



**ROTAVIRUS**  
*Multiple Serotypes and the  
Argument for Rotavirus Vaccination*

Artist's rendering of rotavirus particles. For illustration purposes only.

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## ***Introduction/Executive Summary***

In December 2007, a roundtable of infectious disease experts convened in New York City to discuss the latest scientific information on the epidemiology, classification, prevention, and treatment of rotavirus. Rotavirus is a leading cause of acute gastroenteritis in infants and young children worldwide, infecting nearly all children by the age of 5. Prevalent in both developed and developing countries, rotavirus is responsible for substantial morbidity and mortality and represents a substantial economic burden.

Studies show that gastroenteritis caused by rotavirus can be more severe than that caused by other pathogens. Additionally, the rates of rotavirus infection have not responded well to improvements in water supply, sanitation, or hygiene that have effectively reduced bacterial and parasitic diarrhea. For these reasons, development of rotavirus vaccines that are effective has long been a high priority. Recently, both a live, orally administered human-bovine pentavalent reassortant vaccine and a live, orally administered attenuated monovalent human vaccine have been licensed in many countries in the world. The introduction of these vaccines adds momentum to ongoing efforts to understand rotavirus and to reduce the impact of rotavirus worldwide.

Roundtable participants highlighted the efficacy and safety profile of the vaccines, as demonstrated from the results of large clinical trials, and discussed current research aimed at elucidating the heterogeneity and prevalence of circulating rotavirus strains. The participants were in agreement that this is an important moment in the fight against rotavirus and expressed the belief that routine vaccination of infants should significantly reduce the enormous health burden of rotavirus diarrhea.

<p>At the time of this roundtable meeting in December 2007, RotaTeq<sup>®</sup> was the only rotavirus vaccine licensed in the U.S. Rotarix was approved in the U.S. in April 2008. Information in this manuscript for both vaccines was subsequently reviewed by all participants.</p>
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## Addressing the Challenge of Rotavirus

Rotavirus is a leading cause of acute gastroenteritis in infants and young children worldwide, infecting nearly all children by the age of 5, often more than once. [Matson 2003] Each year rotavirus causes approximately 111 million episodes of gastroenteritis, 25 million outpatient visits, and 2 million hospitalizations in children under age 5 worldwide (about one-third of all hospitalizations for gastroenteritis). [Parashar 2003; Parashar 2006]

### Number (range) of Episodes of Rotavirus Disease (x 1,000)

Setting	Developing countries	Industrialized countries	Total
Home	104,280 (51,496–157,063)	7,122 (2,123–17,881)	111,402 (53,619–174,946)
Outpatient	23,233 (18,537–27,188)	1,781 (708–3,576)	25,017 (19,245–30,764)
Inpatient	1,920 (1,551–2,596)	223 (142–358)	2,143 (1,693–2,954)

(Table 1) Annual Global Illness Incidence From Rotavirus Diarrhea Among Children <5 Years Age, By Setting [Adapted from Parashar 2003]

Importantly, more than 600,000 deaths occur per year worldwide. [Parashar 2006] The majority of these deaths occur in developing countries, and mortality is particularly high in South Asia and sub-Saharan Africa. [Parashar 2006] In industrialized countries, fatal outcomes are relatively rare; however, rotavirus infection can cause serious morbidity and represents a severe burden in terms of resource use, with estimates of approximately \$1 billion U.S. dollars per year (calculated using 2006 dollars) in direct and indirect costs, including lost work time for parents, in the United States alone. [Widdowson, 2006]

*In high-income countries, fatal outcomes are relatively rare; however, rotavirus infection can cause serious morbidity and represents a severe burden in terms of resource use worldwide.*

In the United States, an estimated 55,000-70,000 hospitalizations, more than 200,000 emergency room visits, approximately 400,000 outpatient physician visits, and approximately 20-60 deaths from rotavirus disease occur each year among children under age 5 years. [Parashar 2006] In the European Union, rotavirus leads to more than 87,000 hospitalizations and approximately 700,000 outpatient visits annually. [Soriano-Gabarró 2006] Indirect costs, which include loss of workdays for parents, may exceed direct medical costs. [Widdowson]

It is noteworthy that the incidence of rotavirus illness is comparable in developed and developing countries. [de Zoysa 1985] Rates of rotavirus infection have not decreased despite improvements in water supply, sanitation, or hygiene that have effectively reduced bacterial and parasitic diarrhea. [de Zoysa 1985; Parashar 2006] Moreover, gastroenteritis caused by rotavirus can be more severe than that caused by other pathogens. In a recent European study, rotavirus-positive gastroenteritis was associated with higher frequencies of dehydration, vomiting, fever, and signs of lethargy, and a greater estimated rate of hospitalization than rotavirus-negative diarrhea. [Giaquinto 2007 (S26-S35)]

*The incidence of rotavirus illness is comparable in developed and developing countries. [de Zoysa 1985]*

Given the prevalence and potential serious consequences of rotavirus infection, vaccination is expected to play a critical role in reducing the tremendous burden of disease. Accordingly, routine immunization of U.S. infants is recommended by the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics (AAP). [CDC 2006; AAP 2007; CDC 2008] Similarly, the European Society for Paediatric Infectious Disease (ESPID) and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommend rotavirus vaccination of infants in Europe. [Vesikari 2008] The World Health Organization (WHO) supports vaccination in countries where efficacy data suggest a benefit, and where necessary infrastructure and financing are available. WHO recommends inclusion of rotavirus vaccines into national immunization programs in regions where clinical data support their use. [World Health 2007; World Health Organization 2008] Large trials that were conducted primarily in Western industrialized countries and Latin America showed safety, immunogenicity, and efficacy resulting in recent licensure of two rotavirus vaccines in many countries.

## ***Rotavirus: Clinical and Epidemiologic Features***

Most severe cases of rotavirus occur among children 6 to 24 months of age. Rotavirus diarrhea can have a variable course, ranging from asymptomatic to severe. The classic presentation is fever, vomiting and watery diarrhea. [Rodriguez 1977; Staat 2002] In severe cases, repeated episodes of diarrhea or vomiting can lead to loss of fluid and electrolytes, placing the child at risk for severe dehydration. One hospital-based study enrolling 862 infants and children evaluated the clinical spectrum of rotavirus infections resulting in hospitalizations and short stay visits. Among children who presented with vomiting, diarrhea and fever, rotavirus was identified more frequently in children 6 months of age or older compared with those less than 6 months of age. [Staat 2002]

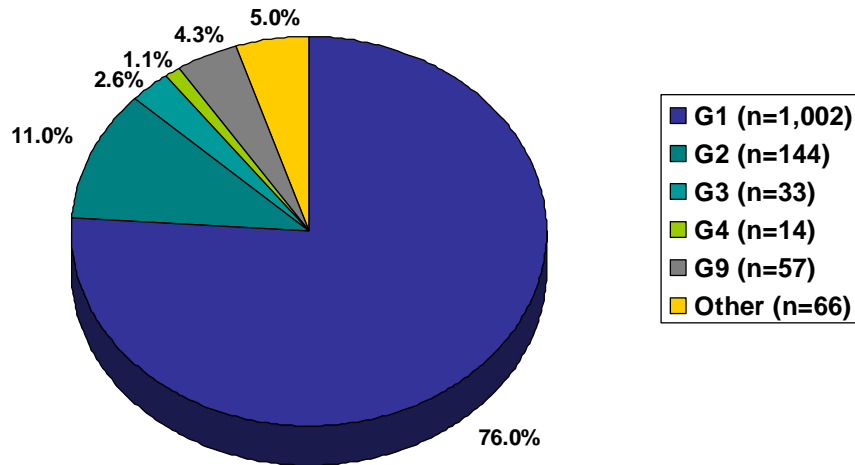
Rotavirus is highly contagious, and is transmitted from person to person via the fecal-oral route. There is some evidence that the virus may also spread through respiratory droplets, which could complicate infection control. The incubation period is approximately two days, and rotavirus diarrhea episodes can last from three to eight days. In tropical countries, transmission occurs year-round, whereas in countries with a temperate climate, rotavirus exhibits a marked seasonality, with annual winter epidemics. [Matson 2003]

Diagnosis of rotavirus infection is typically made by testing stool specimens for rotavirus antigen. In some studies, infection has been detected only by the presence of rotavirus antibodies in the blood. [Blutt 2007; Velazquez 1996] Additionally, one study demonstrated cases in which fecal excretion of virus was found, but there was no serologic response. [Velazquez 1996] These findings raise the possibility that the incidence of rotavirus diarrhea may be underestimated.

## Virology

Rotaviruses are small (100-nm) icosahedral viruses that encode 11 segments of double-stranded RNA. [Estes and Kapikian 2007] They are classified into multiple serotypes based on two structural viral proteins on the outer layer: VP7, the glycoprotein or G protein, and VP4, the protease-cleaved or P protein. In humans, four common G-P combinations (G1, G3, and G4 with P[8] and G2 with P[4]) are of principal epidemiologic importance. These four strains are responsible for approximately 88 percent of rotavirus infections worldwide, [Santos 2005] although their relative proportions may vary by year and region. [Matson 1990] An analysis of rotavirus G serotypes identified during three rotavirus seasons in the United States (1996-1999) showed that the predominant serotype was G1 (76 percent), followed by G2 (11 percent).

### Rotavirus Serotypes Identified in the U.S. (n=1,316)



**(Figure 1)** Rotavirus G Serotypes Identified During Three Rotavirus Seasons in the United States From 1996 to 1999 [Adapted from Griffin 2000]

Other globally or regionally common strains have been described, including serotypes G5, G6, G8, and G9. Serotype G9 (often in conjunction with P[6] or P[8]) has become prevalent in many geographic regions. First described in the United States and Japan in the 1980s, it has subsequently been found globally. Studies have shown that it is now established as a fifth globally important G serotype. [Cunliffe 2001; Santos 2005; Van Damme 2007 (S17-S25)] Because different serotypes can circulate simultaneously in a given region and vary from year to year, it is difficult to predict the serotype to which an individual may be exposed.

## Treatment and Prevention of Rotavirus

Whereas antimicrobial therapies are effective against some bacterial and parasitic agents, there is no specific treatment for rotavirus infection. Oral rehydration therapy is essential to prevent loss of fluids. Such therapy may be difficult to administer in children with vomiting, a frequent manifestation of rotavirus diarrhea. In serious cases, children may require hospitalization for intravenous fluids.

*Because different serotypes can circulate simultaneously in a given region and vary from year to year, it is difficult to predict the serotype to which an individual may be exposed.*

As already noted, sanitation and water treatment measures do not appear to be effective in significantly reducing rotavirus diarrhea. Studies have found, however, that natural immunity develops after exposure to the virus. A widely cited study by Velazquez et al. (1996) of 200 children in Mexico attempted to quantify the level of protection conferred by natural rotavirus infection against subsequent infection and rotavirus diarrhea and to determine the serotypes causing a first and second infection. [Velazquez 1996]

*Sanitation and water treatment measures do not appear to be effective in significantly reducing rotavirus diarrhea.*

The Velazquez study found that natural infection, both asymptomatic and symptomatic, is associated with protection against rotavirus diarrhea of any severity, but that protection was greatest against moderate-to-severe disease. The first infection was likely to be the most severe; however, protection increased with each new infection and a high level of protection from all severity of rotavirus diarrhea was achieved after three infections. In a subset of infants, a second infection with the same G type was less likely to occur, suggesting that immunity after a first infection is serotype-specific. [Velazquez 1996]

		Second Infection				Total
		G1	G2	G3	G4	
First Infection	G1	1	4	4	0	9
	G2	0	0	1	1	2
	G3	2	7	1	1	11
	G4	0	0	0	0	0
Total		3	11	6	2	22

*The boxes indicating a shared G type are shaded.*

**(Table 2)** Distribution of Rotavirus G Types Identified in Fecal Specimens Obtained During the First and Second Infections in 22 Children [Adapted from Velazquez 1996]

*The first infection is likely to cause the most severe disease. In one study, a second infection with the same G type was less likely to occur, suggesting that immunity after a first infection may be serotype-specific.*

Findings from this and other studies have indicated that the first infection stimulates a predominantly serotype-specific (homotypic) response, while subsequent infections elicit broader, heterotypic protection. [Jiang 2002]

The high incidence of rotavirus gastroenteritis during the first years of life, coupled with the significant health and economic burden, underscore the importance of rotavirus vaccination to help protect infants and children against this potentially serious, but preventable disease.

This observation that immunity to rotavirus develops after natural infection provided a starting

point for the development of vaccine candidates. Vaccines, based on human strains and human-animal reassortants containing the common serotype antigens of human strains, have been developed. The first vaccine, a tetravalent, human-rhesus reassortant vaccine (RRV-TV; RotaShield<sup>®</sup>, Wyeth Laboratories) was introduced in 1998 in the United States, but was voluntarily withdrawn from the market after concerns about an association with intussusception. Two live, orally administered rotavirus vaccines have recently been licensed in many countries. The pentavalent<sup>1</sup> human-bovine reassortant vaccine expressing human serotypes G1, G2, G3, G4 and P[8] (PRV or RV5; RotaTeq<sup>®</sup> (rotavirus vaccine, live, oral pentavalent),<sup>2</sup> Merck) is licensed in 85 countries as of May 9, 2008. As of April 3, 2008, the monovalent live attenuated human (RIX4414) rotavirus vaccine containing serotype G1P[8] (HRV or RV1; Rotarix<sup>®</sup> (rotavirus vaccine, live, oral)<sup>3</sup> GlaxoSmith Kline) is licensed in more than 100 countries. These vaccines have been approved by the U.S. FDA for prevention of rotavirus gastroenteritis; RotaTeq on February 3, 2006 and Rotarix on April 3, 2008.

RotaTeq is indicated in the United States for the prevention of rotavirus gastroenteritis in infants and children caused by the serotypes G1, G2, G3, and G4 when administered as a three-dose series to infants between the ages of 6 to 32 weeks. RotaTeq should not be administered to infants with a demonstrated history of hypersensitivity to any component of the vaccine.

Rotarix is indicated in the United States for the prevention of rotavirus gastroenteritis caused by G1 and non-G1 types (G3, G4, and G9) when administered as a two-dose series in infants and children. Rotarix should not be administered to infants with a history of uncorrected congenital malfunction of the gastrointestinal tract that would predispose to intussusception.

<sup>1</sup> RotaTeq is a live, oral pentavalent vaccine that contains five live reassortant rotaviruses. [RotaTeq Prescribing Information]

<sup>2</sup> Please see page 22 for select safety information for RotaTeq. For full Prescribing Information, please visit [www.Rotateq.com](http://www.Rotateq.com).

<sup>3</sup> Note – Some data on Rotarix, which was approved in the U.S. after the roundtable discussion, were obtained from the vaccine's U.S. Prescribing Information. For full Prescribing Information for Rotarix, please visit [http://us.gsk.com/products/assets/us\\_rotarix.pdf](http://us.gsk.com/products/assets/us_rotarix.pdf).

The exact immunologic mechanism by which the current rotavirus vaccines protect against rotavirus gastroenteritis is unknown. According to one view, serotype-specific immunity is important to achieving a high level of protection. This led to the development and evaluation of multivalent vaccines. The second view is that a single rotavirus infection of any serotype will induce protection against other rotavirus serotypes. This led to the development and evaluation of a monovalent vaccine. [Ward 2004]

*The high incidence of rotavirus gastroenteritis during the first years of life, coupled with the significant health and economic burden, underscore the importance of rotavirus vaccination to help protect infants and children against this potentially serious but preventable disease.*

## ***The Safety and Efficacy of Rotavirus Vaccination***

Recent trials indicate that the rotavirus vaccines helped protect against rotavirus diarrhea to a degree comparable to the protection induced by natural infection. Both vaccines are more efficacious against severe than mild disease, and both reduced hospitalizations.

Given the prior association between RotaShield and intussusception, both RotaTeq and Rotarix were closely evaluated for intussusception in Phase III clinical trials. No increased risk was identified between vaccine and placebo. [Murphy 2001] There are no head-to-head

clinical trials comparing the two rotavirus vaccines.

### ***Efficacy data for RotaTeq (rotavirus vaccine, live, oral pentavalent)***

The Rotavirus Efficacy and Safety Trial (REST) for RotaTeq was a large-scale, double-blind, placebo-controlled clinical trial conducted in 11 countries. Healthy infants 6- to 12-weeks old were randomly assigned to receive three oral doses of pentavalent rotavirus vaccine (PRV) or placebo, four to 10 weeks apart (n=69,274). [Vesikari 2006] Safety and clinical efficacy were assessed, as was the need for hospitalization or emergency care. Data from a subset of infants (n=5,673) from the United States and Finland in the clinical efficacy substudy indicate that the pentavalent vaccine provided protection (74 percent; 95 percent CI 66.8; 79.9) against rotavirus gastroenteritis of any severity caused by serotypes G1, G2, G3, or G4 through the first rotavirus season post-vaccination. Data from the substudy also indicate that the pentavalent vaccine was highly efficacious (98 percent; 95 percent CI 88.3; 100) against severe rotavirus disease caused by these same serotypes through the first rotavirus season post-vaccination. In addition, among all infants enrolled in REST, hospitalizations for G1, G2, G3, and G4 rotavirus gastroenteritis were reduced by 96 percent (95 percent CI 90.5; 98.2) and emergency department visits for G1, G2, G3, and G4 rotavirus gastroenteritis were reduced by 94 percent (95 percent CI 88.8; 96.5) through two years following the third dose. [Vesikari 2006]

Serotype	Number of Rotavirus Gastroenteritis Cases		Percent Rate Reduction (95% CI)
	Pentavalent Rotavirus Vaccine Group (N = 34,035)	Placebo Group (N = 34,003)	
<b>G1</b>	16	328	<b>95</b> <b>(91;97)</b>
<b>G2</b>	1	8	<b>88</b> <b>(&lt;0;99)</b>
<b>G3</b>	1	15	<b>93</b> <b>(49;99)</b>
<b>G4</b>	2	18	<b>89</b> <b>(52;98)</b>
<b>G9</b>	0	13	<b>100</b> <b>(67;100)</b>

*The number of subjects in each group is the number who received at least one dose. Some subjects had more than one event.*

**(Table 3)** Reduction in the Numbers of Hospitalizations and Emergency Department Visits in the Per-Protocol Population of the Large Scale Study, According to G Serotype Identified in the Subject's Stool [Adapted from Vesikari 2006]

An additional post-hoc analysis showed that efficacy as demonstrated by the reduction in hospitalization and emergency department visits due to G9P[8] rotavirus gastroenteritis was 100 percent (95 percent CI: 69.6; 100).

A post-hoc analysis of healthy premature infants between 25 and 36 gestational weeks demonstrated a 100 percent reduction (95 percent CI 74; 100) in hospitalizations and ED visits due to G1, G2, G3, G4 rotavirus gastroenteritis for up to two years among 1,581 evaluable infants. Vaccine efficacy was 70.3 percent (95 percent CI -15.4; 94.7) against rotavirus cases of any severity through the first full rotavirus season (n=153, of which 75 were vaccine recipients), although this percentage was not statistically significant. Healthy premature infants appear to

be at higher risk of hospitalization from rotavirus gastroenteritis than term infants. [Goveia 2007]

**Efficacy data for Rotarix (rotavirus vaccine, live, oral)**

A recently published double-blind, placebo-controlled, randomized trial in six European countries assigned healthy infants (n= 3,994) aged 6 to 14 weeks to either two oral doses of human rotavirus vaccine (HRV) or placebo. [Vesikari 2007] Vaccine efficacy against rotavirus gastroenteritis of any severity during the first efficacy follow-up period (from two weeks post-dose two, to the end of the first rotavirus season) was shown to be 87.1 percent (95 percent CI 79.6; 92.1) (n=3874). Efficacy through the end of the second rotavirus season was 78.9 percent (95 percent CI 72.7; 83.8) against any severity and 90.4 percent (95 percent CI 85.1; 94.1) against severe rotavirus gastroenteritis. Hospitalizations due to rotavirus gastroenteritis were reduced by 100 percent (95 percent CI 81.8; 100) through the first season and 96 percent through the second season (95 percent CI 83.8, 99.5). Type-specific vaccine efficacy against severe rotavirus gastroenteritis through two seasons is shown in Table 4.

Serotype	Number of Rotavirus Gastroenteritis Cases		Percent Rate Vaccine Efficacy (95% CI)
	HRV Group (N = 2,572)	Placebo Group (N = 1,302)	
<b>G1</b>	4	57	<b>96 (90;99)</b>
<b>G2</b>	2	7	<b>86 (24;99)</b>
<b>G3</b>	1	8	<b>94 (53;100)</b>
<b>G4</b>	1	11	<b>95 (68;100)</b>
<b>G9</b>	13	44	<b>85 (72;93)</b>

**(Table 4)** Serotype-specific Efficacy of HRV Against Severe Rotavirus Disease in Europe Through the Second Rotavirus Season [Adapted from Vesikari 2007]

A large randomized, double-blind phase III study of HRV was conducted in 11 Latin American countries and Finland involving 63,225 infants receiving vaccinations at approximately two and

four months of age. A subgroup of 20,169 infants from Latin America (10,159 vaccine and 10,010 placebo recipients) were evaluated for the prevention of severe rotavirus gastroenteritis from two weeks after the second dose until one year of age (the primary efficacy endpoint). [Ruiz-Palacios 2006] Vaccine efficacy in this study was 85 percent (95 percent CI 72; 92) against severe disease. Efficacy against gastroenteritis associated with specific circulating rotavirus types is shown in Table 5. Reduction in hospitalizations due to rotavirus gastroenteritis was 85 percent (95 percent CI 70; 94) through one year of age.

Serotype	Number of Cases		Percent Rate Reduction (95% CI)
	Vaccine Group (N = 9,009)	Placebo Group (N = 8,858)	
G1	3	36	92 (74.1 to 98.4)
G2	6	10	41 (<0;82)
G3	1	8	88 (8.3;99.7)
G4	1	2	Not available
G9	2	21	91 (62;99)

**(Table 5)** Percentage of Patients Reporting Severe Rotavirus Gastroenteritis Episodes and Efficacy of HRV from Two Weeks After Dose Two up to Visit Four, by Rotavirus Serotypes [ATP Efficacy Cohort] [Adapted from Ruiz-Palacios]

### Safety data

The safety profile for each of the two rotavirus vaccines has been demonstrated in their respective clinical trials.

### Safety profile of RotaTeq (rotavirus vaccine, live, oral pentavalent)

More than 71,000 infants were evaluated in three Phase III placebo-controlled clinical trials including REST. Serious adverse events occurred in 2.4 percent of recipients of RotaTeq when compared to 2.6 percent of placebo recipients within the 42-day period of a dose.

Hematochezia, reported as a serious adverse event for RotaTeq compared to placebo, was less than 0.1 percent versus less than 0.1 percent of placebo recipients. The most frequently reported serious adverse events for RotaTeq were comparable in frequency to placebo and were bronchiolitis, gastroenteritis, pneumonia, fever, and urinary tract infection.

In a subset of more than 11,000 infants in these trials, the presence of adverse events was reported for 42 days after each dose. Fever was observed at similar rates in vaccine and placebo recipients (42.6 percent versus 42.8 percent). Adverse events that occurred at a statistically higher incidence within 42 days of any dose among recipients of RotaTeq as compared with placebo recipients were diarrhea (24.1 percent versus 21.3 percent), vomiting (15.2 percent versus 13.6 percent), otitis media (14.5 percent versus 13.0 percent), nasopharyngitis (6.9 percent versus 5.8 percent), and bronchospasm (1.1 percent versus 0.7 percent).

RotaTeq or placebo was administered to 2,070 pre-term infants (25 to 36 weeks gestational age, median 34 weeks) according to their age in weeks since birth in REST. All pre-term infants were followed for serious adverse experiences; a subset of 308 infants was monitored for all adverse experiences. No cases of intussusception were reported. Serious adverse experiences occurred in 5.5 percent of vaccine and 5.8 percent of placebo recipients. The most common serious adverse experience was bronchiolitis, which occurred in 1.4 percent of vaccine and 2.0 percent of placebo recipients.

The REST study, which was specifically designed to evaluate safety with respect to intussusception within 42 days of any dose, which was the primary safety endpoint, did not show an increased risk of intussusception for RotaTeq when compared to placebo. [Veskari 2006] In post-marketing experience, cases of intussusception (including death) and Kawasaki disease have been reported in infants who have received RotaTeq. Post marketing safety surveillance and studies of RotaTeq are ongoing, including a post-licensure study to monitor intussusception, Kawasaki disease and general safety.

### ***Safety profile of Rotarix (rotavirus vaccine, live, oral)***

Solicited and unsolicited adverse events, serious adverse events and cases of intussusception were collected in seven clinical studies. Cases of intussusception and serious adverse events were collected in an additional large safety study. These eight clinical studies evaluated a total of 71,209 infants who received Rotarix (n= 36,755) or placebo (n= 34,454). [Physician Desk Reference 2008]

Serious Adverse Events (SAEs): Infants were monitored for serious adverse events that occurred in the 31-day period following vaccination in eight clinical studies. Serious adverse events occurred in 1.7 percent of recipients of Rotarix (n= 36,755) as compared with 1.9 percent of placebo recipients (n= 34,454). Among placebo recipients, diarrhea (placebo 0.07 percent, Rotarix 0.02 percent), dehydration (placebo 0.06 percent, Rotarix 0.02 percent), and gastroenteritis (placebo 0.3 percent, Rotarix 0.2 percent) occurred at a statistically higher incidence (95 percent CI of Relative Risk excluding one) as compared with recipients of Rotarix. [Physician Desk Reference 2008]

Solicited Adverse Events: In seven clinical studies, detailed safety information was collected by parents/guardians for eight consecutive days following vaccination with Rotarix (i.e., day of vaccination and the next seven days). A diary card was completed to record fussiness/irritability, cough/runny nose, the infant's temperature, loss of appetite, vomiting, or diarrhea on a daily basis during the first week following each dose of Rotarix or placebo. Adverse events among recipients of Rotarix and placebo occurred at similar rates. Unsolicited Adverse Events: Infants were monitored for unsolicited serious and non-serious adverse events

that occurred in the 31-day period following vaccination. The following adverse events occurred at a statistically higher incidence (95 percent CI of Relative Risk excluding one) among recipients of Rotarix (n= 5,082) as compared with placebo recipients (n= 2,902): irritability (Rotarix 11.4 percent, placebo 8.7 percent), and flatulence (Rotarix 2.2 percent, placebo 1.3 percent). [Physician Desk Reference 2008]

In the phase III study in Latin America and Finland, the risk of intussusception was evaluated in 63,225 infants (31,673 received Rotarix and 31,552 received placebo). The primary safety objective was to evaluate the risk of definite intussusception within 31 days after each dose. No increased risk of intussusception following administration of Rotarix was observed when compared with placebo. Post-marketing adverse events reported for Rotarix since its introduction outside the United States includes intussusception and idiopathic thrombocytopenic purpura. Post-marketing surveillance and studies of Rotarix are planned to monitor intussusception, with other measures for Kawasaki disease, convulsions, deaths from all causes and hospitalizations due to acute lower respiratory tract infections (including pneumonia).

## ***Areas of Current Research***

### ***Rotavirus serotypes***

The mechanisms of rotavirus pathogenesis and immunity and of rotavirus heterogeneity and evolution are yet to be fully understood. Nonetheless, there is a growing understanding of the important role of rotavirus serotypes in these processes. Following the introduction of RotaShield, the first rotavirus vaccine, surveillance networks were established in different parts of the world to monitor the temporal and geographic distribution of circulating rotavirus strains. [Santos 2005] Still other studies have examined the possible association of serotype with disease severity. [Linhares 2006; Bahl 2005]

### ***Serotype-specific immunity***

The importance of serotype-specific immunity is a matter of ongoing debate. According to one view, serotype specific immunity is important to achieving a high level of protection. The second view is that a single rotavirus infection of any serotype will induce protection against all other relevant rotavirus strains. Because many rotavirus strains coexist, serotype-specific immunity is an area for further study. While the available vaccines reflect different designs, it is important that they each protect against common rotavirus serotypes in circulation. The exact immunologic mechanism by which the current rotavirus vaccines protect against rotavirus gastroenteritis is unknown.

*In regions in which many strains coexist, serotype-specific immunity is an area for further study.*

*It is important that vaccines protect against a range of rotavirus serotypes in circulation, including serotypes G1, G2, G3, G4 and G9, which are of epidemiologic importance because of prevalence.*

## **Conclusion**

Because of the tremendous burden of rotavirus infection throughout the world, rotavirus has long been a priority target for vaccination. The development of rotavirus vaccines that are effective against the prevalent serotypes constitutes a major step in the fight against acute rotavirus gastroenteritis. Rotavirus is a multi-

serotype disease, and serotypes can vary from year to year, so it is difficult to predict which serotype a child will be exposed to in any given region any year. It is therefore important to protect children from the many serotypes that cause most of the disease. Large clinical trials are underway to confirm the efficacy and tolerability of the rotavirus vaccines in developing countries and their role in reducing the toll of childhood morbidity due to rotavirus gastroenteritis. These vaccines are expected to help reduce the burden of rotavirus in both developed and developing countries.

## ***Additional Safety Information About RotaTeq (rotavirus vaccine, live, oral pentavalent)***

- RotaTeq should not be administered to infants with a demonstrated history of hypersensitivity to the vaccine or any component of the vaccine.
- No safety or efficacy data are available for the administration of RotaTeq to infants who are potentially immunocompromised or infants with a history of gastrointestinal disorders.
- Caution is advised when considering whether to administer RotaTeq to individuals with immunodeficient contacts.
- RotaTeq may not protect all vaccine recipients against rotavirus.

Before administering RotaTeq, please read the [Prescribing Information](#) and [Patient Product Information](#).

***Additional Safety Information About Rotarix (rotavirus vaccine, live, oral)***

- Rotarix should not be administered to infants with previous hypersensitivity to any component of the vaccine including latex rubber (contained in oral applicator).
- Administration of Rotarix in infants suffering from acute diarrhea or vomiting should be delayed.
- Safety and effectiveness of Rotarix in infants with chronic gastrointestinal disorders have not been evaluated.
- Since Rotarix is a live virus safety and effectiveness in infants with known primary or secondary immunodeficiencies have not been evaluated.

[Download Complete Prescribing Information for ROTARIX.](#)

## **Figure and Table Legends**

**Table 1.** Parashar UD, Hummelman EG, Bresee JS, et al. Global illness and deaths caused by rotavirus diarrhea in children. *Emerg Infect Dis.* 2003; 9:568. Adapted from Parashar 2003.

**Table 2.** Velázquez FR, Matson DO, Calva JJ, et al. Rotavirus infection in infants as protection against subsequent infections. *N Engl J Med.* 1996;335:1027. Adapted from Velazquez 1996.

**Table 3.** Vesikari T, Matson DO, Dennehy P, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N Engl J Med.* 2006; 354:31. [REST trial]. Adapted from Vesikari 2006.

**Table 4.** Ruiz-Palacios GM, Pérez-Schael I, Velázquez FR, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *N Engl J of Med.* 2006; 354:18. Adapted from Ruiz-Palacios 2006.

**Table 5.** Ruiz-Palacios GM, Pérez-Schael I, Velázquez FR, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *N Engl J of Med.* 2006; 354:11-22. Adapted from Ruiz-Palacios 2006.

**Figure 1.** Griffin DD, Kirkwood CD, Parashar UD, et al. Surveillance of rotavirus strains in the United States: Identification of unusual strains. *J Clin Microbiol.* 2000; 38:2785. Adapted from Griffin 2000.

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