuevas LE, Cunliffe NA, Hart CA. Anticipating rotavirus vaccines in Brazil: detection and molecular characterization of emerging rotavirus serotypes G8 and G9 among children with diarrhoea in Recife, Brazil. *J Med Virol.* 2007 Mar;79(3):335-40.

In 2006, Brazil will initiate universal immunization of its 4-million infants with a live attenuated serotype G1P[8] human rotavirus vaccine. In anticipation of the national immunization program, this study was undertaken to characterize rotavirus strains circulating among children in Recife, one of the largest cities in the northeast region of Brazil. Group A rotaviruses were detected in 102 (35%) of 290 faecal specimens collected from children under 5 years of age who presented with acute diarrhoea during a 1-year period between May 2004 and April 2005. In addition to the globally common G1P[8] serotype that accounted for 49% of strains, emerging rotavirus serotypes G8P[6] and G9P[8] represented 2% and 29% of strains, respectively. Following cell culture adaptation, RNA-RNA hybridization demonstrated that two Brazilian G8P[6] rotavirus strains shared a high level of genomic RNA homology with Malawian G8P[6] strains, and a Brazilian G9P[8] strain was related most closely to a G9P[8] strain from India. The results suggest that certain rotavirus strains have a much wider global circulation than generally appreciated. Continued global spread of such strains might challenge the efficacy of current rotavirus vaccines.

Desselberger U, Wolleswinkel-van den Bosch J, Mrukowicz J, Rodrigo C, Giaquinto C, Vesikari T. Rotavirus types in Europe and their significance for vaccination. *Pediatr Infect Dis J.* 2006 Jan;25(1 Suppl):S30-41.

The degree of diversity of cocirculating human rotavirus wild-type strains is high. This article reviews the occurrence and frequency of rotavirus types in European children younger than 5 years of age during the past 10-15 years. To enable greater understanding of the overall epidemiologic situation, rotavirus types found in animals in Europe are described. In addition, rotavirus types occurring in children outside Europe are considered. Taken together, these data provide an essential background to the development of rotavirus vaccines. The different concepts of immunization with the 2 main rotavirus candidate vaccines are briefly discussed, and their potential impact on the epidemiology of

cocirculating rotavirus wild-type viruses is considered. A case is made for comprehensive surveillance of cocirculating human rotavirus types in Europe after the implementation of rotavirus vaccination.

Ramachandran M, Das BK, Vij A, Kumar R, Bhambal SS, Kesari N, Rawat H, Bahl L, Thakur S, Woods PA, Glass RI, Bhan MK, Gentsch JR. Unusual diversity of human rotavirus G and P genotypes in India. J Clin Microbiol. 1996 Feb;34(2):436-9.

Between April and December 1993, we determined P and G genotypes of group A rotavirus strains obtained from children admitted to diarrhea treatment centers in five Indian cities. From a total of 63 rotavirus-positive specimens, we identified 10 different strains with five different G genotypes and four distinct P types by using reverse transcription-PCR. The common worldwide strains G1P8, G2P4, G3P8, and G4P8 were underrepresented among Indian children (33%), whereas strains of P type 6 (G1P6, G2P6, G3P6, G4P6, and G9P6), which primarily infect asymptomatic newborns but are rare in children with diarrhea were common in India (43%). Of these, G9P6, a strain not previously reported to be found in children with diarrhea, was the most prevalent (22%). Eleven percent of the strains were nontypeable, and another 11% of the specimens had mixed infections. Using digoxigenin-labeled, genotype-specific hybridization probes, we confirmed all G9 strains and mixed infections tested and identified three nontypeable strains (one G9 and two P8). The epidemiological significance of G9 rotavirus strains, if confirmed in other settings, may have important implications for vaccine development.

Gentsch JR, Laird AR, Bielfelt B, Griffin DD, Banyai K, Ramachandran M, Jain V, Cunliffe NA, Nakagomi O, Kirkwood CD, Fischer TK, Parashar UD, Bresee JS, Jiang B, Glass RI. Serotype diversity and reassortment between human and animal rotavirus strains: implications for rotavirus vaccine programs. J Infect Dis. 2005 Sep 1;192 Suppl 1:S146-59.

The development of rotavirus vaccines that are based on heterotypic or serotype-specific immunity has prompted many countries to establish programs to assess the disease burden associated with rotavirus infection and the distribution of rotavirus strains. Strain surveillance helps to determine whether the most prevalent local strains are likely to be covered by the serotype antigens found in current vaccines. After introduction of a vaccine, this surveillance could detect which strains might not be covered by the vaccine. Almost 2 decades ago, studies demonstrated that 4 globally common rotavirus serotypes (G1-G4) represent >90% of the rotavirus strains in circulation. Subsequently, these 4 serotypes were used in the development of reassortant vaccines predicated on serotype-specific immunity. More recently, the application of reverse-transcription polymerase chain reaction genotyping, nucleotide sequencing, and antigenic characterization methods has confirmed the importance of the 4 globally common types, but a much greater strain diversity has also been identified (we now recognize strains with at least 42 P-G combinations). These studies also identified globally (G9) or regionally (G5, G8, and P2A[6]) common serotype antigens not covered by the reassortant vaccines that have undergone efficacy trials. The enormous diversity and capacity of human rotaviruses for change suggest that rotavirus vaccines must provide good heterotypic protection to be optimally effective.

Cascio A, Vizzi E, Alaimo C, Arista S. Rotavirus gastroenteritis in Italian children: can severity of symptoms be related to the infecting virus? Clin Infect Dis. 2001 Apr 15;32(8):1126-32.

The aim of our study was to determine whether the severity of rotavirus gastroenteritis may be related to the different characteristics of infecting viral strains. The severity of clinical symptoms in 401 children with acute rotavirus gastroenteritis was assessed using a scoring system for frequency and duration of vomiting, diarrhea, and fever, as well as the patients' requirements for intravenous rehydration. Rotavirus strains were characterized by determining the electropherotype of their double-stranded RNA, the G type and subgroup by a panel of monoclonal antibodies, and the P type by reverse transcription-polymerase chain reaction. Strains with a short electropherotype, G2P[4] type, and subgroup I were associated with more-severe gastroenteritis and affected children older than those infected with strains with a long electropherotype, G1P[8] or G4P[8] type, and subgroup II. Minor differences in clinical symptoms were also detected in children infected with different long electropherotypes and with G1P[8] and G4P[8] specificities.

Disease

Staat MA, Azimi PH, Berke T, Roberts N, Bernstein DI, Ward RL, Pickering LK, Matson DO. Clinical presentations of rotavirus infection among hospitalized children. *Pediatr Infect Dis J*. 2002 Mar;21(3):221-7.

BACKGROUND: Although rotaviruses (RVs) are the most common cause of severe gastroenteritis in children, there is a lack of information detailing the spectrum of clinical manifestations of RV disease resulting in hospitalization. **OBJECTIVE:** To characterize the clinical spectrum of RV-associated hospitalizations, including short stay visits in children. **METHODS:** Active RV disease surveillance was conducted at three children's hospitals Sundays through Thursdays in children 15 days through 4 years of age admitted with diarrhea (D), vomiting (V) and/or unexplained fever (F) between November, 1997, and June, 1998. Stool specimens were collected and tested for RV by enzyme immunoassay. **RESULTS:** Of the 862 children enrolled, 763 (88%) had a stool specimen tested for RV. Overall 31% of children excreted RV. RV excretion was highest when all 3 symptoms (D, V and F) occurred in the same child (56%), lower when 2 symptoms occurred together (38% DV; 19% DF; 13% VF) and lowest when each symptom occurred alone (3% D; 11% V; 6% F). Nine percent of the children without diarrhea excreted RV. Children admitted without diarrhea were more likely to have rotavirus if they developed diarrhea during their hospitalization. **CONCLUSIONS:** RV detection was greatest when diarrhea, vomiting and fever occurred together and lowest when each symptom occurred alone. The spectrum of symptoms of rotavirus disease in children at the time of admission to the hospital or short stay unit may be broader than previously recognized.

Ruuska T, Vesikari T. Rotavirus disease in Finnish children: use of numerical scores for clinical severity of diarrhoeal episodes. *Scand J Infect Dis*. 1990;22(3):259-67.

65 episodes of rotavirus diarrhoea, detected during a longitudinal follow-up of 336 infants from birth to 24-32 months of age, were analyzed for clinical symptoms. Rotavirus gastroenteritis was characterized by watery diarrhoea, vomiting (particularly in older children), fever and dehydration. A 0-20 point numerical score was devised according to the distribution of clinical features in the patients. Using this system, the mean severity score for the 65 episodes of rotavirus diarrhoea was 11.0 +/- 3.7 as compared to 5.6 +/- 3.2 for the 183 episodes of non-rotavirus diarrhoea in the same population (p less than 0.0001, t-test). The 20 point score is proposed for analysis of efficacy studies of candidate rotavirus vaccines.

Immune response

Franco MA, Angel J, Greenberg HB. Immunity and correlates of protection for rotavirus vaccines. *Vaccine*. 2006 Apr 5;24(15):2718-31.

Rotaviruses are the most common cause of severe, dehydrating diarrhea in children worldwide. The tremendous global incidence of rotavirus gastroenteritis, especially in developing countries, emphasizes the need for vaccines to prevent associated morbidity and mortality. However, immunity to rotavirus is not completely understood. At this time, total serum RV IgA, measured shortly after infection, appears to be the best marker of protection against rotavirus. This review describes the current understanding of rotavirus immunity, including mechanisms of protection against rotavirus from selected animal models, and correlates of protection associated with natural infection or vaccination from humans.

Ward RL, Bernstein DI, Smith VE, Sander DS, Shaw A, Eiden JJ, Heaton P, Offit PA, Clark HF. Rotavirus immunoglobulin a responses stimulated by each of 3 doses of a quadrivalent human/bovine reassortant rotavirus vaccine. *J Infect Dis*. 2004 Jun 15;189(12):2290-3.

A quadrivalent precursor to the pentavalent rotavirus vaccine candidate RotaTeq was evaluated in a 3-dose, 439-subject study. To determine immunogenicity, the quantity of rotavirus immunoglobulin A (IgA) in stool specimens obtained, at 1 of 10 study sites, from 37 placebo and 37 vaccine recipients was measured. None of the placebo recipients showed a clinically important (≥ 3 -fold) increase in stool rotavirus IgA, whereas 31 vaccine recipients showed an increase after at least 1 dose of vaccine. In total, 16, 19, and 15 vaccine recipients had increases after 1, 2, and 3 doses, respectively, indicating that a 3-dose regimen increased the immune response elicited by this vaccine.

Fischer TK, Valentiner-Branth P, Steinsland H, Perch M, Santos G, Aaby P, Molbak 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 vaccine.

Clemens J, Rao M, Ahmed F, Ward R, Huda S, Chakraborty J, Yunus M, Khan MR, Ali M, Kay B, et al. Breast-feeding and the risk of life-threatening rotavirus diarrhea: prevention or postponement? *Pediatrics*. 1993 Nov;92(5):680-5.

PURPOSE. To assess the relationship between breast-feeding and the risk of life-threatening rotavirus diarrhea among Bangladeshi infants and children younger than 24 months of age. **DESIGN.** Case-control study. **SETTING.** A rural Bangladesh community. **PARTICIPANTS.** One hundred two cases with clinically severe rotavirus diarrhea detected in a treatment center-based surveillance system during 1985 and 1986, and 2587 controls selected in three surveys of the same community during the same calendar interval. **OUTCOMES.** Cases and controls were compared for the frequency of antecedent breast-feeding patterns. **RESULTS.** Compared with other feeding modes, exclusive breast-feeding of infants was associated with significant protection against severe rotavirus diarrhea (relative risk (RR) = 0.10; 95% confidence interval [CI] = 0.03, 0.34). However, during the second year of life, the risk of this outcome was higher in breast-fed than in non-breast-fed children (RR = 2.85; 95% CI = 0.37, 21.71), and no overall protection was associated with breast-feeding during the first 2 years of life (RR = 2.61; 95% CI = 0.62, 11.02). **CONCLUSIONS.** Although exclusive breast-feeding appeared to protect infants against severe rotavirus diarrhea, breast-feeding per se conferred no overall protection during the first 2 years of life, suggesting that breast-feeding temporarily postponed rather than prevented this outcome. While not detracting from efforts to promote breast-feeding to alleviate the burden of diarrhea due to nonrotaviral enteropathogens, our findings cast doubt on whether such efforts will impact on the problem of severe rotavirus diarrhea.

Rotavirus vaccines

Previous vaccines and the problem of intussusception

Kapikian AZ. A rotavirus vaccine for prevention of severe diarrhoea of infants and young children: development, utilization and withdrawal. *Novartis Found Symp*. 2001;238:153-71; discussion 171-9.

The importance of rotaviruses (RVs) as the single most important cause of severe diarrhoea of infants and young children is well recognized. At NIH, we developed a quadrivalent (tetravalent [TV]) vaccine to protect against the four epidemiologically important RV serotypes. It is comprised of live attenuated rhesus RV (RRV), a VP7 serotype G3 strain (the 'Jennerian' approach), and three reassortant RVs, each containing 10 RRV genes and one human RV gene that codes for the major outer protein, VP7, that determines serotype G1, G2 or G4 specificity (the 'modified Jennerian' approach). The vaccine was safe and effective against severe diarrhoea in a major prelicensure collaborative effort of phase III trials. In February 1998 and again in June 1998, the Advisory Committee on Immunization Practices (ACIP) recommended routine immunization with three oral doses at 2, 4 and 6 months of age. The tetravalent vaccine (RotaShield) was licensed in the USA by the FDA in August 1998. In July 1999, after about 1.5 million doses had been given, the CDC recommended suspending administration of the vaccine because post-licensure surveillance of adverse events had suggested an association with intussusception. After further investigation by CDC, in October 1999, the ACIP withdrew its recommendation concluding that intussusception occurs with significantly increased frequency in the first 1-2 weeks after vaccination with RRV-TV, particularly following the first dose'. The implications of these developments from a practical, epidemiological, analytical and ethical perspective are discussed.

Peter G, Myers MG; National Vaccine Advisory Committee; National Vaccine Program Office. Intussusception, rotavirus, and oral vaccines: summary of a workshop. Pediatrics. 2002 Dec;110(6):e67.

Rotavirus gastroenteritis continues to cause substantial morbidity and mortality worldwide, despite widespread breastfeeding and use of oral rehydration therapy. This burden of disease indicates that an effective, safe rotavirus vaccine is needed, and in 1998 the first rhesus-human reassortant rotavirus tetravalent vaccine, Rotashield, was licensed in the United States. However, the recommendations for its use were withdrawn in 1999 because of the recognition of an uncommon but serious adverse event, intussusception. A workshop in September 2001 was held to review the subsequent developments and research regarding this association, the proceedings of which are summarized here. Although the pathogenesis of this association remains unknown, epidemiologic evidence supports a causal relationship, with a population attributable risk of approximately 1 per 10 000 (range of 1 in 5000 to 1 in 12 000) vaccine recipients. Whether this association will exist with other candidate rotavirus vaccine strains and whether the attributable risk for intussusception would be similar in other populations administered this vaccine are unclear. Because perceptions of vaccine safety derive from the relative disease burdens of the illness prevented and adverse events induced, the acceptance of rare adverse events may vary substantially in different settings. Nevertheless, a continuing consensus on the need for a safe and effective vaccine to prevent rotavirus gastroenteritis, especially for use in developing countries, exists.

Bines J. Intussusception and rotavirus vaccines. Vaccine. 2006 May 1;24(18):3772-6.

The association between the first oral rotavirus vaccine to be licensed in the U.S. (Rotashield) and intussusception has presented a major challenge to the effort to reduce the global burden related to rotavirus infection. Although the risk of developing intussusception following immunization with Rotashield is low, debate continues about the estimation of intussusception risk and the events surrounding the withdrawal of the vaccine. The experience with Rotashield has highlighted the wisdom of parallel clinical trials in developing and developed countries and the value of post-licensure surveillance for the detection of uncommon adverse events. This review retraces the steps leading up to the withdrawal of the Rotashield vaccine and reflects on how this experience has influenced the development of other rotavirus vaccines.

Simonsen L, Viboud C, Elixhauser A, Taylor RJ, Kapikian AZ. More on RotaShield and intussusception: the role of age at the time of vaccination. J Infect Dis. 2005 Sep 1;192 Suppl 1:S36-43

BACKGROUND: RotaShield, a vaccine intended to prevent severe rotavirus diarrhea, was withdrawn in July 1999, 9 months after it became available in the United States, because of a temporal association with intussusception events that occurred in vaccinated infants. We explore here the effect of age on the risk of intussusception. **METHODS:** We reanalyzed a case-control database of the Centers for Disease Control and Prevention by use of a 21-day window, to define vaccine-associated events. We obtained data on vaccine use from the National Immunization Survey and estimated the age-stratified background incidence of intussusception by use of Healthcare Cost and Utilization Project data. We combined these data to estimate how absolute risk varies with age and to model the projected population-attributable risk associated with 3 different vaccination schedules. **RESULTS:** We found that the incidence of intussusception associated with the first dose of vaccine increased with age. Infants \geq 90 days old accounted for 80% of cases of intussusception associated with a first dose but had received only 38% of first doses. Modeling of the recommended schedule of vaccination at ages 2, 4, and 6 months projected 1

intussusception event/11,000-16,000 vaccine recipients; modeling of a 2-dose schedule beginning in the neonatal period projected 1 intussusception event/38,000-59,000 vaccine recipients. **CONCLUSIONS:** The practice of initiating immunization after age 90 days, which we call "catch-up" vaccination, contributed disproportionately to the occurrence of intussusception associated with the use of RotaShield. A fully implemented 2-dose vaccination schedule begun during the neonatal period would lead to, at most, a 7% increase in the incidence of intussusception above the annual background incidence.

Review papers on new rotavirus vaccines

O'Ryan M. Rotarix (RIX4414): an oral human rotavirus vaccine. *Expert Rev Vaccines*. 2007 Feb;6(1):11-9.

Rotavirus is the most common cause of severe gastroenteritis in children younger than 3 years of age worldwide. New rotavirus vaccine candidates were required to confer early protection against the most common rotavirus serotypes and to be well tolerated and not associated with intussusception. RIX4414 is a human-attenuated G1(P8) oral rotavirus vaccine administered in two doses at approximately 6-24 weeks of age. The first dose may be administered from the age of 6 weeks. There should be an interval of at least 4 weeks between doses and the vaccination course should preferably be given before 16 weeks of age and must be completed, according to the manufacturer, by the age of 24 weeks. In a worldwide development program involving more than 70,000 children in six Phase I-III field trials, this vaccine proved to be nonreactogenic, well tolerated and not associated with intussusception. The vaccine provides over 85-96% protection against moderate-to-severe gastroenteritis caused by G1 and non-G1 serotypes, as demonstrated in Latin American and European clinical trial settings, respectively; and reduces gastroenteritis-related hospitalizations by more than 40% in Latin America and by 75% in European settings.

Clark HF, Offit PA, Plotkin SA, Heaton PM. The new pentavalent rotavirus vaccine composed of bovine (strain WC3) -human rotavirus reassortants. *Pediatr Infect Dis J*. 2006 Jul;25(7):577-83.

BACKGROUND: Infantile gastroenteritis caused by human rotaviruses is a prevalent disease throughout the world, causing dehydration and hospitalization in all countries. In developing countries, it is associated with a high mortality. A licensed vaccine against rotavirus was withdrawn because of a causal association with intussusception. A new vaccine has been developed and is a candidate for licensure. **METHODS:** To recount the early development and recent demonstration of the safety and efficacy of the new vaccine. A bovine rotavirus attenuated for humans was isolated and reassorted with human rotaviruses of serotypes G1-4 and P1 to create a pentavalent vaccine. Multiple placebo-controlled clinical trials, including one involving approximately 70,000 infants, were conducted in multiple developed countries. **RESULTS:** The pentavalent vaccine was well tolerated by infants less than 8 months of age, and the incidence of intussusception was similar among vaccine and placebo recipients. More than 90% of infants had a significant rise in serum antirotavirus IgA titer after 3 doses. Efficacy of 95% against severe disease causing hospitalization or emergency care was demonstrated, and pentavalent vaccine prevented 74% of all rotavirus disease. **CONCLUSIONS:** If widely used, pentavalent vaccine would control rotavirus disease in the United States and other developed countries and could also have a major effect in developing countries.

Glass RI, Bresee JS, Turcios R, Fischer TK, Parashar UD, Steele AD. Rotavirus vaccines: targeting the developing world. J Infect Dis. 2005 Sep 1;192 Suppl 1:S160-6.

For the past 2 decades, rotavirus infection, the most common cause of severe diarrhea in children, has been a priority target for vaccine development. This decision to develop rotavirus vaccines is predicated on the great burden associated with fatal rotavirus disease (i.e., 440,000 deaths/year), the firm scientific basis for developing live oral vaccines, the belief that increased investment in development at this time could speed the introduction of vaccines in developing countries, and the appreciation that implementation of a vaccine program should result in a measurable decrease in the number of hospitalizations and deaths associated with rotavirus disease within 2-3 years. RotaShield (Wyeth-Ayerst), the first rotavirus vaccine licensed in the United States, was withdrawn after 9 months because of a rare association of the vaccine with the development of intussusception. In the developing world, this vaccine could still have had a measurable effect, because the benefits of preventing deaths due to rotavirus disease would have been substantially greater than the rare risk of intussusception. Two live oral vaccines being prepared by GlaxoSmithKline and Merck have completed large-scale clinical trials. The GlaxoSmithKline vaccine has been licensed in Mexico and the Dominican Republic, and the Merck vaccine could be licensed in the United States within 1 year; several other candidate vaccines are in earlier stages of testing. However, many challenges remain before any of these vaccines can be incorporated into childhood immunization programs in the developing world. First, vaccine efficacy, which has already been demonstrated in children in industrialized and middle-income countries, needs to be proven in poor developing countries in Africa and Asia. The safety of vaccines with regard to the associated risk of intussusception must be demonstrated as well. Novel financing strategies will be needed to ensure that new vaccines are affordable and available in the developing world. Decision makers and parents in developing countries need to know about this disease that has little name recognition and is rarely diagnosed. Finally, for the global effort toward the prevention of rotavirus disease to be successful, special efforts will be required in India, China, and Indonesia, because one-third of all deaths due to rotavirus disease occur in these countries, and because these countries depend almost entirely on vaccines manufactured domestically.

Immunogenicity, efficacy and safety trials

Block SL, Vesikari T, Goveia MG, Rivers SB, Adeyi BA, Dallas MJ, Bauder J, Boslego JW, Heaton PM; Pentavalent Rotavirus Vaccine Dose Confirmation Efficacy Study Group. Efficacy, immunogenicity, and safety of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine at the end of shelf life. Pediatrics. 2007 Jan;119(1):11-8.

BACKGROUND: Rotavirus is the leading cause of dehydrating acute gastroenteritis in infants worldwide. Previous studies of a live pentavalent human-bovine reassortant rotavirus vaccine have shown it to be efficacious across a range of potencies. **OBJECTIVE:** Our goal was to evaluate the efficacy, immunogenicity, and safety of pentavalent rotavirus vaccine at the end of shelf life in healthy infants. **PATIENTS AND METHODS:** During 2002-2004, 1312 healthy infants approximately 6 to 12 weeks old from the United States (47%) and Finland (53%) were randomly assigned to receive 3 oral doses of vaccine (vaccine at approximately 1.1×10^7 infectious U per dose) or placebo approximately 4 to 10 weeks apart. Infants were to be followed for acute gastroenteritis through 1 rotavirus season after vaccination and for adverse events postvaccination. **RESULTS:** Three doses of pentavalent rotavirus vaccine at the end of shelf life demonstrated efficacy against rotavirus

gastroenteritis caused by human G-serotypes included in the vaccine (G1-G4). Efficacy against severe rotavirus gastroenteritis was 100%, and efficacy against any rotavirus gastroenteritis regardless of severity was 72.5%. A threefold rise in G1 serum neutralizing was observed in 57% and in anti-rotavirus immunoglobulin A in 96% of pentavalent rotavirus vaccine recipients. No statistically significant increase in vomiting, diarrhea, or irritability was observed among pentavalent rotavirus vaccine recipients compared with placebo recipients within the 7-day period from each dose. A statistically significant increase in fevers ($>$ or $=$ 100.5 degrees F, rectal equivalent) was observed among pentavalent rotavirus vaccine recipients compared with placebo recipients after dose 1. CONCLUSIONS: This pentavalent human-bovine rotavirus vaccine was generally well tolerated, efficacious, and immunogenic at the end of shelf life.

Vesikari T, Clark HF, Offit PA, Dallas MJ, DiStefano DJ, Goveia MG, Ward RL, Schodel F, Karvonen A, Drummond JE, DiNubile MJ, Heaton PM. Effects of the potency and composition of the multivalent human-bovine (WC3) reassortant rotavirus vaccine on efficacy, safety and immunogenicity in healthy infants. Vaccine. 2006 May 29;24(22):4821-9.

BACKGROUND: Rotavirus gastroenteritis, which causes substantial infant mortality and morbidity worldwide, is a vaccine-preventable disease. The purpose of this study was to evaluate different compositions and potencies (vaccine virus titers) of a live multivalent human-bovine (WC3) reassortant rotavirus vaccine in order to select the potency and composition of the vaccine for further development. METHODS: The efficacy, safety, and immunogenicity of a G1, G2, G3, G4, and P1A pentavalent composition at three different potencies, a G1, G2, G3, G4 quadrivalent composition, and a P1A monovalent composition of an oral human-bovine (WC3) reassortant rotavirus vaccine were compared in a blinded, placebo-controlled trial conducted between 1998 and 2001 enrolling 1,946 healthy Finnish infants 2-8 months of age. RESULTS: All potencies of the pentavalent and quadrivalent vaccines were efficacious (58-74%) against wild-type rotavirus gastroenteritis of any severity and 100% protective against severe rotavirus disease caused by vaccine G-serotypes through the first rotavirus season post-vaccination. The monovalent P1A vaccine was 53% efficacious against moderate-and-severe rotavirus gastroenteritis. Protection against rotavirus gastroenteritis of any severity was demonstrated through two and three rotavirus seasons for all vaccine compositions. After the third dose, the percentage of infants with $>$ or $=$ 3-fold rise in baseline serum neutralizing antibody titers against G1 ranged from 62% to 86% for recipients of the pentavalent vaccine, depending on the potency. The incidence of fever, irritability, vomiting, and diarrhea did not significantly differ between vaccine and placebo groups. A 7-month-old male developed intussusception 9 days after the first dose of the low-potency pentavalent vaccine. CONCLUSIONS: Based on the results of this trial, a pentavalent composition (G1, G2, G3, G4, and P1A) of human-bovine (WC3) reassortant rotavirus vaccine with a potency similar to that of the middle-potency pentavalent vaccine (approximately 8×10^6 plaque-forming units/dose) was selected for further development.

Vesikari T, Matson DO, Dennehy P, Van Damme P, Santosham M, Rodriguez Z, Dallas MJ, Heyse JF, Goveia MG, Black SB, Shinefield HR, Christie CD, Ylitalo S, Itzler RF, Coia ML, Onorato MT, Adeyi BA, Marshall GS, Gothefors L, Campens D, Karvonen A, Watt JP, O'Brien KL, DiNubile MJ, Clark HF, Boslego JW, Offit PA, Heaton PM; Rotavirus Efficacy and Safety Trial (REST) Study Team. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. N Engl J Med. 2006 Jan 5;354(1):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.

Ruiz-Palacios GM, Perez-Schael I, Velazquez FR, Abate H, Breuer T, Clemens SC, Chevart B, Espinoza F, Gillard P, Innis BL, Cervantes Y, Linhares AC, Lopez P, Macias-Parra M, Ortega-Barria E, Richardson V, Rivera-Medina DM, Rivera L, Salinas B, Pavia-Ruz N, Salmeron J, Ruttimann R, Tinoco JC, Rubio P, Nunez E, Guerrero ML, Yarzabal JP, Damaso S, Tornieporth N, Saez-Llorens X, Vergara RF, Vesikari T, Bouckennooghe A, Clemens R, De Vos B, O'Ryan M; Human Rotavirus Vaccine Study Group. 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.

Salinas B, Perez Schael I, Linhares AC, Ruiz Palacios GM, Guerrero ML, Yarzabal JP, 3 Cervantes Y, Costa Clemens S, Damaso S, Hardt K, De Vos B. Evaluation of safety, immunogenicity and efficacy of an attenuated rotavirus vaccine, RIX4414: A randomized, placebo-controlled trial in Latin American infants. *Pediatr Infect Dis J.* 2005 Sep;24(9):807-16.

BACKGROUND: A live attenuated monovalent rotavirus vaccine RIX4414 was developed with a human strain of G1P1A P[8] specificity to reduce the rotavirus burden in children. **METHODS:** A double blind, randomized, placebo-controlled study evaluated the efficacy, immunogenicity, safety and reactogenicity of 2 oral doses of RIX4414 (10(4.7), 10(5.2) or 10(5.8) focus-forming units) at 2 and 4 months coadministered with routine vaccinations and oral poliovirus vaccine given for study purposes at least 14 days apart. The 2155 infants (1618 vaccine/537 placebo) enrolled in Brazil, Mexico and Venezuela were followed until 1 year of age. **RESULTS:** Antirotavirus IgA seroconversion rates 2 months after dose 2 ranged between 61% (10(4.7) ffu group) and 65% (10(5.8) ffu group), and most of the infants had seroprotective levels of antibodies to coadministered routine vaccinations. The reactogenicity profile of RIX4414 was similar to that of the placebo, and no vaccination-related serious adverse events were reported. Protective efficacy against severe and any rotavirus gastroenteritis from 15 days post-dose 2 was highest in the 10(5.8) ffu group [86%; 95% confidence interval (95% CI), 63-96% and 70% (95% CI 46-84%), $P < 0.001$, 2-sided Fisher's exact test]. The efficacy against hospitalization was 79% (95% CI 48-92%) for pooled vaccine groups. Multiple rotavirus serotypes [G1 (50%), G9 (40%), G2, G3 and G4] were identified from gastroenteritis stools (enzyme-linked immunosorbent assay and reverse transcription-polymerase chain reaction) during the study period. For severe gastroenteritis caused by G9 serotypes, the protection reached 77% (95% CI 18-96%) in the 10(5.8) ffu group, providing proof of concept that the monovalent G1P1A P[8] human rotavirus vaccine elicits cross-protection against the G9 strain. A reduction in any and severe rotavirus gastroenteritis was already observed at post-dose 1 (period: day of dose 1 to 14 days post-dose 2) in vaccinees compared with placebo recipients. **CONCLUSIONS:** Two doses of RIX4414 are highly efficacious, providing cross-protection (G1 and G9 strains, prevalent during this study) and early protection against any and severe rotavirus gastroenteritis and hospitalization to infants in Latin America.

Phua KB, Quak SH, Lee BW, Emmanuel SC, Goh P, Han HH, De Vos B, Bock HL. Evaluation of RIX4414, a live, attenuated rotavirus vaccine, in a randomized, double-blind, placebo-controlled phase 2 trial involving 2464 Singaporean infants. *J Infect Dis.* 2005 Sep 1;192 Suppl 1:S6-S16.

BACKGROUND: At present, no rotavirus vaccine is commercially available for use worldwide. Hence, a live, attenuated monovalent vaccine was developed with human strain RIX4414 (G1P1A P[8] specificity). Vaccination trials involving infants are ongoing in developed and developing countries. **METHODS:** This study was a randomized, double-blind, placebo-controlled trial conducted at pediatric hospitals and polyclinics in Singapore for the evaluation of the immunogenicity, reactogenicity, and efficacy of 2 oral doses of RIX4414. In total, 2464 healthy infants (who were 11-17 weeks old when the first dose was administered, which is in accordance with the local immunization schedule) were enrolled to receive RIX4414 at 3 concentrations of virus (10(4.7), 10(5.2), or 10(6.1) focus-forming units) or placebo at 1-month intervals, concomitantly with routinely administered infant vaccines. **RESULTS:** The RIX4414 vaccine was highly immunogenic, and virtually all vaccine recipients (98%-100%) experienced "vaccine take" (i.e., a combined immunogenicity end point based on seroconversion and/or shedding of RIX4414 in postvaccination stool samples) after receipt of 2 doses at all 3 dosage levels. Depending on the virus concentration, the anti-rotavirus IgA seroconversion rate varied from 76% (95% confidence interval [CI], 68%-83%) to 91% (95% CI, 85%-95%). Two doses of RIX4414 were well tolerated, with no increase in high fever, severe diarrhea, or vomiting after either dose or with increased viral concentration, compared with placebo. There was no

observed interference with routine vaccinations of infants when RIX4414 was coadministered. The calculated efficacy of RIX4414 against rotavirus gastroenteritis was 82% (P = .046); however, this result was considered to be of limited conclusive value because of the low number of rotavirus gastroenteritis episodes identified during the follow-up period. **CONCLUSIONS:** The live, attenuated rotavirus vaccine (RIX4414) was well tolerated and highly immunogenic in Singaporean infants. The immunogenicity of routinely administered infant vaccines was not impaired by concomitant administration of RIX4414 vaccine.

Ward RL, Bernstein DI, Smith VE, Sander DS, Shaw A, Eiden JJ, Heaton P, Offit PA, Clark HF. Rotavirus immunoglobulin a responses stimulated by each of 3 doses of a quadrivalent human/bovine reassortant rotavirus vaccine. J Infect Dis. 2004 Jun 15;189(12):2290-3.

A quadrivalent precursor to the pentavalent rotavirus vaccine candidate RotaTeq was evaluated in a 3-dose, 439-subject study. To determine immunogenicity, the quantity of rotavirus immunoglobulin A (IgA) in stool specimens obtained, at 1 of 10 study sites, from 37 placebo and 37 vaccine recipients was measured. None of the placebo recipients showed a clinically important (≥ 3 -fold) increase in stool rotavirus IgA, whereas 31 vaccine recipients showed an increase after at least 1 dose of vaccine. In total, 16, 19, and 15 vaccine recipients had increases after 1, 2, and 3 doses, respectively, indicating that a 3-dose regimen increased the immune response elicited by this vaccine.

Vaccine schedule

Parashar UD, Alexander JP, Glass RI; Advisory Committee on Immunization Practices (ACIP), Centers for Disease Control and Prevention (CDC). Prevention of rotavirus gastroenteritis among infants and children. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2006 Aug 11;55(RR-12):1-13.

In February 2006, a live, oral, human-bovine reassortant rotavirus vaccine (RotaTeq) was licensed for use among U.S. infants. The Advisory Committee on Immunization Practices recommends routine vaccination of U.S. infants with 3 doses of this rotavirus vaccine administered orally at ages 2, 4, and 6 months. The first dose should be administered between ages 6-12 weeks. Subsequent doses should be administered at 4-10 week intervals, and all 3 doses should be administered by age 32 weeks. Rotavirus vaccine can be co-administered with other childhood vaccines. Rotavirus vaccine is contraindicated for infants with a serious allergic reaction to any vaccine component or to a previous dose of vaccine.

Cost effectiveness analyses

Podewils LJ, Antil L, Hummelman E, Bresee J, Parashar UD, Rheingans R. Projected cost-effectiveness of rotavirus vaccination for children in Asia. J Infect Dis. 2005 Sep 1;192 Suppl 1:S133-45.

BACKGROUND: New rotavirus vaccines may soon be licensed, and decisions regarding implementation of their use will likely be based on the health and economic benefits of vaccination. **METHODS:** We estimated the benefits and cost-effectiveness of rotavirus vaccination in Asia by using published estimates of rotavirus disease incidence, health care

expenditures, vaccine coverage rates, and vaccine efficacy. **RESULTS:** Without a rotavirus vaccination program, it is estimated that 171,000 Asian children will die of rotavirus diarrhea, 1.9 million will be hospitalized, and 13.5 million will require an outpatient visit by the time the Asian birth cohort reaches 5 years of age. The medical costs associated with these events are approximately 191 million US dollars; however, the total burden would be higher with the inclusion of such societal costs as lost productivity. A universal rotavirus vaccination program could avert approximately 109,000 deaths, 1.4 million hospitalizations, and 7.7 million outpatient visits among these children. **CONCLUSIONS:** A rotavirus vaccine could be cost-effective, depending on the income level of the country, the price of the vaccine, and the cost-effectiveness standard that is used. Decisions regarding implementation of vaccine use should be based not only on whether the intervention provides a cost savings but, also, on the value of preventing rotavirus disease-associated morbidity and mortality, particularly in countries with a low income level (according to 2004 World Bank criteria for the classification of countries into income groups on the basis of per capita gross national income) where the disease burden is great.

Lee BP, Azimi PH, Staat MA, Louie L, Parada E, Berke T, Ward RL, Bernstein DI, Matson DO. Non-medical costs associated with rotavirus disease requiring hospitalization. *Pediatr Infect Dis J.* 2005 Nov;24(11):984-8

BACKGROUND: As the most common cause of severe diarrhea among children, rotavirus has a significant economic impact. Previous studies focused on the direct medical costs of rotavirus infections; however, nonmedical costs account for the majority of the financial burden from this disease. Herein, we report the results from the largest prospective study in the United States determining the nonmedical costs of severe rotavirus infections.

METHODS: Prospective, active, gastroenteritis case surveillance was conducted between November 1997 and December 1999 at 3 pediatric medical centers. Rotavirus infection was identified for 548 children admitted between 2 weeks and 5 years of age. Detailed information about nonmedical costs during the prehospitalization, hospitalization and posthospitalization periods was obtained through interviews. **RESULTS:** The average nonmedical cost per case of rotavirus disease was USD \$448.77, including \$359.04 for missed work, \$56.66 for transportation, \$11.90 for oral rehydration solutions, \$9.59 for diapers, \$6.83 for child care changes, \$3.82 for special foods and \$0.93 for formula changes. More than one-half of these expenses (53%) occurred outside the hospitalization period, and 80% of the cost was attributable to missed work. **CONCLUSIONS:** With an estimated 50,000 hospitalizations attributable to rotavirus each year in the United States, the nonmedical costs of severe rotavirus infections may exceed USD \$22 million annually. Previous cost effectiveness analyses of rotavirus vaccines substantially underestimated this burden, suggesting that the nonmedical costs associated with mild to moderate rotavirus disease have been similarly underestimated. These findings are needed to assess accurately the cost effectiveness of future rotavirus immunization strategies.

Rheingans RD, Heylen J, Giaquinto C. Economics of rotavirus gastroenteritis and vaccination in Europe: what makes sense? *Pediatr Infect Dis J.* 2006 Jan;25(1 Suppl):S48-55

Rotavirus is a major cause of gastroenteritis in children throughout Europe and the world. In addition to causing morbidity and mortality in children, rotavirus gastroenteritis (RVGE) creates a major economic burden on health care systems and families in Europe. The costs of hospital admissions for RVGE and nosocomial infections generate significant medical treatment costs throughout the region. Less information is available on the costs associated with less severe episodes and the costs borne by families, including lost time from work.

The availability of rotavirus vaccines presents an effective opportunity to prevent RVGE and these associated economic costs, as well as providing protection to each child and hence benefiting the child's family. The adoption of rotavirus vaccine by health authorities in Europe will require a comparison of the costs and benefits. Economic evaluations that compare the costs of vaccination to the economic benefits of rotavirus vaccination will provide an estimate of its financial impact on health care systems and society. However, to provide a complete picture, economic evaluations of rotavirus vaccines will need to account for both the reduced costs and the reduced morbidity from prevented RVGE. Cost-effectiveness analyses based on quality-adjusted life years (QALYs) provide a systematic approach for assessing vaccination as a health investment, comparing the incremental costs associated with rotavirus vaccination and the reduced morbidity and mortality. QALYs provide a standardized approach for quantifying and comparing reductions in health-related quality of life and premature mortality. Although methodologic limitations exist in applying the QALY approach to childhood vaccines, their use in cost effectiveness analyses allows decision makers to consider the full health benefits of rotavirus and other vaccines.

Miller MA, McCann L. Policy analysis of the use of hepatitis B, Haemophilus influenzae type b-, Streptococcus pneumoniae-conjugate and rotavirus vaccines in national immunization schedules. Health Econ. 2000 Jan;9(1):19-35

After the development of national vaccine programmes to deliver six vaccines to infants, new vaccine adoption has been limited. Analysis of the health and economic implications of new vaccination options can help national policy-makers. Country specific quantitative policy analyses were conducted to estimate the impact of vaccination against hepatitis B (HB), Haemophilus influenzae type b (Hib), Streptococcus pneumoniae (SP) and rotavirus. Disease burden, programme costs and the potential reduction of disease from vaccination was assessed for each vaccine. Without vaccination, these four vaccine preventable diseases contribute up to 4.1 million deaths in each successive birth cohort. Routine scheduled use of HB and Hib vaccines could prevent up to 1.7 million deaths; SP and rotavirus vaccines, an additional 1.4 million deaths, annually. The global cost per life-year saved ranged from \$29 to \$150 with great variation by income and economic groups. With a few exceptions for a few countries, these vaccines would cost a fraction of average per-capita gross domestic product to save a life-year. The addition of HB and Hib vaccines, should be considered for integration in all national immunization programmes. SP and rotavirus vaccines, with the given assumptions, would also be cost-effective. Proactive analysis of the economic and epidemiologic impact of these vaccines can hasten their introduction into national vaccination schedules.

Other WHO documents

**GACVS fall 2006 (WER Jan 2007)
Global Advisory Committee on Vaccine Safety
15 February 2007**

Statement on RotaTeq® vaccine and intussusception

WHO and the Global Advisory Committee on Vaccine Safety (GACVS)¹ have taken note of the United States Food and Drug Administration (FDA) Public Health Notification to health-care providers and consumers about reports of intussusception following the use of RotaTeq® vaccine (Rotavirus, Live, Oral, Pentavalent vaccine manufactured by Merck and Co., Inc.) in the United States of America. The reported cases were detected through routine monitoring of RotaTeq® vaccine by the United States Vaccine Adverse Event

Reporting System (VAERS). It should be noted that the number of intussusception cases reported to date after RotaTeq® administration does not exceed the number of cases expected based on background rates in the United States infant population, and therefore does not suggest an increased risk of intussusception with RotaTeq®. However, continued monitoring is warranted.

GACVS has previously concluded that clinical trial data and preliminary data from adverse event reports in the post-marketing phase, from the United States of America and elsewhere, did not show an increased risk for intussusception following RotaTeq®; the current information from the United States of America does not change the previous GACVS conclusions. The Committee is in agreement with the steps taken by the FDA and the United States Centers for Disease Control and Prevention (CDC) to remind health-care providers and consumers to maintain a high level of attention to the diagnosis and reporting of intussusception in order to appropriately investigate their potential association with rotavirus vaccination. WHO and the GACVS will continue to review the data for cases of intussusception reported in the United States of America by the CDC and FDA as well as reports from other countries which have introduced rotavirus vaccine.

Ward RL and Bernstein DI: The immunological basis for Immunization Series. Module X: Rotavirus. Update 2007. Draft spring of 2007, WHO Geneva.

Acute intussusception in infants and children; incidence, clinical presentation and management: a global perspective. WHO/V&B/02.19

WWW.who.int/vaccines-duments/DocsPDF02/www640.pdf