MERCK

Research Laboratories

RotaTeq™
(rotavirus vaccine, live, oral, pentavalent)

FDA Advisory Committee
Background Information

Presented to:

Vaccines and Related Biological Products Advisory Committee

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1. Introduction and Organization of the Document

Rotavirus is the leading cause of severe diarrhea in infants and young children in both developed and developing countries. Rotavirus infects nearly all children by 5 years of age regardless of socioeconomic status or environmental conditions. Annually, rotavirus is responsible for 2 million hospitalizations and over a half million deaths worldwide [1]. In the United States, rotavirus is responsible for 55,000 to 70,000 hospitalizations and 20 to 70 deaths annually [3]. Merck & Co., Inc. has developed a multivalent vaccine, RotaTeq™[1] (rotavirus vaccine, live, oral, pentavalent), to prevent rotavirus gastroenteritis and the associated morbidity and mortality.

An original Biologics Licensing Application (BLA) for the use of RotaTeq™ was filed in April 2005. This briefing document provides a summary of the safety, efficacy, and immunogenicity data to support licensure of this vaccine. Since the submission, additional safety data from a large-scale efficacy and safety clinical trial (Protocol 006 – Rotavirus Efficacy and Safety Trial [REST]) have been obtained and the data were submitted in a separate Safety Update Report (SUR) in August 2005. The study results displayed in this briefing document include a cumulative dataset from the Original Application and the SUR. This document is organized according to the following outline:

Section 1 Introduction and Organization of the Document.

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[1] RotaTeq is a trademark of Merck & Co., Inc., Whitehouse Station, New Jersey, U.S.A.

2. Synopsis

2.1 Introduction

Rotavirus is the leading cause of severe diarrhea in infants and young children in both developed and developing countries. Rotavirus infects nearly all children by 5 years of age regardless of socioeconomic status or environmental conditions, resulting in 25 million clinic visits, 2 million hospitalizations, and 352,000 to 592,000 deaths worldwide [2]. In the United States, rotavirus is responsible for 410,000 clinic visits, 55,000 to 70,000 hospitalizations, and 20 to 70 deaths annually [3].

RotaTeq™ was developed to provide broad protection against the most common rotavirus serotypes causing gastroenteritis in infants and young children. Phase III studies have demonstrated that RotaTeq™ is generally well tolerated. Because of the association of intussusception with the rhesus rotavirus tetravalent vaccine, RRV-TV (RotaShield™, Wyeth-Lederle), a large-scale trial (Protocol 006 [REST]) of over 70,000 subjects was conducted, which showed that RotaTeq™ is well tolerated with respect to intussusception and other serious adverse experiences. The Phase III studies have also demonstrated that RotaTeq™ is clinically efficacious in preventing rotavirus gastroenteritis, and that the excellent clinical efficacy markedly reduces healthcare encounters for rotavirus gastroenteritis including a decrease in hospitalizations and emergency department visits.

Based on the study results summarized within this document, the proposed indication for RotaTeq™ is as follows:

RotaTeq™ is an oral pentavalent vaccine indicated for the prevention of rotavirus gastroenteritis in infants and children caused by the serotypes G1, G2, G3, G4, and G-serotypes that contain P1 (e.g., G9). RotaTeq™ may be administered as early as six weeks of age.

The clinical development program for RotaTeq™ is exceptional with regard to the scope and size of the safety and efficacy databases pre-licensure. The safety and efficacy results from the clinical trials strongly support the licensure of RotaTeq™. Given the absence of identified risk factors for severe disease and the universal nature of rotavirus gastroenteritis, this vaccine is an important public health priority.

2.2 Basis for Development of a Rotavirus Vaccine

2.2.1 Public Health Burden and Clinical Manifestations of Rotavirus Disease

Nearly all children in the United States will be infected with rotavirus by their fifth birthday. Approximately 2 out of 3 will be symptomatic from their infection, and approximately 1 out of 65 will be hospitalized. In total, rotavirus accounts for 4% of all U.S. pediatric hospitalizations. Figure 2-1 displays the annual burden and risk by age 5 years for deaths, hospitalizations, emergency department and outpatient visits, and acute gastroenteritis episodes (AGEs) that occur in infants in the United States [3].

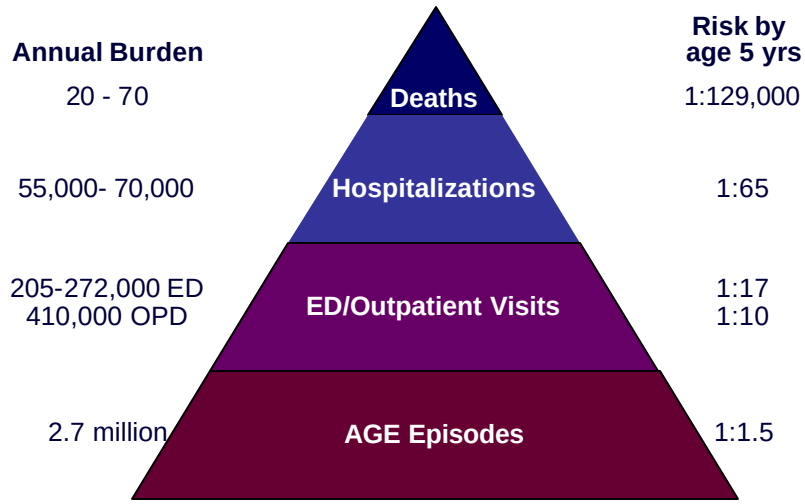
Rotavirus infection causes a spectrum of clinical manifestations ranging from asymptomatic infection to mild diarrhea to severe dehydrating gastroenteritis that can be fatal [4]. Rotavirus gastroenteritis is characterized by the classic symptoms associated

with childhood gastroenteritis including diarrhea, vomiting, and fever. Symptoms begin after an incubation period of 2 to 3 days and persist on average for 6 days [5]. The clinical features of rotavirus gastroenteritis that distinguish it from gastroenteritis of other etiologies are the high proportion of children with vomiting (approximately 80 to 90%) and significant dehydration [6]. The predominance of vomiting with diarrhea and the resulting dehydration are the reasons why rotavirus is responsible for a disproportionately high percentage of hospitalizations for gastroenteritis when compared with other enteric pathogens.

Currently, there is no antiviral therapy available to treat rotavirus gastroenteritis in the United States. Previously, there was a rotavirus vaccine that was licensed in the United States; however, the manufacturer withdrew the rotavirus vaccine from the market due to an association with a rare adverse experience, intussusception (see Section 3.3.1). Therefore, the only treatment is supportive oral or intravenous (IV) rehydration for dehydration. The universal nature of rotavirus and the high prevalence in areas with clean water supplies and adequate sanitation support vaccination as the primary intervention against rotavirus gastroenteritis.

Figure 2-1

U.S. Annual Burden of Rotavirus Gastroenteritis



ED = Emergency Department.
OPD = Outpatient Department.
AGE = Acute Gastroenteritis Episode.

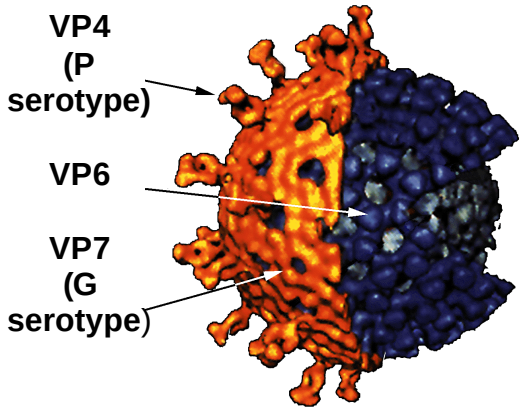
2.2.2 Virology and Seroepidemiology of Rotavirus

Rotaviruses are large, nonenveloped icosahedral particles composed of 11 segments of double-stranded RNA enclosed in a triple layered protein capsid [7]. As shown in Figure

2-2, the 2 outer capsid proteins are VP4 and VP7, which independently elicit neutralizing antibodies and are used to classify rotavirus strains into P-serotypes (for protease-sensitive) and G-serotypes (for glycoprotein), respectively [7]. Rotaviruses are usually identified by their G-serotype and P-serotype or genotype, which is designated in brackets (e.g., G1, P1[8]). The most prevalent human rotavirus serotypes are G1, G3, and G4 in conjunction with P1[8], and G2 in conjunction with P2[4]. These are the G-types responsible for over 88% of all rotavirus gastroenteritis worldwide [8]. Serotype G9, which is associated with multiple VP4 genotypes including P1[8], P[6], and P[4], is also emerging as another prevalent G-serotype [8].

Figure 2-2

Schematic Representation of the Rotavirus Dissected Particle Structure and Surface Proteins



2.2.3 Immunity With Wild-Type Rotavirus Infection

The basis for developing a rotavirus vaccine rests on the observation that wild-type rotavirus infection immunizes children against subsequent disease [9; 10; 11; 12]. The immunity from wild-type infection does not prevent all subsequent infections; however, it provides nearly complete protection against severe disease and substantial protection against mild disease. The mechanism(s) by which wild-type rotavirus infection induces immunity is not well defined. Children typically have repeated infections and develop high titers of anti-rotavirus IgA and IgG in serum and duodenal fluid over the first 24 to 36 months of life [13; 14; 15]. G-serotype-specific neutralizing antibody is observed with the primary rotavirus infection; broader, heterotypic responses to multiple G-serotypes appear only after repeated infections [15]. Although some longitudinal studies have shown that high titers of these antibodies appear to correlate with protection against subsequent disease and/or infection, a single, definitive immunological surrogate of efficacy has not yet been identified [13; 14; 15; 16].

Regardless of the lack of clarity around immunologic correlates of protection, the efficacy data from studies of wild-type rotavirus infection and early rotavirus vaccine candidates provide important empiric evidence regarding the mechanism of protection against rotavirus gastroenteritis. These studies clearly indicate that G-serotype-specific neutralizing antibody is required to achieve comprehensive protection against rotavirus gastroenteritis in infants and young children who are immunologically naïve to rotavirus; protection after primary wild-type infection is largely serotype specific and vaccines without human rotavirus surface glycoproteins have had limited efficacy. Therefore, a multivalent vaccine is necessary to provide the broadest protection against rotavirus gastroenteritis.

2.3 Development of the Human-Bovine (WC3) Reassortant Rotavirus Vaccine, RotaTeq™

The development of Merck's rotavirus vaccine is briefly described in this section and in further detail within Section 3. The first rotavirus vaccines were developed from rotaviruses isolated from simian and bovine hosts. The parent strain of Merck's rotavirus vaccine candidate, RotaTeq™, is a bovine rotavirus, the Wistar Calf 3 (WC3) strain, which was isolated from a calf in Chester County, Pennsylvania, U.S.A. in 1981 [17]. This bovine rotavirus is not pathogenic for humans but induces some cross-protection against human rotavirus strains. The efficacy of this vaccine was inconsistent and variable [18]. Therefore, a human-bovine rotavirus reassortant was developed, which was the WC3 bovine rotavirus with a single human rotavirus outer shell glycoprotein of serotype G1. Serotype G1 as well as several other reassortants of human-bovine rotavirus including serotypes G2 and P1 were evaluated in early clinical trials. These clinical trials showed that the human-bovine reassortant rotavirus vaccines were generally well tolerated and had consistent efficacy against mild and severe rotavirus disease. Section 3 of this briefing document provides an overview of the clinical trials of the WC3 vaccine and earlier WC3 reassortant vaccines.

Merck began clinical development of the human-bovine (WC3) reassortant rotavirus vaccine in 1993 with Phase I studies of a quadrivalent (G1, G2, G3, and P1) vaccine formulation. Phase I and Phase II clinical trials of this and several other vaccines of different serotype compositions, doses, and formulations were conducted with favorable results. Ultimately, a pentavalent rotavirus vaccine, RotaTeq™, containing 5 human-bovine reassortant rotavirus strains (WI79-9, SC2-9, WI78-8, BrB-9, and WI79-4 – designated as G1, G2, G3, G4, and P1[8], respectively, for simplicity) was developed and evaluated in 3 Phase III clinical trials. These G-serotypes were included in RotaTeq™ because these are the G-serotypes responsible for over 88% of all rotavirus gastroenteritis worldwide [8].

RotaTeq™ consists of the 5 human-bovine reassortants suspended in a liquid buffer/stabilizer that is stored refrigerated. It was administered as a 3-dose regimen beginning at age 6 to 12 weeks with 4- to 10-week intervals between doses. The vaccine was evaluated at potencies (viral titers) ranging from approximately 1.0×10^7 to 12.4×10^7 infectious units per dose in the 3 Phase III studies.

2.4 Clinical Efficacy

The primary efficacy objective of the clinical development program for RotaTeq™ was to demonstrate that a 3-dose regimen would be efficacious against rotavirus gastroenteritis caused by the serotypes included in the vaccine (G1, G2, G3, or G4) occurring at least 14 days following the third dose. Two (2) Phase III clinical trials, Protocol 006 (REST) and Protocol 007, provide the efficacy data to support licensure of this vaccine.

The efficacy of RotaTeq™ was evaluated in 2 different ways in these 2 clinical trials (Protocol 006 [REST] and Protocol 007). In a subset of subjects in Protocol 006 (REST) and all subjects in Protocol 007, efficacy against all rotavirus gastroenteritis caused by the serotypes G1, G2, G3, and G4 for the first rotavirus season postvaccination was evaluated for the primary efficacy objective. The large sample size of Protocol 006 (REST) also provided a unique opportunity to evaluate efficacy against healthcare encounters for rotavirus gastroenteritis caused by the serotypes G1, G2, G3, and G4 including hospitalizations, emergency department visits, and office visits for up to 2 years following vaccination Visit 1. In order to be included in these efficacy analyses, the subject had to meet both the clinical and laboratory criteria of the case definition of rotavirus gastroenteritis. These criteria are further described in Section 4.2 within this briefing document.

RotaTeq™ provided protection (approximately 73%) against rotavirus gastroenteritis of any severity and was highly efficacious (approximately 98%) against severe rotavirus disease, a pattern of immunity similar to that observed after wild-type rotavirus infection. The clinical efficacy translated into a marked reduction in healthcare encounters for rotavirus gastroenteritis. In Protocol 006 (REST), the rates of hospitalizations and emergency department visits for rotavirus gastroenteritis were reduced by 96% and 93%, respectively, in the group that received vaccine as compared with placebo group. Several secondary analyses of efficacy including efficacy through a second rotavirus season, efficacy against individual vaccine and nonvaccine serotypes, efficacy by breast-feeding status, and efficacy in different populations were also evaluated and are described in detail in Section 4. The results of these secondary analyses provide added support that RotaTeq™ was efficacious against rotavirus gastroenteritis.

2.5 Immunogenicity

The immunogenicity data to support licensure of RotaTeq™ was obtained from 3 Phase III clinical trials (Protocol 006 [REST]), (Protocol 007), and (Protocol 009). An immunologic surrogate of efficacy has not been identified in any of the clinical trials of RotaTeq™ or the vaccines from which it was derived. Thus, the use of immunogenicity data for RotaTeq™ has been limited to the demonstration of manufacturing consistency for observational comparisons between populations described in Section 5, and in studies of the concomitant use of RotaTeq™ with other childhood vaccines. Immunogenicity has not been used in making decisions about dose (viral titer) or in assessing potential protection against rotavirus disease.

The primary immunogenicity assays for RotaTeq™ evaluated serum anti-rotavirus immunoglobulin A (IgA) responses and serum neutralizing antibody (SNA) responses to the VP7 and VP4 serotypes in the vaccine including human G1, G2, G3, G4, and P1[8], and the bovine G6 and P7[5]. The magnitude of responses in these assays varied with potency. In general, a high proportion of children had significant (=3-fold rise in titer, from baseline) increases in serum anti-rotavirus IgA and G1 SNA, a modest proportion had significant increases in G4 and P1 SNA, and a low proportion had significant increases in G2 and G3 SNA. However, serotype-specific SNA responses did not correlate with efficacy.

Concomitant use of RotaTeq™ with licensed pediatric vaccines was evaluated in Protocol 006 (REST), including diphtheria, tetanus, and acellular pertussis (DTaP), inactivated polio virus (IPV), *Haemophilus influenzae* type b (Hib), hepatitis B (Hep B), and pneumococcal conjugate. To look for potential interference between RotaTeq™ and these vaccines, the immunogenicity of these vaccines when given concomitantly with RotaTeq™ was compared with the immunogenicity of these vaccines when given concomitantly with placebo. Responses to the vaccines were similar in the RotaTeq™ and placebo groups with the exception of the response to the pertactin component of pertussis. All immunogenicity results for RotaTeq™ and the licensed pediatric vaccines are provided in Section 5.

2.6 Clinical Safety

The safety data to support licensure of RotaTeq™ come from 3 Phase III clinical trials, Protocol 006 (REST), Protocol 007, and Protocol 009. Overall, 71,799 subjects (36,203 recipients of RotaTeq™) received at least one dose of RotaTeq™ or placebo. All subjects were evaluated for all serious adverse experiences, including intussusception, which was a side effect associated with the rhesus rotavirus tetravalent vaccine, RRV-TV (RotaShield™, Wyeth-Lederle). A total of 11,722 vaccinated infants (6,143 recipients of RotaTeq™) were also evaluated for all nonserious and serious clinical adverse experiences (Detailed Safety Substudy). RotaTeq™ was well tolerated.

Active safety surveillance for intussusception was utilized in all 3 Phase III clinical trials for 42 days following each vaccination. This surveillance included telephone contacts or home visits on Days 7, 14, and 42 following each vaccination. In Protocol 006 (REST), subjects were also followed every 6 weeks for up to 365 days following vaccination Visit 1. For the subjects participating in the Detailed Safety Substudy, clinical adverse experiences were monitored for 42 days following any vaccination. These clinical adverse experiences were recorded by the parent/legal guardian on a Vaccination Report Card (VRC). Daily temperatures and the number of episodes of vomiting and diarrhea were also recorded during the 7-day period after each dose.

The results of the large-scale study (Protocol 006 [REST]) provide a high level of confidence in the safety of RotaTeq™ with regard to intussusception. The prespecified statistical criteria for demonstrating safety were met. There were 11 positively-adjudicated intussusception cases within 42 days following vaccination, the time period upon which the primary safety hypothesis was based. Six (6) cases occurred among recipients of RotaTeq™ and 5 cases among placebo recipients. The relative risk was 1.6,

with 95% confidence interval (CI) of 0.4 to 6.4 (adjusted for multiplicity due to the group-sequential design of Protocol 006 [REST], see Section 6.3.1). There were no cases of intussusception reported within the 2-week period after the first dose, the time interval during which the risk of intussusception with RRV-TV (Wyeth-Lederle) was highest. Within 365 days following vaccination Visit 1, there were 28 subjects who had a positively-adjudicated (confirmed) case of intussusception. Thirteen (13) occurred among recipients of RotaTeq™ and 15 cases among placebo recipients. No cases of intussusception were reported in the other Phase III clinical trials (Protocol 007 and Protocol 009). Within the Phase I/II clinical trials conducted, there was only 1 case of intussusception reported and this case is further discussed in Section 6.1.

RotaTeq™ was also well tolerated with respect to other adverse experiences of special clinical interest for this vaccine. An evaluation of the integrated safety data from the 3 Phase III clinical trials showed that the incidences of fever (temperature =100.5ºF rectal equivalent) were comparable in the vaccine and placebo groups during the week after any dose. The incidence of vomiting and diarrhea was slightly increased (1.3% excess) in the vaccine as compared with the placebo group during the week after the first dose. The vast majority of these adverse experiences were classified as mild by the investigator. Other adverse experiences that were statistically significantly greater in the vaccine as compared with placebo groups during the 42-day period after any dose were nasopharyngitis (6.9% versus 5.8%), otitis media (14.5% versus 13.0%), and bronchospasm (1.1% versus 0.7%). Overall, the differences in the proportions of infants with these adverse experiences were small and not clinically concerning. The safety of RotaTeq™ was also evaluated by gender, race, gestational age, and region of origin. RotaTeq™ was well tolerated in all these populations in the 3 Phase III clinical trials, with a safety profile that was comparable to that observed in the overall population.

2.7 Post-Licensure Surveillance Study for Intussusception

Despite having seen no signal that would indicate an association of RotaTeq™ with intussusception, further post-licensure follow-up of this uncommon event is planned. A 2-component plan is proposed consisting of routine passive surveillance and an active post-licensure surveillance study. Section 7 briefly describes the details of the post-licensure surveillance plan.

2.8 Overall Summary and Conclusions: Benefits Versus Risks

Rotavirus is a major cause of childhood morbidity and mortality resulting in 25 million clinic visits, 2 million hospitalizations, and 352,000 to 592,000 deaths annually worldwide, and 55,000 to 70,000 annual hospitalizations in the United States [2]. Merck developed a pentavalent vaccine, RotaTeq™, which is clinically efficacious in preventing 98% of severe rotavirus disease caused by the serotypes responsible for over 88% of rotavirus disease worldwide (G1, G2, G3, and G4). A large-scale trial, Protocol 006 (REST), demonstrated that the excellent clinical efficacy markedly reduces health care encounters for rotavirus gastroenteritis. RotaTeq™ significantly reduced the rate of hospitalizations for rotavirus gastroenteritis by 96% and reduced the rate of emergency department visits for rotavirus gastroenteritis by 93% as compared with placebo. The

Phase III trials also confirmed that RotaTeq™ is well tolerated as demonstrated by the overall clinical safety profile.

The clinical development program for RotaTeq™ is unprecedented with regard to the scope of the safety and efficacy databases pre-licensure. The results of the clinical trials strongly support the licensure of RotaTeq ™. There was no signal indicating that RotaTeq™ is associated with intussusception. The excellent clinical efficacy, especially against severe rotavirus disease and rotavirus-associated hospitalizations, greatly outweighs the slight increase in risk of mild diarrhea and mild vomiting associated with vaccination. Given the absence of identified risk factors for severe disease and the universal nature of rotavirus gastroenteritis, this vaccine is an important public health priority.

3. Development of the Human-Bovine (WC3) Reassortant Rotavirus Vaccine, RotaTeq™

The first rotavirus vaccines were developed from rotaviruses isolated from simian and bovine hosts. Animal rotaviruses are species-specific; therefore, it was expected that these viruses would not cause disease in infants but would induce cross-protection against human rotavirus strains.

3.1 Bovine (WC3) Rotavirus, the Parent Strain of RotaTeq™

Dr. H Fred Clark, currently of Children's Hospital of Philadelphia (CHOP), isolated the Wistar Calf 3 (WC3) bovine rotavirus, the parent strain of RotaTeq™, from a calf in Chester County, Pennsylvania, U.S.A. in 1981 [17]. This bovine rotavirus replicates poorly in humans and other heterologous species in which it has been evaluated. Although well tolerated in infants, the efficacy of the WC3 vaccine was inconsistent across studies and did not induce neutralizing antibodies against human rotavirus G-serotypes [19]. Therefore, a human-bovine rotavirus reassortant was developed, which consists of the WC3 bovine rotavirus with a human rotavirus outer shell glycoprotein of serotype G1. The G1 reassortant was also well tolerated, induced neutralizing antibodies to human rotavirus G1, and demonstrated consistent efficacy across 2 clinical trials. Merck licensed the technology for the human-bovine (WC3) rotavirus reassortants from CHOP in 1991 and continued development of a multivalent vaccine.

3.2 Development of Merck's Rotavirus Vaccine, RotaTeq™

Merck began clinical development of the human-bovine (WC3) reassortant rotavirus vaccine in 1993 evaluating several different reassortant compositions of the vaccine in Phase I and Phase II clinical trials (see Section 3.2.1). Ultimately, a multivalent rotavirus vaccine, RotaTeq™, containing 5 human-bovine reassortant rotavirus strains (WI79-9, SC2-9, WI78-8, BrB-9, and WI79-4 – designated as G1, G2, G3, G4, and P1, respectively for simplicity) was developed and evaluated in 3 Phase III clinical trials. The G1, G2, G3, and G4 rotavirus reassortants contain the 4 human rotavirus VP7 surface proteins, G1, G2, G3, and G4, and the bovine VP4, P7[5]. The P1 rotavirus reassortant has a human rotavirus VP4, P1[8], and a bovine rotavirus VP7, G6. Table 3-1 summarizes the human and bovine rotavirus parent strains of the reassortants in RotaTeq™, and the resulting reassortant outer surface G (VP7) and P (VP4) proteins.

Table 3-1

Antigenic Composition of the 5 Reassortant Rotavirus Vaccine Strains Contained in RotaTeq™

Reassortant Strain	Bovine Rotavirus Parent Strain	Human Rotavirus Parent Strain	Surface Protein Composition **(Human Rotavirus Component in Bold)**
WI79-9	WC3	WI79	**G1**, P7[5]
SC2-9	WC3	SC2	**G2**, P7[5]
WI78-8	WC3	WI78	**G3**, P7[5]
BrB-9	WC3	BrB	**G4**, P7[5]
WI79-4	WC3	WI79	G6, **P1[8]**

Merck has developed a multivalent vaccine to provide comprehensive protection against rotavirus gastroenteritis in infants and young children. Serotypes G1, G2, G3, and G4 were included in RotaTeq™ because these are the G-types responsible for over 93% of all rotavirus gastroenteritis in the United States and 88% of all rotavirus gastroenteritis worldwide [8; 75]. The P1 reassortant was included because it is the most common P-type associated with human rotavirus strains worldwide. Studies suggest that immunity to serotype P1[8] may cross-protect against other G-serotypes (containing the P1[8] serotype) [20].

RotaTeq™ consists of the 5 human-bovine reassortants suspended in a fully liquid buffered-stabilized formulation for oral administration. This formulation protects the reassortants from gastric acid and stabilizes the vaccine, allowing for storage at refrigerator temperatures (2 to 8ºC) for 24 months. The vaccine is provided in a squeezable plastic dosing tube with a twist-off cap designed to allow for delivery of the vaccine directly to the infant from the tube. The vaccine was evaluated at potencies (viral titers) ranging from approximately 1.1×10^7 to 12.4×10^7 infectious units per dose in the 3 Phase III studies. The aggregate potencies for the 3 Phase III trials were approximately 6.72×10^7 to 12.4×10^7 infectious units (IU)/dose for Protocol 006 (REST), approximately 1.1×10^7 IU/dose for Protocol 007, and approximately 6.91×10^7 to 8.81×10^7 IU/dose across 3 lots in Protocol 009.

In the Phase III clinical trials, 3 doses of RotaTeq™ were given beginning at age 6 to 12 weeks with 4- to 10-week intervals between doses (including 2-, 4-, 6-month, 2-, 3-, 4-month, and 2-, 3-, 5-month schedules). The decision to administer a 3-dose regimen was based on a previous study conducted at the Children's Hospital of Philadelphia and the University of Rochester in 1992 and 1993. This study demonstrated that 3 doses of WI79-9 (a human-bovine G1 reassortant rotavirus vaccine candidate) induced a significant immune response (i.e., a =3-fold rise in G1 SNA titer from baseline to Postdose 3) in a larger proportion of infants than a 2-dose regimen of WI79-9. This study was completed prior to Merck assuming clinical development of the human-bovine rotavirus reassortants; therefore, all subsequent studies completed by Merck have utilized a 3-dose regimen [21].

The results of the Phase I, II, and III clinical trials have shown that RotaTeq™ and its predecessors have been generally well tolerated, immunogenic, and efficacious in preventing rotavirus gastroenteritis. A summary of the Phase I/II studies is provided in Section 3.2.1 followed by a detailed discussion of the efficacy, immunogenicity, and safety findings from the 3 Phase III studies of RotaTeq™ (see Section 3.2.2).

3.2.1 Overview of Phase I/II Studies

Five (5) Phase I/II studies of the predecessors of RotaTeq™, which included vaccines of different formulations and reassortant compositions, were conducted involving 3,186 infants (2,470 vaccine recipients) and 46 adults (30 vaccine recipients). In addition to demonstrating the overall efficacy and tolerability, the results of these studies were utilized to select the formulation, potency (dose or viral titer), and reassortant composition of RotaTeq™, which was then evaluated in the Phase III clinical trials. The results and implications of the Phase I and Phase II studies may be summarized as follows: 1.) The vaccine was generally well tolerated; 2.) The liquid buffered-stabilized formulation was immunogenic and well-tolerated; and 3.) The P1 reassortant contributes to efficacy and should be included in the vaccine for licensure; and 4.) The vaccine is efficacious across a broad range of doses (potencies or viral titers). A dose of approximately 2.0 x 10^6 pfu/reassortant was selected as the assigned expiry dose for the vaccine intended for licensure, the efficacy of which was confirmed in the Phase III clinical trial, Protocol 007. The major objectives and outcomes of these studies are summarized in Table 3-2.

Table 3-2

Objectives and Outcomes of Phase I/II Studies

<table>
<tr><th>Objective</th><th>Outcome</th></tr>
<tr><td>To demonstrate that multivalent vaccine compositions would be well tolerated particularly with respect to common adverse experiences (Protocols 001-005), and to evaluate fecal shedding of vaccine-virus strains (Protocols 001-005).</td><td>• All 5 studies demonstrated that the vaccines were well tolerated with respect to all adverse experiences including diarrhea, fever, irritability, and vomiting.
• Fecal shedding of vaccine-virus strains was uncommon and occurred almost exclusively after Dose 1, where it occurred in 2.2% to 6.8% of infants.</td></tr>
<tr><td>To demonstrate that multivalent vaccine compositions would be efficacious against any severity of rotavirus gastroenteritis and severe disease (Protocols 002 and 005).</td><td><table>
<tr><td rowspan="2">Disease Severity</td><td colspan="2">% Efficacy (95% CI)</td></tr>
<tr><td>Protocol 002
~1.0 x 10^7 pfu/reassortant</td><td>Protocol 005
~1.6 x 10^6 pfu/reassortant</td></tr>
<tr><td>Any</td><td>75 (50,88)</td><td>74 (38,91)</td></tr>
<tr><td>Severe</td><td>100 (44,100)</td><td>100 (35,100)</td></tr>
</table></td></tr>
<tr><td>To identify an immunologic correlate of efficacy (Protocols 002, 003, and 005).</td><td>No definitive immunologic surrogate of efficacy was confirmed. In one study (Protocol 005), Postdose 3 titers of serum neutralizing antibody (SNA) to G1 correlated with the risk of developing rotavirus gastroenteritis.</td></tr>
<tr><td>To identify a safe and immunogenic liquid vaccine formulation consisting of a buffer/stabilizer that would protect the vaccine against gastric acid so that it could be administered directly to infants and that would allow for refrigerated storage for 24-months (Protocol 003)</td><td>All the candidate buffered-stabilized formulations evaluated were generally well tolerated and had similar immunogenicity as the unbuffered formulation when administered with antacid or pre-feeding. These data and in-vitro stability data served as the basis for selection of the final buffered-stabilized vaccine formulation that was administered in all Phase III studies and is intended for licensure.</td></tr>
<tr><td>To define the end-expiry (end-of-shelf-life) dose and determine the final reassortant composition (i.e., +/- P1[8]) (Protocol 005).</td><td>• The expiry potency of the vaccine intended for licensure was based on that of the middle potency pentavalent arm, which was 74% (95% CI 38%, 91%) efficacious against rotavirus gastroenteritis of any severity. The efficacy of the expiry potency of the final vaccine was confirmed in a Phase III study (Protocol 007).
• A pentavalent composition (+P1) was selected for the final vaccine because the P1 monovalent vaccine was generally well tolerated and demonstrated efficacy against moderate-and-severe and severe disease through the first rotavirus season postvaccination and any severity of rotavirus gastroenteritis through the second rotavirus season postvaccination.</td></tr>
</table>

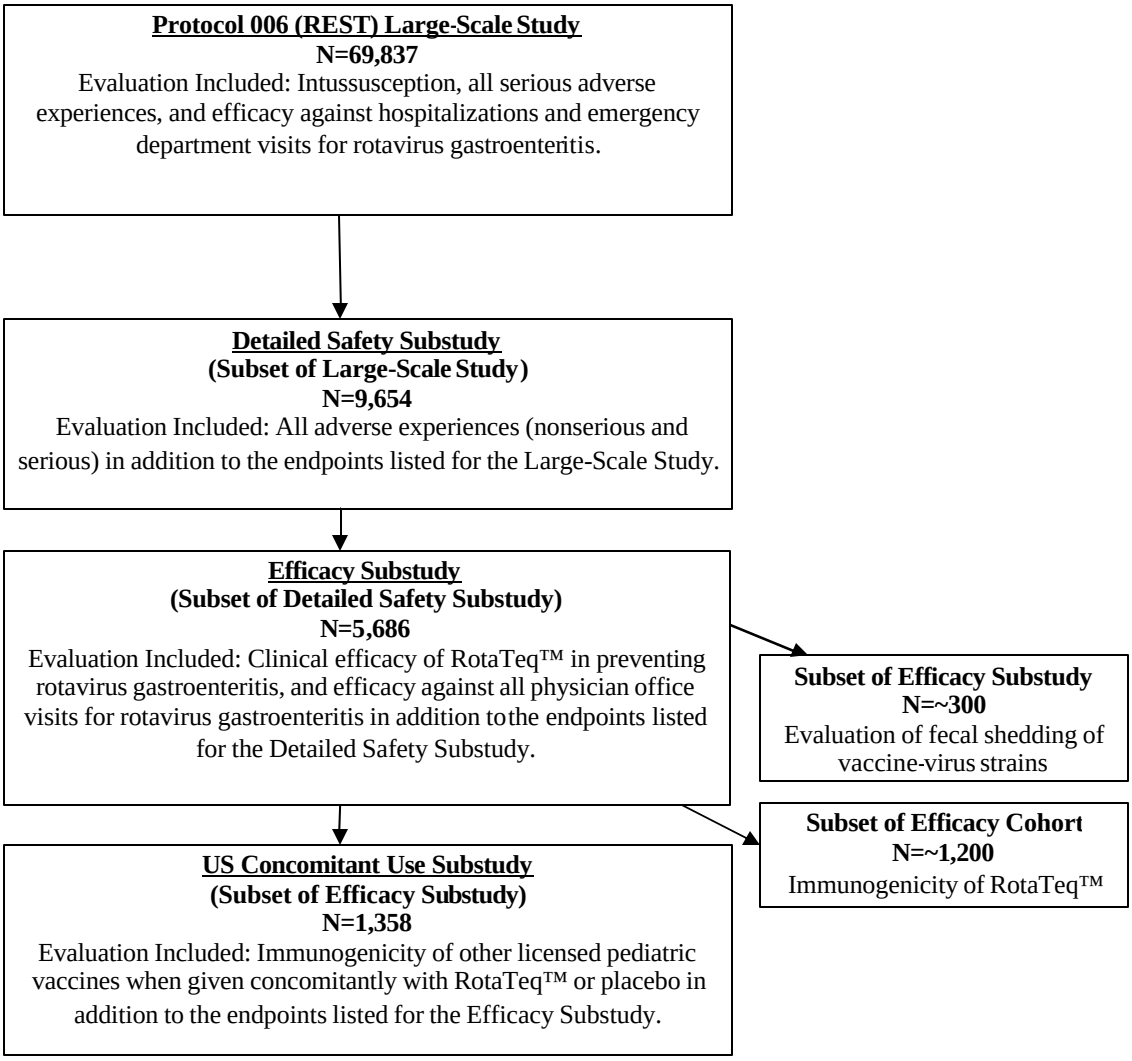
3.2.2 Overview of Phase III Studies

Three (3) Phase III studies were conducted involving 71,799 vaccinated infants, 36,203 of whom received the final formulation of RotaTeq™ intended for licensure and 35,596 who received placebo. These 3 Phase III studies have provided the efficacy, immunogenicity, and safety data that are outlined throughout this briefing document. These 3 Phase III studies include: 1) The large-scale Rotavirus Efficacy and Safety Trial, REST (Protocol 006), which evaluated the efficacy, immunogenicity, and safety of RotaTeq™, particularly with regard to intussusception; 2) The Dose-Confirmation Efficacy Study, Protocol 007, which confirmed the efficacy of the end-expiry potency of RotaTeq™ in the final formulation intended for licensure; and 3) The Consistency Lots Study, Protocol 009, which provided a clinical evaluation (i.e., immunogenicity) of the consistency of the manufacturing process. Because of the large sample size required for Protocol 006 (REST) for the intussusception evaluation, several substudies were nested within this study to allow for simultaneous evaluation of other efficacy, immunogenicity, and safety endpoints. A diagram illustrating the multiple substudies embedded within Protocol 006 [REST] is shown in Figure 3-1.

The 3 Phase III studies were conducted in 11 countries including Belgium, Costa Rica, Finland, Germany, Guatemala, Jamaica, Italy, Mexico, Sweden, Taiwan, and the United States, including Puerto Rico and the Navajo and White Mountain Apache Nations. Approximately 48% of subjects were enrolled in the United States, approximately 33% in Finland, and the remaining 19% from the other listed countries. Healthy infants 6 to 12 weeks of age were eligible for enrollment. Three (3) doses of RotaTeq™ were to be given beginning at age 6 to 12 weeks with 4- to 10-week intervals between doses (including 2-, 4-, 6-month, 2-, 3-, 4-month, and 2-, 3-, 5-month schedules). Infants born prematurely (gestational age =36 weeks) were eligible for enrollment according to their chronological age if they were healthy. There were no restrictions on breast-feeding or on the prior or concomitant use of licensed vaccines except for oral poliovirus vaccine. Subjects in the concomitant use immunogenicity substudy of Protocol 006 (REST) received prespecified licensed vaccines concomitantly with RotaTeq™ on the recommended schedule. Infants who had pre-existing congenital abdominal disorders, intussusception, or abdominal surgery were excluded from the studies as were infants who were immunocompromised or had immunocompromised household members. All 3 studies utilized the same methods for case finding and data collection, the same case definitions for safety and efficacy endpoints, and the same immunologic assays.

Figure 3-1

Overall Organization of Substudies Within Protocol 006 (REST) and the Corresponding Objectives



N = Number of subjects randomized.

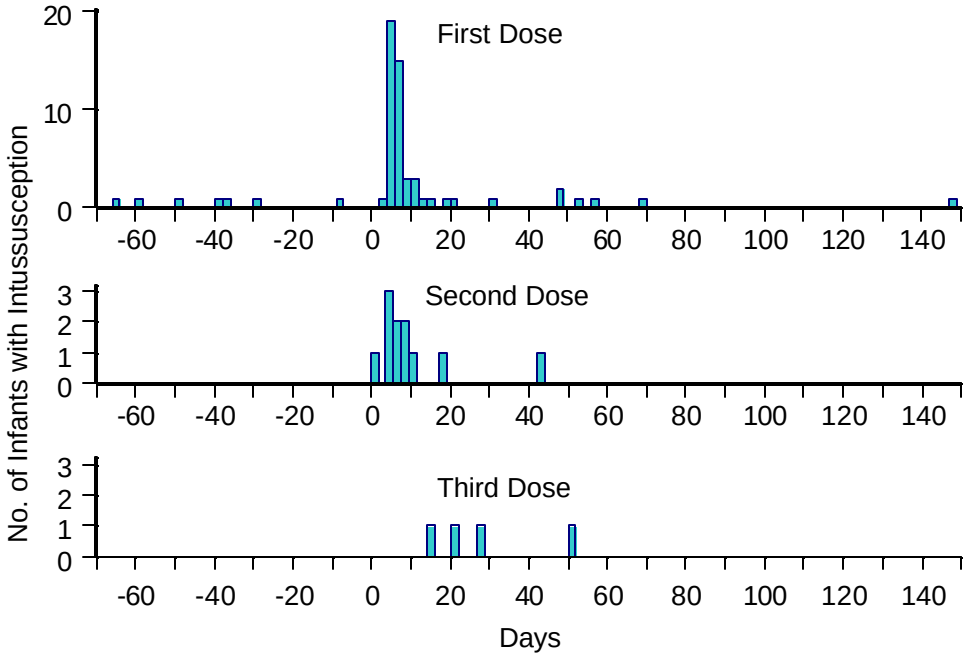
3.3 Intussusception and the Phase III Clinical Development Program for RotaTeq™

3.3.1 Association of Intussusception With RRV-TV (Wyeth-Lederle)

In July 1999, Centers for Disease Control and Prevention (CDC) communicated that the Vaccine Adverse Event Reporting System (VAERS) had received an increased number of reports of intussusception, a form of bowel obstruction in which the intestine telescopes into a caudal portion, among infants who had received an oral tetravalent rhesus-human reassortant rotavirus vaccine (RRV-TV), RotaShield™ (Wyeth-Lederle) [22]. As displayed in Figure 3-2, a case-control investigation confirmed that the risk of intussusception was increased among recipients of RRV-TV (Wyeth-Lederle) during the 3- to 14-day period after the first dose and during the 3- to 7-day period after the second dose [23]. The risk of intussusception was increased after the first dose in younger infants (i.e., 1 to 3 months old, when background intussusception is rare) as well as older infants 3 to 11 months of age [23; 24]. The association between RRV-TV (Wyeth-Lederle) and intussusception significantly influenced the Phase III development program for RotaTeq™; the demonstration of the safety of RotaTeq™ with regard to intussusception became an important clinical study objective.

Figure 3-2

Risk of Intussusception with RRTV was Highest During the Two-Weeks after Doses 1 and 2



3.3.2 Background Intussusception: Epidemiology, Clinical Manifestations, Treatment, and Etiology

Intussusception is an uncommon illness occurring annually in approximately 1 per 2000 (50/100,000) infants. The reported incidence varies by country and within countries ranging from 18 to 66 per 100,000 infant-years among infants <12 months of age [17; 25; 26; 27; 28; 29]. The peak age of diagnosis is 5 to 9 months [26; 27; 29]. Intussusception is 1.5 to 4 times more common in males than females, the reason for which is unknown [30; 31; 32; 33]. Symptoms include irritability, lethargy, intermittent colicky abdominal pain, vomiting, and stools containing blood or mucus. If diagnosed promptly, intussusception usually can be successfully reduced with a contrast or air enema [33; 34; 35; 36; 37]. Spontaneous reduction of cases has been reported [38]. In some cases, surgical reduction and/or intestinal resection may be necessary. If there is a delay in diagnosis, intestinal ischemia may lead to necrosis of the bowel, perforation, peritonitis, and rarely, death [26; 30].

The etiology of intussusception is unknown. Most cases in infants and young children are idiopathic [30; 31; 32]. The infectious agent that has most consistently been demonstrated to be associated with intussusception is respiratory adenovirus [39; 40; 41; 42; 43]. Studies suggest that wild-type rotavirus infection is not associated with intussusception. Two (2) recent studies in New York State and the Southern California Kaiser Permanente Health Care Plan showed that during the winter months, when there was a sharp peak in the rate of hospitalizations for rotavirus, there was no corresponding increase in the rate of hospitalizations for intussusception [29; 44; 45]. Thus, if wild-type rotavirus infection is associated with intussusception, it does not appear to be a major contributing factor.

3.3.3 Rationale for Moving Forward With the Clinical Development of RotaTeq™

Merck decided to continue development of RotaTeq™ despite the intussusception reports associated with RRV-TV (Wyeth-Lederle) based on 4 primary reasons:

1) There is a public health need for a safe and effective rotavirus vaccine. As previously described, rotavirus is a significant cause of childhood morbidity and mortality worldwide.

2) Results from the Phase I and Phase II studies indicated that RotaTeq™ would be well tolerated and efficacious in preventing rotavirus gastroenteritis. The human-bovine rotavirus reassortants (=8 x 10^6 plaque-forming units [PFU]/dose) demonstrated 68 to 75% efficacy against any severity of rotavirus gastroenteritis, 100% efficacy against severe disease, and were generally well tolerated. Only a single case of intussusception had been reported among the 2,470 infants who had received active vaccine in the Phase I and Phase II clinical trials of the human-bovine rotavirus reassortants (see Section 6.1).

3) There are several preclinical and clinical differences that distinguish RotaTeq™ from RRV-TV (Wyeth-Lederle). These differences are likely driven by the different background rotaviruses that make up the reassortants for the 2 vaccines [46]. One preclinical difference is that the rhesus rotavirus spreads systemically in Balb/c (normal) and SCID (immunodeficient) mice, whereas, the WC3 bovine rotavirus does not. After receiving oral rhesus rotavirus, these mice developed hepatitis and nearly all SCID mice died. These adverse experiences were not seen in the mice that received oral WC3 bovine rotavirus and human rotavirus [47; 48]. Clinically, the 2 reassortant vaccines also exhibit different side effect profiles. RRV-TV was associated with fever and irritability after the first dose; however, clinical studies of RotaTeq™ have shown no increase in fever or irritability. Although their relevance to the pathogenesis of intussusception is unknown, these differences were striking and supported Merck moving forward with clinical development of RotaTeq™.

4) The increase in intussusception risk with RRV-TV (Wyeth-Lederle) was possibly unique to that vaccine and will not be associated with all rotavirus vaccines (i.e., is not a class effect). This conclusion is supported by the studies

previously discussed indicating that wild-type rotavirus infection is not associated with intussusception.

3.3.4 Impact of Intussusception on the Phase III Clinical Development Program for RotaTeq™

As a result of the association between RRV-TV and intussusception, the demonstration of safety of RotaTeq™ with respect to intussusception became a primary goal of the Phase III clinical development program. However, designing a study to evaluate the safety of RotaTeq™ with regard to intussusception pre-licensure presented several challenges. Because intussusception is an uncommon event (approximately 1 per 2000 infant-years), the sample size had to be large enough to provide a clinically meaningful evaluation of the risk of intussusception among vaccine recipients as compared with placebo recipients yet feasible to study. It was also important to get consensus on safety criteria for demonstrating that the vaccine is acceptable for licensure. In May 2000, the Center for Biologics Research and Evaluation (CBER) of the U.S. Food and Drug Administration (FDA) was consulted regarding the overall study design of the large-scale rotavirus efficacy and safety trial, Protocol 006 (REST). Merck met with officials from CBER and the Vaccine and Related Biologics Products Advisory Committee (VRBPAC) to discuss the design of a large clinical trial to evaluate the safety of RotaTeq™ with regard to intussusception and the statistical criteria for defining clinical acceptability for licensure. CBER and VRBPAC approved the study design with some minor modifications. Merck moved forward with the large-scale study to evaluate the safety of RotaTeq™ with respect to intussusception, which included pre-established criteria for declaring safety with respect to intussusception and an intensive active surveillance system for interim safety monitoring of study participants. The study design including the details of the success criteria and the safety monitoring system are provided in Section 6.3.

4. Clinical Efficacy

Following a brief review of the Phase II clinical efficacy trials and the study design for the Phase III clinical trials, this section provides an overview of the analyses for the primary and secondary efficacy objectives for Protocol 006 (REST) and Protocol 007; which include: 1) Efficacy by disease severity, 2) Efficacy in reducing health care encounters for rotavirus gastroenteritis, 3) Efficacy by serotype, 4) Efficacy through the second rotavirus season postvaccination, 5) Efficacy by population, 6) Efficacy when administered concomitantly with other pediatric vaccines, 7) Efficacy in breastfed infants, and 8) Intention-to-treat efficacy analyses.

4.1 Overview of Phase II Efficacy Studies

The efficacy of the human-bovine reassortant rotavirus vaccine was demonstrated in 2 Phase II efficacy studies. The proof-of-concept study (Protocol 002) of 439 infants (218 vaccine recipients) showed that the quadrivalent (G1, G2, G3, and P1) human-bovine reassortant rotavirus vaccine was 75% (95% CI: 50%, 88%) efficacious against rotavirus gastroenteritis regardless of severity or serotype and 100% (95% CI: 44%, 100%) efficacious against severe rotavirus disease. The

second efficacy study of 1,946 infants (1,624 vaccine recipients) was a dose-ranging efficacy study (Protocol 005) of 3 potencies of pentavalent vaccine, and a single potency of quadrivalent and monovalent P1 vaccines. This study showed that the pentavalent (G1, G2, G3, G4, and P1) and quadrivalent (G1, G2, G3, and G4) vaccines were efficacious (58 to 74%) against rotavirus gastroenteritis of any severity caused by the G-serotypes in the vaccine (G1, G2, G3, G4) through the first rotavirus season postvaccination. The P1 monovalent reassortant was efficacious (53%; 95% CI: 8%, 77%) against moderate-and-severe rotavirus gastroenteritis caused and severe disease (88%; 95% CI: 11%, 100%) by serotypes G1, G2, G3, and G4 through the first rotavirus season postvaccination. Efficacy persisted for all the vaccines through 2 rotavirus seasons postvaccination.

The data from the Phase III studies were used to select the final buffered-stabilized formulation and dose of RotaTeq™, which was evaluated in the Phase III studies. The efficacy of RotaTeq™ was remarkably similar to that of its predecessors when made at manufacturing scale for the Phase III clinical trials, as is discussed in the section that follows.

Vaccine for Protocol 001 through Protocol 005 was released using plaque assay to determine potency. The plaque assay measures total plaque forming units (PFU) per mL, but cannot distinguish the potencies of the individual reassortants within a multivalent vaccine. Therefore, Merck developed and validated a multivalent quantitative PCR-based potency assay (M-QPA) that enables the measurement of individual rotavirus reassortants. The unit of potency for the M-QPA is infectious units/ml (IU/mL). All vaccine lots used in the pivotal Phase III studies were released using the M-QPA. Potency values from the M-QPA and plaque assays are comparable; studies have shown that for vaccine lots released using both assays, the ratio of plaque to M-QPA potencies ranged from approximately 0.5 to 1.0. In the 3 Phase III studies, the vaccine was evaluated at potencies (viral titers) ranging from approximately 1.1×10^7 to 12.4×10^7 infectious units per dose.

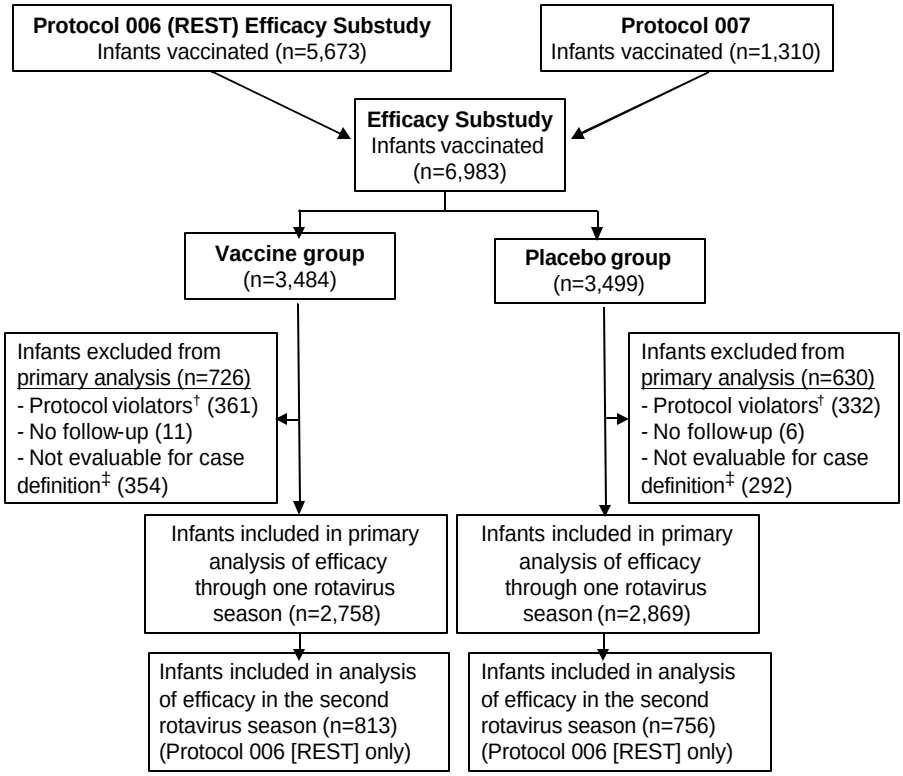
4.2 Overview of Phase III Efficacy Studies Including Important Features of Study Design

The efficacy of the final formulation of RotaTeq™ was evaluated in 2 studies, Protocol 006 (REST) and Protocol 007. There were a total of 6,983 vaccinated subjects combined in these 2 Phase III studies; 5,673 vaccinated subjects that participated in the Efficacy Substudy for Protocol 006 and 1,310 subjects from Protocol 007. Efficacy was not evaluated in Protocol 009; this clinical trial evaluated the manufacturing consistency of RotaTeq™ utilizing immunogenicity only. The primary efficacy hypothesis was that RotaTeq™ would be efficacious against rotavirus disease caused by serotypes G1, G2, G3, and G4 that occurred at least 14 days after the third vaccination through one rotavirus season postvaccination. This was selected as the primary endpoint because the intent of vaccination is to provide broad protection against all severities of rotavirus gastroenteritis caused by these prevalent serotypes. Figure 4-1 provides an accounting of subjects who were included in the primary efficacy analyses.

Additionally, efficacy in reducing health care encounters including hospitalizations and emergency room visits for rotavirus gastroenteritis was also evaluated in Protocol 006 (REST) and is further discussed in Section 4.3.2.

Figure 4-1

Accounting of Subjects Contributing to the Integrated Efficacy Analyses (Protocol 006 [REST] and Protocol 007)



†The large majority (>90%) of protocol violators did not receive all 3 doses.
‡Includes infants with incomplete clinical or laboratory data, wild-type rotavirus EIA -positive stool before the third dose, or stool samples collected >14 days after symptom onset.

Several secondary efficacy objectives were also evaluated. These objectives and the rationale are described below:

1) The efficacy of RotaTeq™ against moderate-and-severe and severe rotavirus gastroenteritis (as determined by a clinical scoring system) was assessed.

   An oral rotavirus vaccine will have greater efficacy against severe disease than mild disease.

2) In Protocol 006 (REST), the efficacy of the vaccine in reducing hospitalizations and emergency department visits for rotavirus gastroenteritis was assessed in all subjects (68,038 infants of which 34,035 were vaccine recipients).

   An oral rotavirus vaccine should be efficacious in preventing the significant morbidity and mortality of rotavirus gastroenteritis worldwide.

3) The efficacy of RotaTeq™ against non-vaccine G-serotypes was evaluated.

   As previously described, protection against other G-serotypes not included in the vaccine may be provided by the P1 reassortant, which was shown to independently contribute to efficacy in Protocol 005.

4) The efficacy of RotaTeq™ against rotavirus gastroenteritis through a second rotavirus season was also evaluated.

   A large proportion of hospitalizations for rotavirus gastroenteritis occur during the second year of life [49].

In order to evaluate the efficacy of RotaTeq™, it was necessary to establish the case definition for an acute gastroenteritis episode (AGE) attributable to rotavirus; apply a clinical scoring system to measure the severity of rotavirus gastroenteritis; and define the rotavirus season. These parameters are discussed in further detail in the subsections that follow.

Case Definition of Rotavirus Gastroenteritis

The clinical case definition that was used in the efficacy evaluation for both Phase III studies (Protocol 006 (REST) and Protocol 007) is generally consistent with that used by CDC and the World Health Organization (WHO) in rotavirus epidemiology studies. One difference is that the Merck clinical case definition permits cases to be included that have vomiting without diarrhea, which has been a feature of rotavirus gastroenteritis published in some rotavirus epidemiology studies [50; 51].

The case definition of rotavirus gastroenteritis used in the Phase III clinical studies of RotaTeq™ included clinical and laboratory criteria. To meet the clinical case definition of an acute gastrointestinal episode (AGE), an infant must have had 3 or more watery or looser-than-normal stools within a 24-hour period and/or forceful vomiting. The laboratory case definition for rotavirus gastroenteritis required that rotavirus antigen be detected by enzyme immunoassay (EIA) in a stool specimen taken within 14 days after the onset of symptoms, with serotype identification by polymerase chain reaction (PCR). Only naturally-occurring G1-, G2-, G3-, or G4-specific rotavirus gastroenteritis cases that

occurred at least 14 days after the third dose of RotaTeq™ or placebo through one rotavirus season would satisfy the primary efficacy case definition in Protocol 006 (REST) and Protocol 007. For all rotavirus cases identified by EIA, plaque assay with electropherotyping was also performed to determine if vaccine-virus strains were present in the stool; cases with vaccine-virus strains (and no wild-type strains) were not considered to meet the case definition of rotavirus gastroenteritis established for these studies.

Clinical Scoring System

A 24-point clinical scoring system was used to grade the severity of AGEs according to the intensity and duration of the clinical manifestations of rotavirus gastroenteritis including diarrhea, elevated temperature, behavioral changes, and vomiting. Parents/legal guardians recorded the signs and symptoms of acute gastroenteritis on a diary card. These recordings were then used to calculate a clinical score. A score of 1 to 8 points is designated as mild, a score of >8 points but =16 points is designated as moderate, and a score >16 points is designated as severe. The scoring system was validated using data from a Phase II study, Protocol 005, which showed that the information provided by the parents/legal guardians correlated with the physician's assessment of the intensity of the adverse experiences that were part of the AGE [52]. The scoring system was selected from one of several scoring systems and has been used in all of the clinical efficacy trials of RotaTeq™ and its predecessors because it provides an objective assessment of the severity of AGEs. The clinical scoring system is shown in Table 4-1.

Table 4-1

Overview of Clinical Scoring System for Severity of Rotavirus Gastroenteritis (Protocol 006 [REST] and Protocol 007)

Score to be summed according to evaluation of symptoms and durations	1	2	3
Diarrhea			
Number of stools/day†	2 to 4	5 to 7	=8
Duration in days‡	1 to 4	5 to 7	=8
Vomiting			
Number of emeses/day§	1 to 3	4 to 6	=7
Duration in days‡	2	3 to 5	=6
Rectal Temperature			
Degrees in Celsius¦	38.1 to 38.2	38.3 to 38.7	=38.8
Duration in days‡	1 to 2	3 to 4	=5
Behavioral Symptoms			
Description¶	Irritable/Less Playful	Lethargic/Listless	Seizure
Duration in days‡	1 to 2	3 to 4	=5

† Maximum number of watery or looser-than-normal stools/day on any given day over the course of the episode.
‡ Number of days in which the subject had a symptom of any score. Total days did not need to be consecutive.
§ Maximum number of emeses on any given day over the course of the episode.
¦ Highest rectal temperature over the course of the episode (only counted if >38°C, rectal equivalent).
¶ If a subject was reported to have 2 or more symptoms, only the one with the highest score was counted.
For this study, reported temperatures were converted to rectal equivalents by adding 1°F to otic and oral temperatures and 2°F to axillary temperatures.

Surveillance for Rotavirus Gastroenteritis for the Efficacy Analyses

Subjects evaluated for efficacy in Protocol 006 (REST) and Protocol 007 were followed for AGEs immediately following vaccination Visit 1. Active surveillance was implemented every 2 weeks during the rotavirus season by phone contacts or home visits with the parent/legal guardian. The rotavirus season for each study site was prospectively determined using historical epidemiologic data [53].

Surveillance for Health Care Encounters for Rotavirus Gastroenteritis

Active surveillance for healthcare encounters for rotavirus gastroenteritis was conducted at the same time as intussusception surveillance on Days 7, 14, and 42 after any vaccination and every 6 weeks thereafter up to 2 years.

4.3 Clinical Efficacy

4.3.1 Efficacy by Disease Severity

The primary efficacy hypothesis for both Protocol 006 (REST) and Protocol 007 was that RotaTeq™ would be efficacious against rotavirus disease caused by the G-serotypes (G1,

G2, G3, and G4) that occurred at least 14 days after the third vaccination. An analysis of the efficacy of RotaTeq™ against rotavirus gastroenteritis regardless of severity was performed based on subjects meeting the case definition who were not protocol violators. The results of these studies were comparable; as presented in Table 4-2 the integrated data from these studies showed the efficacy of RotaTeq™ against rotavirus gastroenteritis of any severity caused by the serotypes in the vaccine through the first rotavirus season postvaccination was 74% (95% CI: 67% ,79%).

The efficacy of RotaTeq™ against severe (clinical score >16) rotavirus gastroenteritis was also comparable between the Protocol 006 (REST) Efficacy Substudy and Protocol 007. An efficacy analysis based on the integrated data from the 2 studies showed that RotaTeq™ was 98% (95% CI: 90%, 100%) efficacious against severe rotavirus gastroenteritis caused by the serotypes in the vaccine through the first rotavirus season postvaccination. The results of these analyses are presented in Table 4-2.

The efficacy of the human-bovine rotavirus reassortants as demonstrated in all of the Phase II and Phase III efficacy studies was remarkably similar (i.e., 68 to 75% against any severity of G1, G2, G3, and G4 rotavirus gastroenteritis and 98 to 100% against severe disease). These results illustrate the consistency of the human-bovine rotavirus reassortants in the prevention of any severity of rotavirus gastroenteritis and severe disease. The efficacy of RotaTeq™ also compares well to the immunity provided by natural infection. A natural history study of wild-type rotavirus infection showed that 1, 2, and 3 rotavirus infections were 77%, 83%, and 92% efficacious against rotavirus diarrhea of any severity, respectively; and that 1 and 2 rotavirus infections were 87% and 100% efficacious against severe rotavirus diarrhea, respectively, which is similar to the efficacy of RotaTeq™ as demonstrated in the Phase II and Phase III studies [9].

Table 4-2

Per-Protocol† Efficacy Analyses by Disease Severity
(Protocol 006 [REST] and Protocol 007)

Disease Severity	Number of Cases		% Efficacy	95% CI
	Vaccine (N = 3,484)	Placebo (N = 3,499)		
Any	97	369	74	67, 79
Severe‡	1	57	98	90, 100

† Per-protocol population and per-protocol case definition (includes only cases that occurred at least 14 days after Dose 3).
‡ Severity Score >16.
N = Number of subjects vaccinated; CI = Confidence interval.

4.3.2 Intention-to-Treat Analyses

The per-protocol efficacy analyses that were completed in Protocol 006 (REST) and Protocol 007 were also repeated based on a modified intention-to-treat population, which is comprised of all vaccinated subjects. The results of these analyses were generally similar to the analyses that were based on the per-protocol population.

In addition, several intention-to-treat case definitions for rotavirus gastroenteritis were evaluated in the modified intention-to-treat population. One case definition is identical to the per-protocol case definition, except cases are counted starting with the day of the first vaccination instead of 14 days after the third vaccination. Using this case definition, the observed efficacy was 60% (95% CI: 52%, 67%) for Protocol 006 and 58% (95% CI : 34%, 75%) for Protocol 007.

Another intention-to-treat case definition considered as positive any case potentially satisfying the clinical and/or laboratory portions of the per-protocol case definition, and cases were evaluated starting at the time of the first vaccination. For example, a subject who met the clinical portion of the per-protocol case definition but did not submit a stool sample for EIA testing would be counted as a positive case of rotavirus gastroenteritis using the intention-to-treat case definition. The results of these very conservative analyses were: efficacy of 27% (95% CI: 18%, 34%) for Protocol 006 and 45% (95% CI: 24%, 61%) for Protocol 007.

4.3.3 Efficacy in Reducing Health Care Encounters for Rotavirus Gastroenteritis

The efficacy of RotaTeq™ in preventing health care encounters including hospitalizations, emergency department visits, and office visits for rotavirus gastroenteritis was evaluated in Protocol 006 (REST). Efficacy in reducing health care encounters was not analyzed in Protocol 007 because of the smaller sample size. The greatest contribution of RotaTeq™ to the public health of infants and young children in the United States will be the reduction in hospitalizations, emergency department visits,

and office visits for rotavirus gastroenteritis. In Protocol 006 (REST), there were 34,035 vaccine recipients and 34,003 placebo recipients who were evaluated for efficacy in preventing hospitalizations and emergency department visits. The results showed that RotaTeq™ reduced the rate of hospitalizations for rotavirus gastroenteritis by 96% (95% CI: 91%, 98%) and reduced the rate of emergency department visits for rotavirus gastroenteritis by 93% (95% CI: 88%, 96%), relative to placebo. These data are consistent with the clinical efficacy data, which showed that the efficacy of RotaTeq™ against severe rotavirus gastroenteritis, as determined by the clinical scoring system, was 98%. In the Efficacy Substudy of Protocol 006 (REST) (2,834 vaccine recipients and 2,839 placebo recipients), RotaTeq™ was shown to reduce non-urgent health care visits (i.e., physician office visits) for rotavirus gastroenteritis by 86% (95% CI: 74%, 93%). The results of these analyses are presented in Table 4-3.

RotaTeq™ was also associated with an overall reduction in care required for episodes of rotavirus gastroenteritis when they did occur, with only 16% of episodes requiring any type of healthcare contact among vaccine recipients compared with 40% among placebo recipients.

The per-protocol efficacy analyses for health care encounters were conducted based on a modified intention-to-treat population, which is comprised of all vaccinated subjects. The results of these analyses were comparable to the analyses based on the per-protocol population, with a 94% (95% CI: 88%, 97%) reduction in hospitalizations, a 93% (95% CI: 88%, 96%) reduction in emergency department visits, and an 87% (95% CI: 77%, 93%) reduction in office visits for rotavirus gastroenteritis.

Table 4-3

Per-Protocol† Analysis of Efficacy Against Hospital Admissions, Emergency Department Visits, and Non-Urgent Health Care Visits for Rotavirus Gastroenteritis (Protocol 006 [REST])

Type of Health Care Contact	Number of Cases		% Rate Reduction	95% CI
	Vaccine	Placebo		
Hospitalizations‡	6	144	96	91, 98
Emergency Department Visits‡	14	213	93	88, 96
Office Visits§	11	57	86	74, 93

† Per-protocol population and per-protocol case definition (includes only cases that occurred at least 14 days after Dose 3).

‡ N = 34,035 in the vaccine group and 34,003 in the placebo group.

§ N = 2,834 in the vaccine group and 2,839 in the placebo group.

CI = Confidence interval.

4.3.4 Efficacy by Serotype

Serotype-specific efficacy was evaluated in the Protocol 006 (REST) Efficacy Substudy and in all subjects in Protocol 007. The primary circulating serotype that caused rotavirus gastroenteritis among subjects in the studies was G1 followed by G2, G4, G3, and G9. Integrated data from the 2 Phase III efficacy studies showed that RotaTeq™ was efficacious (lower bound on the 95% CI of efficacy was >0%) against rotavirus gastroenteritis of any severity caused by serotypes G1 and G2. Although the data were limited for the other serotypes, the vaccine appeared to be efficacious against serotype G3 (3 vaccine/7 placebo cases), serotype G4 (3 vaccine/6 placebo cases) and serotype G9 (1 vaccine/4 placebo cases) for rotavirus gastroenteritis of any severity. The results of the efficacy analyses by rotavirus serotype are presented in Table 4-4.

Further data supporting serotype-specific efficacy of RotaTeq™ against G1, G2, G3, G4, and G9 come from the Protocol 006 (REST) analysis of efficacy in reducing hospitalizations and emergency department visits for rotavirus gastroenteritis. RotaTeq™ was efficacious (lower bound on the 95% CI of efficacy >0) against hospitalizations and emergency department visits for rotavirus gastroenteritis of serotypes G1 (16 vaccine/316 placebo cases), G3 (1 vaccine/15 placebo cases), G4 (2 vaccine/18 placebo cases), and G9 (0 vaccine/13 placebo cases), and appeared to be efficacious against rotavirus gastroenteritis of serotype G2 (1 vaccine/8 placebo cases). The efficacy estimates and associated 95% confidence intervals are provided in Table 4-5.

A VP4 (P) typing assay has recently been developed and validated. The P type of all G3, G4, and G9 cases included in the analyses were P1[8]. The P type of all G2 cases was P2[4]. The G9 efficacy results suggest that the P1 reassortant included in RotaTeq™ will provide protection against P1-containing G-serotypes not included in the vaccine.

Table 4-4

Analysis of Efficacy Against Any Severity of Rotavirus Gastroenteritis by Serotype in the Per-Protocol Population† Using the Per-Protocol Case Definition
(Protocol 006 [REST] and Protocol 007)

Serotype	Number of Cases		% Efficacy	95% CI
	Vaccine (N = 3,484)	Placebo (N = 3,499)		
G1	85	339	75	68, 81
G2	6	17	63	3, 88
G3	3	7	56	<0, 93
G4	3	6	48	<0, 92
G9	1	4	74	<0, 100

† Per-protocol population and per-protocol case definition (includes only cases that occurred at least 14 days after Dose 3).
N = Number of subjects vaccinated; CI = Confidence interval.

Table 4-5

Analysis of Efficacy by Serotype Against Hospitalizations and Emergency Department Visits for Rotavirus Gastroenteritis in the Per-Protocol Population[†] Using the Per-Protocol Case Definition
(Protocol 006 [REST])

Hospitalizations and Emergency Department Visits				
	Number of Cases			
Serotype	**Vaccine (N = 34,035)**	**Placebo (N = 34,003)**	**% Rate Reduction**	**95% CI**
G1	16	316	95	91, 97
G2	1	8	88	<0, 97
G3	1	15	93	49, 99
G4	2	18	89	52, 98
G9	0	13	100	40, 100

[†] Per-protocol population and per-protocol case definition (includes only cases that occurred at least 14 days after Dose 3).
N = Number of subjects vaccinated; CI = Confidence interval.

4.3.5 Efficacy Through the Second Rotavirus Season Postvaccination

The lengthy study duration of Protocol 006 (REST) provided the opportunity for a portion of the subjects in the Efficacy Substudy to be followed for a second full rotavirus season. The persistence of efficacy through a second rotavirus season is important because a large proportion (55 to 60%) of hospitalizations for rotavirus gastroenteritis occurs between ages 6 and 24 months [49]. Efficacy against rotavirus gastroenteritis of any severity caused by the serotypes in the vaccine occurring in the second season only was 63% (95% CI: 44%, 75%). Efficacy against severe rotavirus gastroenteritis was 88% (95% CI: 49%, 99%); there were 2 severe cases in the group that received RotaTeq™ as compared with 17 in the placebo group. These data demonstrate that the efficacy of RotaTeq™ against rotavirus gastroenteritis caused by the serotypes in the vaccine persists through the second rotavirus season postvaccination. The results of these analyses are presented in Table 4-6.

Table 4-6

Per-Protocol[†] Efficacy Analyses for the Second Rotavirus Season by Disease Severity (Protocol 006 [REST])

Disease Severity	Number of Cases		% Efficacy	95% CI
	Vaccine (N = 2,834)	Placebo (N = 2,839)		
Any	36	88	63	44, 76
Severe[‡]	2	17	88	49, 99

[†] Per-protocol population and per-protocol case definition (includes only cases that occurred at least 14 days after Dose 3).
[‡] Severity Score >16.
N = Number of subjects vaccinated; CI = Confidence interval.

4.3.6 Efficacy by Population

The large sample size of the Efficacy Substudy of Protocol 006 (REST) provided an opportunity to evaluate efficacy in several different populations of interest. Subjects were enrolled at study sites in the United States, Finland, and the Native American Nations to allow for an evaluation of RotaTeq™ in diverse populations and against a variety of rotavirus strains. Efficacy analyses were stratified by region of origin (United States, Native American Nations, and Finland), gender, race, and gestational age (=36 versus >36 weeks gestation). Efficacy analyses by gender and by race were also conducted in Protocol 007.

4.3.6.1 Efficacy by Region of Origin in Protocol 006 (REST) and Protocol 007

Subjects were enrolled in Protocol 006 (REST) at study sites in the United States, Finland, and the Native American Nations to allow for an evaluation of RotaTeq™ in diverse populations when administered on different dosing schedules.

Protocol 006 (REST) was designed for the first dose of RotaTeq™ to be administered at age 6 to 12 weeks with subsequent doses to follow at 4- to 10-week intervals. This regimen is compatible with 2-, 3-, 4-month and 2-, 4-, 6-month vaccination schedules. Study sites were permitted to follow the schedule routinely used for infant immunization. The efficacy of RotaTeq™ against rotavirus gastroenteritis of any severity caused by the serotypes in the vaccine was evaluated by region of origin, where subjects were vaccinated on different schedules. The results were generally similar between these groups. The efficacy of RotaTeq™ among subjects in Finland, where approximately 80% were vaccinated on a 2-, 3-, 4-month schedule, was 75% (95% CI: 66%, 81%). The efficacy of RotaTeq™ among subjects in the United States, where approximately 85% were vaccinated on a 2-, 4-, 6-month schedule, was 66% (95% CI: 17%, 88%). The efficacy of RotaTeq™ among subjects in the Native American Nations where subjects were vaccinated on both schedules was 77% (95% CI: 60%, 88%). The results of the 3 different populations demonstrate that RotaTeq™ will be efficacious in preventing rotavirus gastroenteritis among diverse populations in the industrialized world.

4.3.6.2 Efficacy by Race and Gender in Protocol 006 (REST)

The efficacy of RotaTeq™ against rotavirus gastroenteritis of any severity was evaluated by race and gender among subjects in Protocol 006 (REST) and Protocol 007. The efficacy analysis was stratified by race in the U.S. population only, given the homogeneity of the subjects in Finland (nearly 100% White) and the Native American Nations (100% Native American).

The efficacy among White subjects in Protocol 006 (REST) and Protocol 007 was comparable to that observed for the combined population. The efficacy among Black subjects and Hispanic-American subjects was difficult to evaluate because the number of rotavirus gastroenteritis cases within these racial groups was small; in these subjects, there were only 3 cases of rotavirus gastroenteritis reported, all in the placebo group. The efficacy of RotaTeq™ against rotavirus gastroenteritis of any severity was generally similar among males and females, respectively, in Protocol 006 (REST) (73% versus 75%) and Protocol 007 (72% versus 73%). RotaTeq™ also appeared to be efficacious against rotavirus gastroenteritis of any severity among each race evaluated in both studies.

4.3.6.3 Efficacy by Gestational Age in Protocol 006 (REST)

Premature infants have been known to exhibit suboptimal immune responses to licensed pediatric vaccines. Therefore, the efficacy of RotaTeq™ was also evaluated among a subset of subjects who were born prematurely in Protocol 006 (REST). The efficacy of RotaTeq™ against rotavirus gastroenteritis of any severity caused by the serotypes in the vaccine among 204 vaccinated infants born prematurely (=36 weeks gestation) was 70% (95% CI: -15%, 95%). There were 3 cases in the vaccine group and 10 cases in the

placebo group. There were only 2 cases of severe rotavirus gastroenteritis among these infants; both cases were in the placebo group. Although not statistically significant, the efficacy estimate is consistent with the efficacy demonstrated in full term infants and supports providing the vaccine to healthy infants born prematurely according to their chronological age.

4.3.7 Efficacy When Administered Concomitantly With Other Pediatric Vaccines in Protocol 006 (REST)

For Protocol 006 (REST), all subjects were permitted to receive licensed pediatric vaccines concomitantly (same day or within 42 days of vaccination) with RotaTeq™ or placebo. However, a subset of subjects (662 vaccine recipients and 696 placebo recipients) who participated in the U.S. Concomitant Use Substudy were required to receive pediatric vaccines that were provided by Merck, which included COMVAX™[2] (Haemophilus b conjugate [meningococcal protein conjugate] and hepatitis B [recombinant] vaccine), INFANRIX™ ([diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed], GlaxoSmithKline Biologicals), IPOL™ ([trivalent poliovirus vaccine inactivated], Aventis Pasteur), and PREVNAR™ (pneumococcal 7-valent conjugate vaccine [diphtheria CRM197 protein], Wyeth). These pediatric vaccines were to be administered on the same day as RotaTeq™ or placebo. An efficacy analysis was performed among the subjects enrolled in this substudy to confirm that the pediatric vaccines did not interfere with the efficacy of RotaTeq™. The efficacy was 90% with a 95% CI of (27%, 100%).

This analysis demonstrates that RotaTeq™ is efficacious against rotavirus gastroenteritis of any severity caused by the serotypes contained within the vaccine through the first rotavirus season postvaccination, when given concomitantly with routine childhood immunizations.

4.3.8 Efficacy in Breastfed Infants in Protocol 006 (REST)

There is a theoretical concern that maternal antibodies against rotavirus acquired from breast milk may interfere with an infant's immune response to a rotavirus vaccine. Therefore, the efficacy of RotaTeq™ was evaluated according to breast-feeding status at the time of vaccination. Efficacy was evaluated for 3 groups: 1) infants who were never breastfed, 2) infants who had some breast-feeding, and 3) infants who were exclusively breastfed. The results of these analyses are presented in Table 4-7 and show that breast-feeding does not appear to interfere with immune responses to RotaTeq™.

[2] COMVAX is a trademark of Merck & Co., Inc., Whitehouse Station, New Jersey, U.S.A.

Table 4-7

Per-Protocol† Efficacy Analyses by Breast-Feeding Status
(Protocol 006 [REST])

Breast-Feeding Status	Number of Cases/Number Vaccinated			
	Vaccine	Placebo	% Efficacy	95% CI
Never	19 / 817	60 / 815	68	46, 82
Some	24 / 947	133 / 953	82	72, 89
Exclusive	39 / 799	122 / 767	68	54, 78

† Per-protocol population and per-protocol case definition (includes only cases that occurred at least 14 days after Dose 3).
CI = Confidence interval.

4.4 Summary of Efficacy

The primary efficacy objective of the clinical development program for RotaTeq™ was to demonstrate that a 3-dose regimen would be efficacious against rotavirus disease caused by the serotypes included in the vaccine (G1, G2, G3, or G4) occurring at least 14 days following the third dose. Among healthy infants, 6 to 12 weeks of age at enrollment, who received RotaTeq™ or placebo in the 2 Phase III studies (Protocol 006 (REST) and Protocol 007), the following efficacy conclusions can be drawn regarding the primary efficacy objective as well as the additional objectives that were discussed throughout Section 4:

1. The vaccine is efficacious against rotavirus gastroenteritis of any severity, which is caused by the serotypes contained within the vaccine (G1, G2, G3, and G4) that occurs through the first rotavirus season postvaccination.
2. Vaccine efficacy persists through the second rotavirus season postvaccination.
3. The vaccine is efficacious against severe rotavirus disease, which is caused by the serotypes contained within the vaccine (G1, G2, G3, and G4) that occurs through the first and second rotavirus seasons postvaccination.
4. The vaccine reduces the rate of health care encounters, including hospitalizations, emergency department visits, and non-urgent (i.e., physician office visits) for rotavirus gastroenteritis relative to placebo.
5. Through the first rotavirus season postvaccination, the vaccine is efficacious against rotavirus gastroenteritis caused by each of the serotypes in the vaccine,

including G1, G2, G3, and G4. In addition, the vaccine is efficacious against rotavirus gastroenteritis caused by G9 serotypes containing P1, and will be efficacious against other P1-containing strains not included in the vaccine.

6. The vaccine is efficacious when administered on 2-, 3-, 4-month and 2-, 4-, 6-month vaccination schedules in different geographic regions.
7. In premature infants (gestational age =36 weeks), the vaccine appears efficacious against rotavirus gastroenteritis of any severity.

5. Clinical Immunogenicity

As previously discussed, no definitive immunologic correlate of efficacy has been identified in studies of wild-type rotavirus infection and rotavirus vaccine studies, including Merck's Phase II and Phase III clinical trials of RotaTeq™ and its predecessors. Therefore, efficacy and not immunogenicity studies have been the primary means for confirming the dose and the basis for including the P1 serotype in the vaccine. Immunogenicity measurements have been used primarily for comparisons in demonstrating the consistency of the manufacturing process and in evaluating the concomitant use of RotaTeq™ and other childhood vaccines.

5.1 Overview of Phase III Immunogenicity Studies

The immunogenicity of RotaTeq™ was evaluated in subsets of subjects from the Phase III studies, Protocol 006 (REST) and Protocol 007, and in all subjects from Protocol 009 in order to: 1) Evaluate the immunogenicity of RotaTeq™, including observational comparisons of immunogenicity results with those from Phase II studies, 2) Clinically demonstrate the consistency of the manufacturing process, and 3) Evaluate antibody responses to licensed pediatric vaccines when administered concomitantly with RotaTeq™. This section first describes the assessment of the immunogenicity of RotaTeq™ in the Phase III clinical trials followed by the results of the U.S. Concomitant Use Substudy in Protocol 006 (REST).

5.2 Selection of Assays for Assessing the Immunogenicity of RotaTeq™

The assays selected for the immunogenicity evaluation of RotaTeq™ measure serum neutralizing antibody (SNA) to the G- and P-types in the vaccine including G1, G2, G3, G4, and P1 and serum anti-rotavirus IgA. These assays were selected because, although not confirmed, individual studies of naturally-occurring rotavirus infection have suggested that serum anti-rotavirus IgA and G-serotype-specific neutralizing antibody titers appear to correlate with efficacy [13; 15]. SNA titers to G6 and P7[5], the bovine rotavirus surface proteins, were also evaluated. Because no seroprotection or seroconversion criteria have been established, the antibody responses to RotaTeq™ in the Phase III clinical trials have been summarized by Postdose 3 titers and fold rise in titers between Predose 1 and Postdose 3 A 3-fold rise in titer was considered to be a significant immune response because validation experiments have shown that these assays are sensitive enough to detect a 3-fold difference with 90% power [54; 55; 56; 57]. A summary of assays to evaluate the immunogenicity of RotaTeq™ is provided in Table 5-1.

Antibody responses to RotaTeq™ were assessed in a subset of subjects in Protocol 006 (REST) who were part of the Efficacy Substudy. Immunogenicity was also assessed among subjects in Taiwan to meet a regulatory requirement for licensure in that country. Serum was collected before the first dose and either 14 or 42 days after the third dose.

Table 5-1

Summary of Assays to Evaluate the Immunogenicity of RotaTeq™
by Protocol and the Timing of Specimen Collection
(Protocol 006 [REST], Protocol 007, and Protocol 009)

Specimen	Protocol 006 (REST)	Protocol 007	Protocol 009
Predose 1	(1) SNA to G1, G2, G3, G4, P1, G6, and P7[5] (2) Serum anti-rotavirus IgA	(1) SNA to G1, G2, G3, G4, P1, G6, and P7[5] (2) Serum anti-rotavirus IgA	SNA to G1, G2, G3, G4, and P1
Postdose 3	(1) SNA to G1, G2, G3, G4, P1, G6, and P7[5] (2) Serum anti-rotavirus IgA	(1) SNA to G1, G2, G3, G4, P1, G6, and P7[5] (2) Serum anti-rotavirus IgA	(1) SNA to G1, G2, G3, G4, P1 (2) Serum anti-rotavirus IgA

SNA = Serum neutralizing assay.

5.3 Immunogenicity of RotaTeq™

RotaTeq™ was immunogenic as demonstrated by the SNA responses to G1, G2, G3, G4, and P1 and by anti-rotavirus IgA. The magnitude of the Postdose 3 SNA geometric mean titers (GMTs) varied with potency. The pattern of SNA responses was generally similar to what had been observed in the Phase II studies. Across all 3 Phase III studies and across the different populations evaluated in Protocol 006 (REST), the Postdose 3 GMTs of the SNA responses to G1, G4, and P1, and the anti-rotavirus IgA responses were moderate to high, with lower GMTs for G2 and G3. The low G2 and G3 SNA responses stand in contrast to the G2- and G3-specific efficacy data as discussed in Section 4.3.4. Table 5-2 presents the results of the Postdose 3 GMTs of the SNA response to G1, G2, G3, G4, and P1 and anti-rotavirus IgA for the different populations in Protocol 006 (REST). The proportion of infants with =3-fold rises in anti-rotavirus IgA from baseline to Postdose 3 was high (consistently >90%) across the Phase III studies and across the different populations evaluated in Protocol 006 (REST).

Table 5-2

Immunogenicity Summary for SNA Responses to G1, G2, G3, G4, P1, and Anti-Rotavirus IgA Among Subjects by Region of Origin
(Protocol 006 [REST])

SNA (dilution units)	Postdose 3 GMT			
	Finland (n = 119†)	US Concomitant Use (n = 90†)	Native American Nations (n = 122†)	Taiwan (n = 49†)
G1	272.7 (220,338)	277.7 (199,387)	471.9 (380,587)	336.7 (235,483)
G2	33.9 (28,42)	27.1 (18,42)	26.2 (19,36)	14.9 (10,21)
G3	19.4 (16,24)	18.5 (13,26)	22.9 (17,30)	18.9 (14,26)
G4	80.7 (67,98)	85.5 (61,121)	88.5 (65,120)	70.9 (51,99)
P1	137.9 (111,172)	117.6 (82,169)	194.9 (144,265)	93.9 (65,137)
Anti-rotavirus IgA (units/mL)	522.9 (425,644)	376.8 (301,472)	397.2 (323,488)	305.6 (185,504)

† The number (n) provided is for G1 assay; the "n" may vary slightly for the other assays.

GMT = Geometric mean titer; SNA = Serum neutralizing antibody.

5.4 Demonstration of Consistency of the Manufacturing Process (Protocol 009)

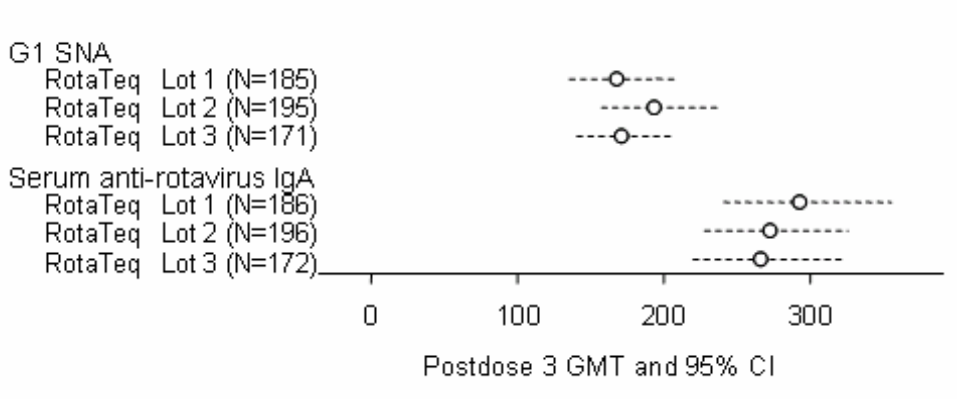
Protocol 009 was designed to clinically demonstrate the consistency of the manufacturing process for RotaTeq™. This was a randomized, double-blind, placebo-controlled study conducted with 793 vaccinated healthy subjects in the United States. Eligible subjects were randomized to RotaTeq™ (Lot 1), RotaTeq™ (Lot 2), RotaTeq™ (Lot 3), or placebo in a ratio of 2:2:2:1.

The primary immunogenicity objective was to demonstrate consistency in the antibody responses to 3 manufactured lots of RotaTeq™ based on SNA Postdose 3 GMTs against rotavirus serotypes G1, G2, G3, G4, and P1. The study showed that the 3 manufactured lots of RotaTeq™ elicited consistent SNA Postdose 3 responses against rotavirus serotypes G1, G2, G3, G4, and P1. The results are presented in Figure 5-1 for G1 and Figure 5-2 for G2, G3, G4, and P1.

.

Figure 5-1

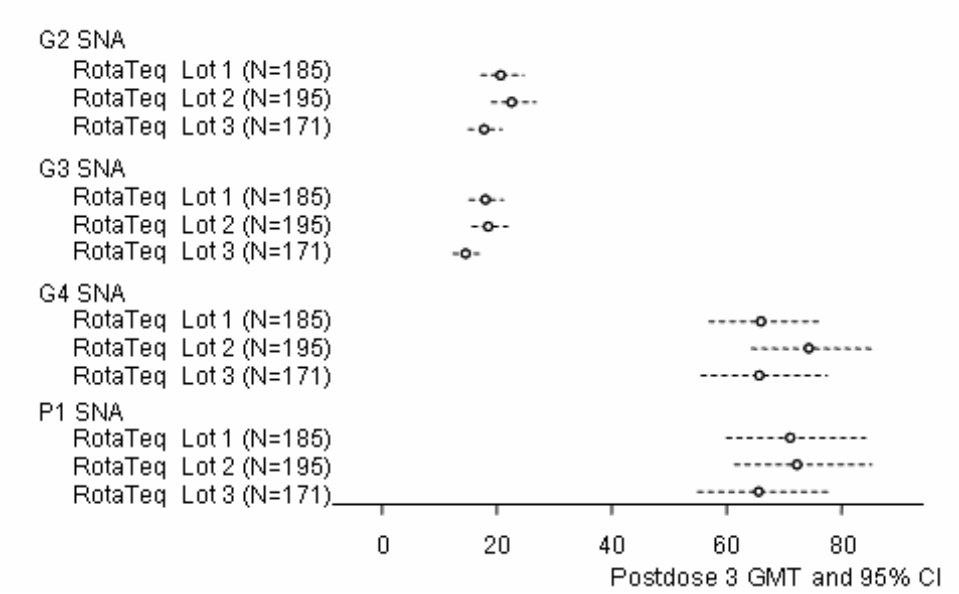
Postdose 3 Geometric Mean Titers and 95% Confidence Intervals for SNA Response to G1 and Serum Anti-Rotavirus IgA
(Protocol 009)



GMT = Geometric mean titer; SNA = Serum neutralizing antibody; CI = Confidence interval.

Figure 5-2

Postdose 3 Geometric Mean Titers and 95% Confidence Intervals for SNA Response to G2, G3, G4, and P1
(Protocol 009)



GMT = Geometric mean titer; SNA = Serum neutralizing antibody; CI = Confidence interval.

5.5 Assessment for an Immunologic Surrogate of Efficacy in the Phase II and Phase III Clinical Trials

Studies of wild-type rotavirus infection have identified several potential immunological parameters that appear to correlate with protection against subsequent episodes of rotavirus gastroenteritis including serum and fecal anti-rotavirus IgA, anti-rotavirus IgG, and G1 serotype-specific neutralizing antibody [13; 15]. In the Phase II study, Protocol 002, an attempt to identify an immunologic correlate of efficacy associated with vaccination was unsuccessful. In the Phase II dose-ranging efficacy study, Protocol 005, several immunological measures were shown to have a statistically significant relationship with rotavirus case status, with notable exceptions being serum and fecal anti-rotavirus IgA. When all of the measures were considered collectively, the optimal titer level cut point that correlated with the presence or absence of a rotavirus gastroenteritis case was a Postdose 3 G1 titer level of 51.0 dilution units. Infants with a Postdose 3 G1 SNA titer =51.0 dilution units had a 4.5-times higher chance of having rotavirus gastroenteritis than infants with a G1 SNA titer >51.0 dilution units. This finding was of particular interest in light of the results from a longitudinal study of children in a day care center showing that G1 SNA titers correlate with protection against

subsequent episodes of rotavirus gastroenteritis [15]. However, the sensitivity and specificity of the 51.0 titer was low (approximately 70% for both) with respect to declaring a specific endpoint. Also, in Protocol 005, the Postdose 3 G1 SNA titers apparently did not correlate with disease severity. Another limitation of the study was a lack of serotype diversity among rotavirus gastroenteritis cases (i.e., the majority of cases were G1 serotype). An assessment of the correlation between efficacy and immunogenicity in the Phase III studies has recently been completed. The investigation demonstrated that increased Postdose 3 G1 SNA titers do correlate with decreased odds of contracting rotavirus gastroenteritis. However, a titer that has both an acceptable level of sensitivity and specificity for predicting protection against rotavirus disease was not identified.

5.6 Immunogenicity of Concomitant Vaccines When Administered With RotaTeq™

As previously mentioned, all subjects were permitted to receive licensed pediatric vaccines concomitantly (same day or within 42 days of vaccination) with RotaTeq™ or placebo in Protocol 006 (REST). However, a subset of subjects (662 vaccine recipients and 696 placebo recipients) who participated in the U.S. Concomitant Use Substudy received prespecified pediatric vaccines, which included COMVAX™, INFANRIX™, IPOL™, and PREVNAR™ for a formal evaluation of concomitant use of RotaTeq™ and these vaccines. The immunogenicity of INFANRIX™, COMVAX™, IPOL™, and PREVNAR™ when administered with RotaTeq™ was evaluated in this subset of subjects.

Responses to diphtheria, tetanus, pertussis, and pneumococcal conjugate vaccine were measured after 3 doses at approximately age 7 to 8 months; responses to Hib, hepatitis B, and polio were measured after 2 doses at approximately age 5 to 6 months. Subjects were required to have received a neonatal dose of hepatitis B vaccine. The antibody responses to these vaccines were compared between recipients of RotaTeq™ and placebo recipients with noninferiority criteria based on: 1) the proportion of subjects achieving the standard seroprotection criteria established for poliovirus types 1, 2, and 3, hepatitis B, *Haemophilus influenzae* type b (as measured by polyribosyl ribitol phosphate [PRP], the primary polysaccharide component of the capsule of *Haemophilus influenzae* type b), diphtheria, and tetanus; and 2) the GMTs to pertussis toxin (PT), pertussis filamentous hemagglutinin (FHA), and pertussis pertactin and to pneumococcal serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F.

The statistical criteria for declaring similarity of immune responses between the 2 treatment groups (RotaTeq™ versus placebo) was that the 95% CI on the difference in proportions of subjects who achieved seroprotection/seroconversion (RotaTeq™ minus placebo) must exclude a decrease of 10 percentage points or more, for poliovirus types 1, 2, and 3, hepatitis B, *Haemophilus influenzae* type b, diphtheria, and tetanus antibody responses, and that the 95% CI on the ratio of GMTs (RotaTeq™ ÷ placebo) must exclude a decrease in 2-fold or more, for pertussis PT, pertussis FHA, pertussis pertactin, and for pneumococcal serotypes 4, 6B, 9V, 14, 18C, 19F, 23F responses.

The statistical criteria for demonstrating that the antibody responses to the concomitant vaccines were similar among recipients of RotaTeq™ as compared with placebo recipients were met for 16 of 17 antigens in the prespecified concomitant vaccines. The only exception was the pertussis pertactin antibody response for which the Postdose 3 GMT was 34.8 ELISA units/mL for subjects who received RotaTeq™ with the concomitant vaccines compared with 59.2 ELISA units/mL for subjects who received placebo with the concomitant vaccines (95% CI on the ratio of RotaTeq™ to placebo: 0.4 to 0.8).

The low pertactin responses suggest that there may be some immunologic interference between RotaTeq™ and the pertactin component of INFANRIX®. However, no interference was seen between RotaTeq™ and the pertussis toxin and pertussis filamentous hemagglutinin responses as these were similar among subjects who received RotaTeq™ and subjects who received placebo. The clinical implications of lower pertactin responses are unclear because no definitive immunologic correlate of protection against rotavirus has been identified. Although pertactin responses were lower among subjects who received RotaTeq™ with the concomitant vaccines as compared with subjects who received placebo with the concomitant vaccines, the differences were modest and the GMTs indicate pertussis vaccine activity. Some studies suggest that the pertactin component of multicomponent pertussis vaccines may contribute to the overall protection against pertussis; however, other studies have demonstrated that pertussis toxoid alone is efficacious in preventing pertussis and that immunoglobulin G (IgG) to pertussis toxoid may correlate with protection [76; 77; 78]. Thus, based on an overall evaluation of the immunogenicity responses to the pertussis antigens, and studies demonstrating the efficacy of one-component and two-component pertussis vaccines, it is highly likely that children receiving RotaTeq™ and pertussis-containing vaccines concomitantly would be protected against pertussis similarly to children receiving pertussis-containing vaccines without concomitant administration of RotaTeq™. This conclusion appears to be supported by safety data from the Phase III studies of RotaTeq™. Sixteen (16) serious adverse experiences of pertussis were reported, 6 in the group that received RotaTeq™ and 10 in the placebo group. Among these, 10 subjects also received a pertussis-containing vaccine, 5 in the group that received RotaTeq™ and 5 in the placebo group. Among the 6 subjects who did not receive a pertussis-containing vaccine with RotaTeq™ or placebo, 1 case of pertussis occurred in the group that received RotaTeq™ and 5 cases occurred in the placebo group. These limited data suggest that concomitant administration of RotaTeq™ and a pertussis-containing vaccine would not increase the likelihood of acquiring pertussis disease.

The responses to the antigens evaluated for each of the vaccines among the infants who received RotaTeq™ concomitantly with these vaccines as compared with the infants who received placebo concomitantly with these vaccines are displayed in Figure 5-3 (for diphtheria, tetanus, Hep B, Hib, and polio), Figure 5-4 (for pertussis toxoid, pertussis FHA, pertussis Pertactin), and Figure 5-5 (for pneumococcal conjugate vaccine).

Figure 5-3

Immunogenicity of Licensed Vaccines When Administered Concomitantly With RotaTeq™ Versus Placebo (Diphtheria, Tetanus, Hep B, Hib, and Polio)
(Protocol 006 [REST] U.S. Concomitant Use Substudy)

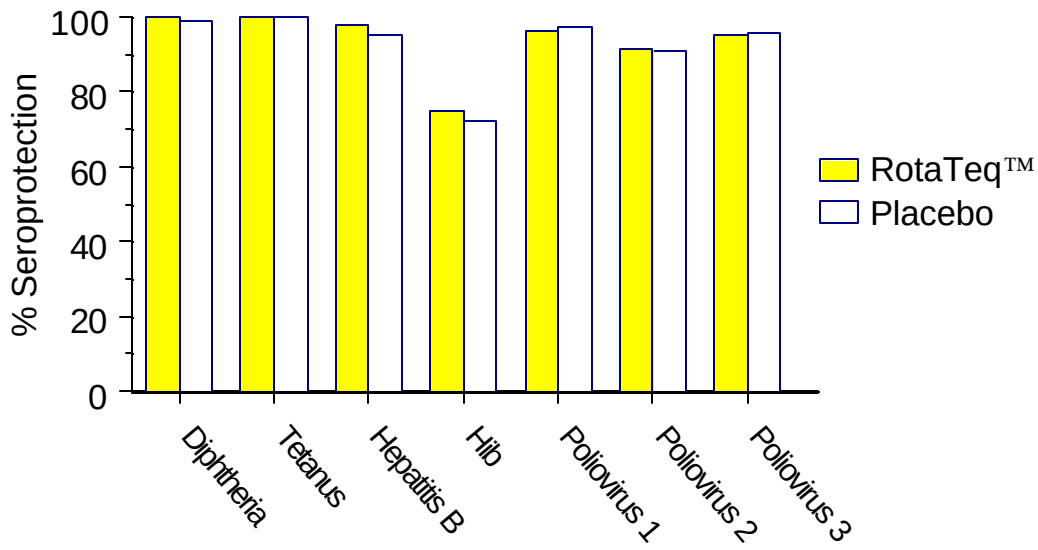
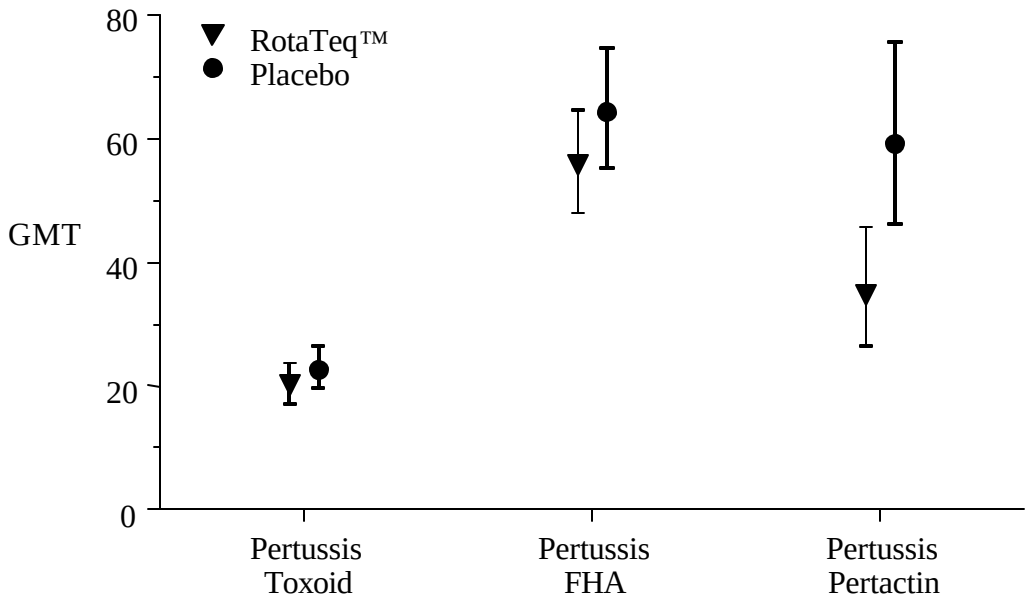


Figure 5-4

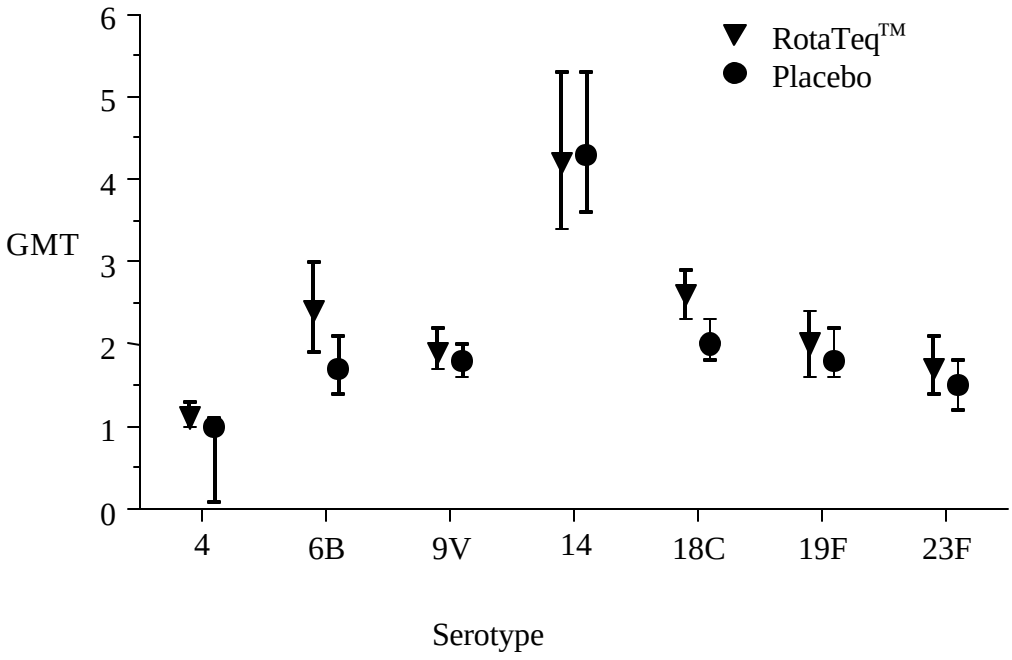
Immunogenicity of Licensed Vaccines When Administered Concomitantly With RotaTeq™ Versus Placebo (Pertussis Toxoid, Pertussis FHA, Pertussis Pertactin)
(Protocol 006 [REST] U.S. Concomitant Use Substudy)



GMT = Geometric mean titers.
FHA = Filamentous hemagglutinin.

Figure 5-5

Immunogenicity of Licensed Vaccines When Administered Concomitantly With RotaTeq™ Versus Placebo (Pneumococcal Conjugate Vaccine)
(Protocol 006 [REST] U.S. Concomitant Use Substudy)



GMT = Geometric Mean Titers.

5.7 Conclusions Regarding Immunogenicity

In summary, RotaTeq™ is generally immunogenic overall; however, antibody responses do not correlate with immunity. Because of a high attack rate of rotavirus, it has been possible to assign vaccine dose (virus titer or potency) using efficacy studies. The continued search for an immunologic correlate is important, because a correlate would be useful for bridging studies (e.g., evaluating RotaTeq™ between different populations or for changes in manufacturing processes).

RotaTeq™ may be administered concomitantly with the licensed pediatric vaccines that were evaluated in the Protocol 006 (REST) U.S. Concomitant Use Substudy. Although the responses to pertactin were lower in the group receiving RotaTeq™ than the placebo group, pertactin antibodies were made and there was no interference with the other pertussis antigens, suggesting that children receiving RotaTeq™ would be protected against pertussis similar to children not receiving RotaTeq™.

6. Clinical Safety

Subjects enrolled in the Phase III studies (Protocol 006 [REST], Protocol 007, and Protocol 009) were evaluated for safety in a similar manner in each study. Safety evaluations consisted of: (1) surveillance for intussusception; (2) monitoring for serious clinical adverse experiences (SAEs); (3) monitoring for clinical adverse experiences and adverse experiences of special clinical interest; and (4) fecal shedding of vaccine-virus strains.

This section summarizes the safety data for RotaTeq™ from the 3 randomized, placebo-controlled Phase III studies. A brief overview of the safety data from the Phase I/II studies is also provided. These studies have demonstrated that RotaTeq™ is generally well tolerated with regard to all adverse experiences, including intussusception. RotaTeq™ is also well tolerated when administered concomitantly with licensed pediatric vaccines. Fecal shedding of vaccine strains is uncommon.

6.1 Overview of Safety in Phase I/II Studies

Several formulations and reassortant compositions of the human-bovine reassortant rotavirus vaccine were administered to 2,470 infants and 30 adults in 5 Phase I/II studies. The vaccines were generally well tolerated in all of the studies with comparable proportions of subjects with diarrhea, fever, behavioral changes (irritability), and vomiting among vaccine recipients as compared with placebo recipients during the 7-day or 42-day period after each dose. There was a single case of intussusception reported in a Phase II study. Details about this case are provided in Section 6.3.

6.2 Overview of Safety in Phase III Studies Including Populations Studied and Extent of Exposure

The vaccine, RotaTeq™, evaluated in the Phase III studies (Protocol 006 [REST], Protocol 007, and Protocol 009), is the final formulation and dose intended for licensure. RotaTeq™ was generally well tolerated in all Phase III studies with regard to all adverse experiences of special clinical interest including intussusception.

Healthy infants 6 to 12 weeks of age were eligible for enrollment. Three (3) doses of RotaTeq™ were to be given at 4- to 10-week intervals (including 2-, 4-, 6-month, 2-, 3-, 4-month, and 2-, 3-, 5-month schedules). Infants born prematurely (gestational age =36 weeks) were eligible for enrollment according to their chronological age if they were healthy. There were no restrictions on breast-feeding or on the prior or concomitant use of licensed vaccines except for oral poliovirus vaccine. Infants who had pre-existing congenital abdominal disorders, intussusception, or abdominal surgery were excluded from the studies as were infants who were immunocompromised or had immunocompromised household members.

Overall, 71,942 subjects were randomized and 71,799 subjects were vaccinated in the 3 Phase III studies (Protocol 006 [REST], Protocol 007, and Protocol 009) with 36,203 subjects receiving RotaTeq™ and 35,596 subjects receiving placebo. Figure 6-1 displays an accounting of all subjects in the Large-Scale Study including subjects who contributed to the Detailed Safety Substudy which is discussed further in Section 6.5. The actual age range of infants at receipt of the first dose of RotaTeq™ or placebo was 3 to 14 weeks, but the vast majority of subjects received the first dose at age 6 to 12 weeks, which is compatible with the recommended age at first dose for routine immunization schedules. The gender distribution was comparable to that of the general population; 50.8% of recipients of RotaTeq™ and 50.7% of placebo recipients were male. Most infants in the study were White (68.8% of vaccine recipients and 69.0% of placebo recipients). Others were Hispanic-American (14.4%), Black (8.2%), Multiracial (5.2%), Asian (1.5%), and Native-American (1.5%); the racial distribution was comparable among the placebo recipients. Table 6-1 provides a summary of subject demographics for the 3 Phase III studies.

Figure 6-1

Accounting of Subjects Contributing to the Large-Scale Study and the Detailed Safety Substudy

(Protocol 006 [REST], Protocol 007 and Protocol 009)

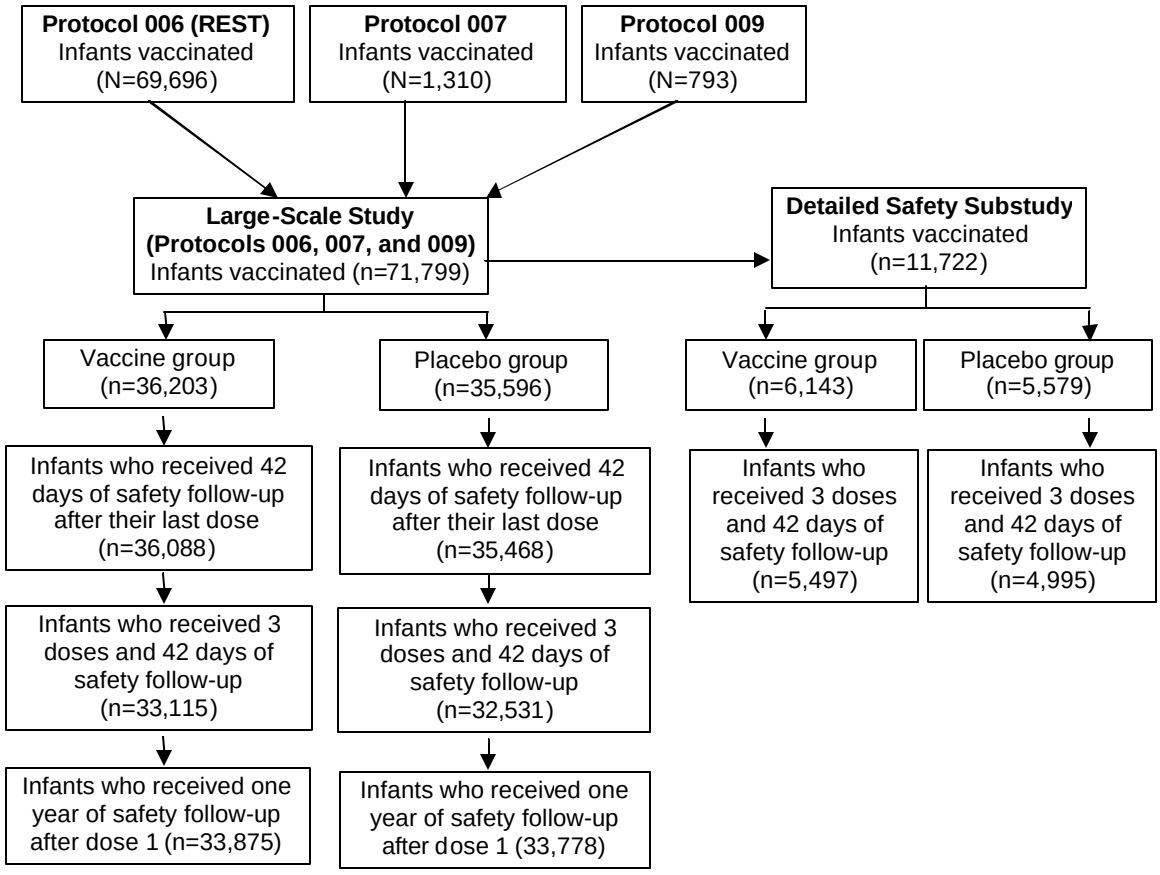


Table 6-1

Summary of Subject Demographics Among Subjects in the Phase III Studies
(Protocol 006 [REST], Protocol 007, and Protocol 009)

	RotaTeq™	Placebo
Randomized (N):	36271	35671
	n (%)	n (%)
Gender		
Male	18441 (50.8)	18083 (50.7)
Female	17830 (49.2)	17588 (49.3)
Age (weeks)		
5 And Under	1 (0.0)	1 (0.0)
6 to 12	36172 (99.7)	35568 (99.7)
Over 12	98 (0.3)	102 (0.3)
Mean	9.8	9.8
SD	1.41	1.42
Median	10.0	10.0
Range	3 to 14	4 to 16
Male	3 to 13	6 to 13
Female	6 to 14	4 to 16
Race		
White	23772 (68.6)	24624 (69.0)
Hispanic American	4963 (14.3)	5025 (14.1)
Black	2990 (8.2)	2985 (8.4)
Multiracial	1873 (5.2)	1849 (5.2)
Asian	553 (1.5)	561 (1.6)
Native American	534 (1.5)	515 (1.5)
Other	138 (0.4)	112 (0.3)

Calculation of percentage: The number of subjects in a given category divided by the number of subjects randomized.
N = Number of subjects randomized; n = Number of subjects in a given category; AN = Allocation number; SD = Standard deviation.

6.3 Safety With Respect to Intussusception

The evaluation of RotaTeq™ with regard to intussusception was the primary safety hypothesis for Protocol 006 (REST). While these data were also actively collected for all subjects enrolled in Protocol 007 and Protocol 009, there was no formal hypothesis regarding RotaTeq™ and intussusception in either of those studies. No cases of intussusception were reported in Protocol 007 or Protocol 009.

The primary safety hypothesis for Protocol 006 (REST) was that RotaTeq™ would not increase the risk of intussusception relative to placebo within 42 days after any vaccination. To satisfy the hypothesis, 2 statistical criteria had to be met: 1) During the study, the vaccine to placebo case ratio must not reach a predefined stopping boundary indicating a statistically significant increase in the risk of intussusception among vaccine recipients for the 1- to 7-day or 1- to 42-day periods after any dose; and 2) At the end of the study, the upper bound (UB) on the 95% CI of the relative risk (RR) of intussusception among vaccine recipients as compared with placebo recipients during the 42-day period following vaccination must be =10. The criterion for declaring safety at

the end of the study (UB on the 95% CI =10) was selected because it encompasses vaccine/placebo case ratios with point estimates of intussusception relative risk <2, based on the total number of cases expected. Such a criterion for an uncommon event is considered to be clinically acceptable.

The primary safety hypothesis was based on the 42-day period after any vaccination to encompass the time frame during which vaccine-related intussusception may occur. The pathogenesis of intussusception is unknown. Some experts believe it is associated with viral replication in the gut followed by release of inflammatory mediators, which affect motility; in which case, intussusception might be expected to occur within a week after vaccination [58; 59]. Others believe that it is caused by lymphadenopathy, which mechanically triggers intussusception; in which case, intussusception might be expected to occur several weeks after vaccination [60; 61; 62]. The 42-day window of safety follow-up with the interim safety monitoring during the 7-day window after each dose covered both of these possibilities.

CBER and the Vaccine and Related Biologics Product Approval Committee (VRBPAC) approved the study design of Protocol 006 (REST) including the statistical criteria for demonstrating clinical safety with regard to intussusception on May 12th, 2000.

6.3.1 Important Features of Study Design With Respect to Intussusception

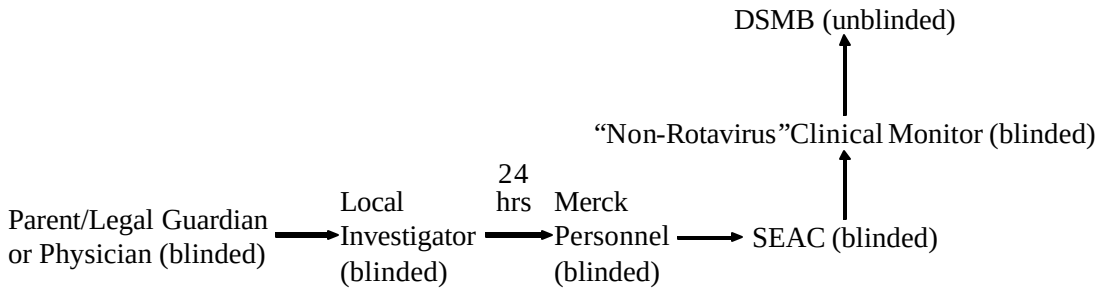
Surveillance System

All subjects in the 3 Phase III studies (Protocol 006 [REST], Protocol 007, and Protocol 009) were actively followed for intussusception for a minimum of 42 days following any vaccination. In Protocol 006 (REST), additional active safety surveillance for intussusception was conducted every 6 weeks from Day 43 Postdose 3 to Day 365 (from Dose 1) or until the study site's end-of-study date, whichever came first. In Protocol 007, potential cases of intussusception occurring after 42 days Postdose 3 were to be reported as serious adverse experiences until the end of the study. However, active surveillance for intussusception was not conducted during this time. For Protocol 009, subjects were considered to have completed the study with the 42-day Postdose 3 follow-up.

Investigators or study personnel were required to report all cases for which the diagnosis of intussusception was suspected at any time during the diagnostic work-up, whether or not the final diagnosis was intussusception. Merck personnel obtained relevant medical records from the study site concerning the details of the case and reported it to a blinded Safety Endpoint Adjudication Committee (SEAC) promptly. A blinded Merck Clinical Monitor, not otherwise associated with the Phase III clinical development program of RotaTeq™, simultaneously alerted an independent Data and Safety Monitoring Board (DSMB) that a potential case of intussusception had occurred. The same SEAC and DSMB were used for all Phase III studies and are described in further detail in the next 2 sections. An overview of the reporting process for a potential case of intussusception is displayed in Figure 6-2.

Figure 6-2

Reporting Process for Potential Cases of Intussusception



SEAC = Safety Endpoint Adjudication Committee.
DSMB = Data and Safety Monitoring Board.
Note: For the parent/legal guardian, investigator, and Merck personnel, blinding refers to treatment arm assignment and the final adjudication results. For the SEAC and the Non-Rotavirus Clinical Monitor, blinding refers to treatment arm assignment.

Adjudication Procedure and Case Definition

An independent, blinded SEAC adjudicated all potential cases of intussusception based on a prespecified case definition, which called for a radiographic, surgical, or autopsy diagnosis. The case definition was identical to that later developed by the Brighton Collaboration Intussusception Working Group (Level 1 of Diagnostic Certainty) with one difference: the Brighton Collaboration case definition calls for confirmation of an ultrasound diagnosis of intussusception by demonstrating resolution of ultrasound findings after intussusception reduction; whereas, an ultrasound diagnosis of intussusception was accepted to define cases in Protocol 006 (REST) without this confirmation [63]. Cases diagnosed by ultrasound alone were permitted to avoid missing cases that may have spontaneously reduced. All positively-adjudicated (confirmed) intussusception cases were communicated to a separate DSMB.

Data and Safety Monitoring Board

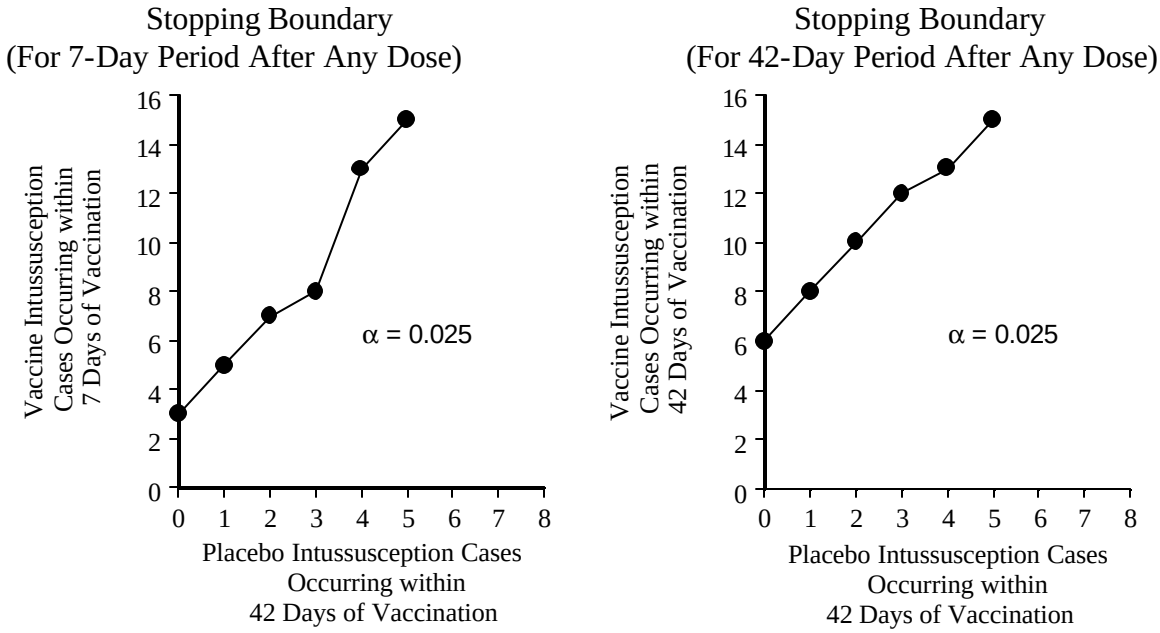
Another independent committee, the DSMB, had 2 important roles in the study. The first was to unblind the treatment arm of positively-adjudicated cases of intussusception as they occurred to make recommendations regarding the ongoing conduct of the study. Graphs with predefined stopping boundaries that defined a statistically significant increase (lower bound of the 95% CI on the RR of intussusception >1.0) were provided as guides to be used along with their clinical judgment when making recommendations regarding the study. These stopping boundaries were designed such that the study would be stopped early if the relative risk of intussusception in any of 2 overlapping day ranges (1 to 7 days and 1 to 42 days after any vaccination) was statistically significantly

increased among vaccine recipients versus placebo recipients. Cases that occurred among the recipients of RotaTeq™ in either day range were compared with cases that occurred among recipients of placebo during the 1 to 42 days postvaccination period and appropriate statistical adjustments were made to account for differential amounts of follow-up between the 2 groups. The 1 to 7 days postvaccination range was selected because it included the time frame of the highest risk of intussusception reported to be associated with RRV-TV (Wyeth-Lederle). Figure 6-3 presents the graphs with the stopping boundaries for cases occurring Days 1 to 7 postdose and Days 1 to 42 postdose, respectively.

The DSMB also made recommendations regarding completion of enrollment in Protocol 006 (REST) based on whether the criteria associated with the primary safety hypothesis had been met. The study employed a group-sequential design, which called for a minimum enrollment of 60,000 subjects, with additional enrollment of groups of 10,000 infants if the statistical criteria for the primary safety hypothesis were not met, to a maximum enrollment of 100,000 subjects. After the enrollment of 70,000 subjects, the DSMB recommended to the blinded Merck Senior Management Committee that enrollment in the study could be stopped and that the study had satisfied the criteria for the primary safety hypothesis with respect to intussusception.

Figure 6-3

Critical Boundary for Stopping Study for Safety Concerns



6.3.2 Safety Results With Respect to Intussusception

Phase II Studies

There was 1 investigator-diagnosed case of intussusception in a Phase II study, Protocol 005, a dose-ranging study that evaluated 5 different doses or compositions of vaccine compared with a single placebo arm. The case occurred in a 7-month-old male 9 days after the first dose of low-potency pentavalent vaccine. Surgical therapy was required, the subject fully recovered, and received Doses 2 and 3. (This case occurred before the reports of an association between RRV-TV [Wyeth-Lederle] and intussusception). No vaccine-virus strains were identified in stool samples collected 3 days after Dose 1 (as part of the routine study procedures) and again at the time of intussusception diagnosis. This case is the only intussusception case that occurred among the 2,470 infants who received active vaccine in the Phase I/II studies, resulting in a an observed rate of intussusception in the Phase I/II studies that is similar to the background rate of intussusception.

Phase III Studies: Protocol 006 (REST), Protocol 007, and Protocol 009

All positively-adjudicated (confirmed by the SEAC) cases of intussusception occurred in Protocol 006 (REST). There were no investigator-diagnosed or positively-adjudicated

(confirmed) cases of intussusception in the other 2 Phase III studies, Protocol 007 and Protocol 009.

Thirty-five (35) investigator-diagnosed cases of potential intussusception were reported in Protocol 006 (REST). Thirty-two (32) of these potential cases were positively adjudicated (confirmed) as intussusception by the SEAC. Twenty-eight (28) cases occurred within the year after Dose 1; 4 cases (all placebo recipients) occurred after the infants had completed the study (i.e., completed 1 year of safety follow-up after Dose 1). The 3 cases that were negatively-adjudicated were all in the placebo group; 1 of these cases occurred within 42 days following a dose (28 days after Dose 1).

There were 11 positively-adjudicated intussusception cases within 42 days following vaccination, the time period upon which the primary safety hypothesis was based. Six (6) cases occurred among recipients of RotaTeq™ and 5 cases among placebo recipients. There were no confirmed cases among recipients of RotaTeq™ during the 42-day period following the first dose and no clustering of cases among recipients of RotaTeq™ during the 2-week period after any dose. The results of the primary analysis are provided in Table 6-2 and also displayed graphically in Figure 6-4. The relative risk was 1.6, with 95% CI of 0.4 to 6.4; all quantities were adjusted for multiplicity due to the group-sequential design. An unadjusted analysis based on the complete data is presented in Table 6-3.

Cases of intussusception in the vaccine and placebo groups and the corresponding relative risk estimates were also evaluated for the 7-day and 14-day periods after any dose and the 365-day period after vaccination Visit 1. These results are summarized in Table 6-3.

The number of cases during the 7-day and 14-day period after any dose was summarized because these are the periods of greatest risk of intussusception reported with RRV-TV (Wyeth-Lederle). One (1) case was reported in the group that received RotaTeq™ during the 7 days after any dose (2 days Postdose 2). Two (2) cases were reported during the 14 days following any dose, which included the case previously mentioned for the 7-day range and 1 case in the placebo group (10 days Postdose 3).

Within 365 days following vaccination Visit 1, there were 28 subjects who had a positively-adjudicated (confirmed) case of intussusception. Of the 28 subjects who had a positively-adjudicated (confirmed) case of intussusception within 365 days following vaccination Visit 1, there were 13 cases in the group that received RotaTeq™ and 15 cases in the group that received placebo(RR=0.9; 95% CI: 0.4, 1.9).

Table 6-2

Summary of Positively-Adjudicated (Confirmed) Cases of Intussusception
in Protocol 006 (REST)
(Within 42 Days Following Any Vaccination)

	RotaTeq™	Placebo
Subjects vaccinated[†]	34002	33969
Subjects with follow-up	34002	33969
Subjects with confirmed cases of intussusception		
Postdose 1	0	1
Postdose 2	4	1
Postdose 3	2	3
Group-sequential adjusted estimate of relative risk and group-sequential adjusted 95% confidence interval[‡]	1.6 (0.4, 6.4)	---
Group-sequential adjusted p-value for relative risk =10.0[‡]	0.006	---
Conclusion[§]	Safe relative to placebo	---

[†] Excludes subjects who were cross-treated. There were no confirmed cases of intussusception among cross-treated subjects.

[‡] In the study, there were 2 observed stages where the criteria for stopping enrollment was evaluated. In Stage 1, there were 6 cases among the group that received RotaTeq™ and 3 cases among the group that received placebo. In Stage 2, there were 0 cases among the group that received RotaTeq™ and 2 cases among the group that received placebo.

[§] A conclusion of "safe relative to placebo" indicates that the criterion for safety was met, i.e., the group-sequential adjusted upper bound of the 95% confidence interval for the relative risk of intussusception does not exceed 10.0.

Figure 6-4

Graphical Display of Positively-Adjudicated (Confirmed) Cases of Intussusception in Protocol 006 (REST)
(Within 42 Days Following Any Vaccination)

6 Vaccine : 5 Placebo
RR=1.6; 95% CI=0.4, 6.4
(All quantities adjusted for group-sequential design)

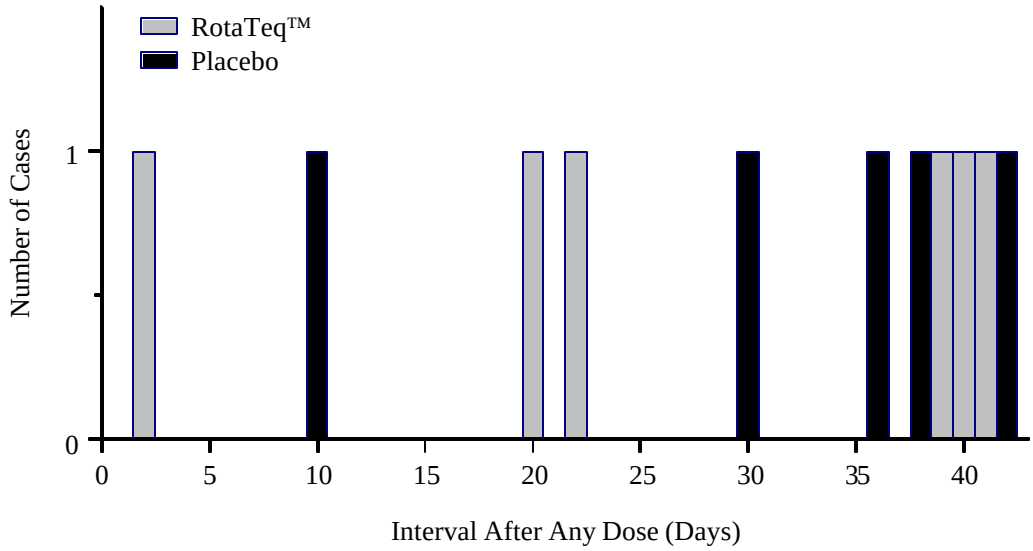


Table 6-3

Summary of Positively-Adjudicated (Confirmed) Cases of Intussusception in Protocol 006 (REST)

Day Range	RotaTeq™ (N = 34,837)	Placebo (N = 34,788)	Relative Risk/95% Confidence Interval
	Number of Confirmed Intussusception Cases		
Within 7 Days of Any Dose	1	0	8 (0.0, 8)[†]
Within 14 Days of Any Dose	1	1	1.0 (0.0, 78.2)[†]
Within 42 Days of Any Dose	6	5	1.2 (0.3, 5.0)[†,‡]
Within 365 Days of Dose 1	13	15	0.9 (0.4, 1.9)[§]

[†]Based on the number of subjects with confirmed cases of intussusception per number of subjects with complete follow-up.
[‡]Unadjusted for multiplicity.
[§]Based on the number of subjects with confirmed cases of intussusception per days of safety follow-up.

6.3.3 Discussion of Safety With Respect to Intussusception

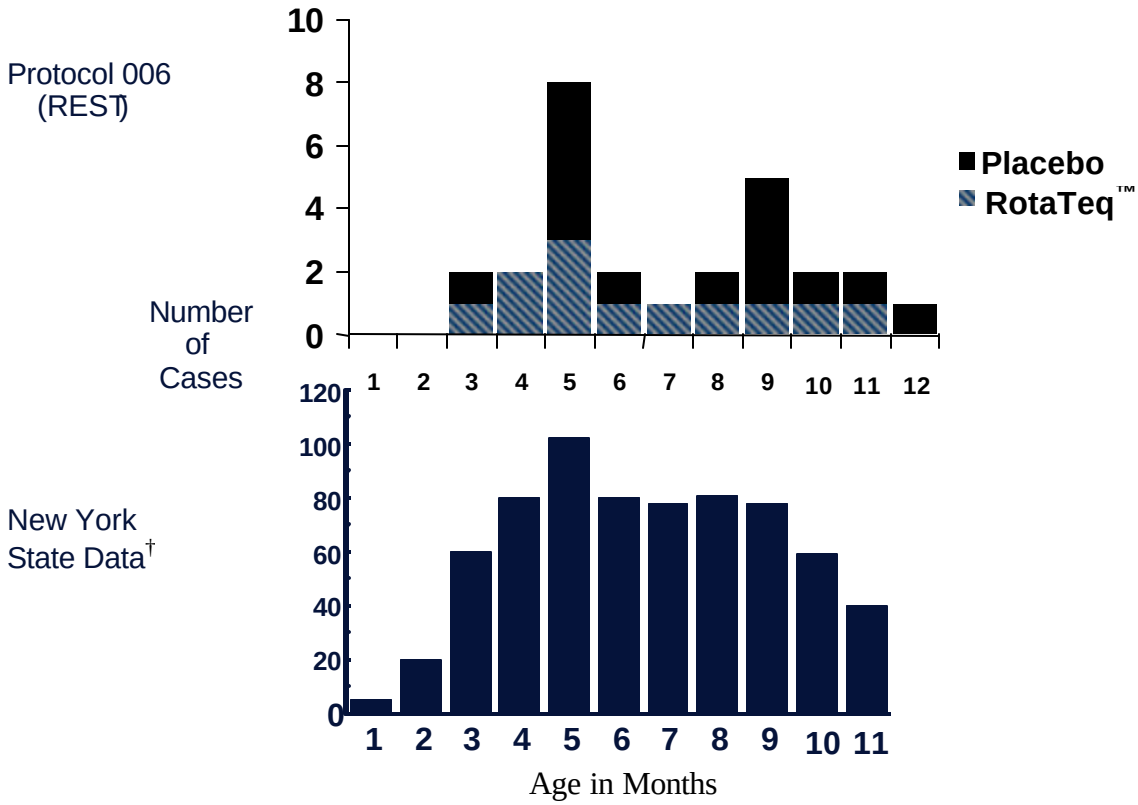
The primary safety hypothesis for the study was satisfied; the upper bound on the 95% CI for the relative risk of intussusception among vaccine recipients as compared with placebo recipients during the 42-day period after any dose was =10. These data provide a high level of confidence in the safety of RotaTeq™ with regard to intussusception. Several other factors support the conclusion that RotaTeq™ has a clinically favorable safety profile with respect to intussusception including: 1) The acceptable ratio of cases among vaccine recipients as compared with placebo recipients for the 7-, 14-, 42-, and 365-day periods after any dose; 2) The random timing of vaccine cases after each dose; and 3) The absence of cases during the peak time of vaccine replication (4- to 6-day period after Dose 1). These characteristics clearly distinguish the risk profile of RotaTeq™ from that of RRV-TV (Wyeth-Lederle), for which the intussusception risk was highest during the first 2 weeks after Dose 1 (see Figure 3-2) [23]. In addition to intussusception, pre-licensure trials of RRV-TV (Wyeth-Lederle) showed that the vaccine was associated with high fever, abdominal cramping, and shedding of vaccine strains in a large proportion (~50 to 100%) of subjects during the week after Dose 1 [64; 65; 66; 67; 68; 69]. Although the pathogenesis of intussusception with RRV-TV (Wyeth-Lederle) is unknown, the time frame during which these adverse experiences and vaccine-virus shedding were observed pre-licensure coincided with the time frame during which intussusception was observed post-licensure. In contrast, RotaTeq™ has demonstrated a favorable safety profile with respect to high fever and abdominal cramping during the week after a dose (Section 6.6 and Section 6.7). Furthermore, fecal shedding of vaccine-virus strains has been observed in a low proportion (8.9%) of subjects after Dose 1 of RotaTeq™. Thus, demonstration of a favorable safety profile for RotaTeq™ with regard to intussusception was not unexpected given the totality of the differences between the 2 vaccines.

The characteristics of the intussusception cases that occurred in Protocol 006 (REST) are similar to the characteristics of background intussusception with respect to gender and age at diagnosis. There was a male predominance of cases; of 28 cases within the year observation period, 17 were male and 11 female. As shown in Figure 6-5, the age range over which intussusception occurred was very similar to the age range reported for background intussusception [29]. Furthermore, there was no evidence of a shift of cases to younger infants as was observed in the CDC studies of RRV-TV (Wyeth-Lederle) [23].

In summary, the results of Protocol 006 (REST) provide a high level of confidence in the safety of RotaTeq™ with regard to intussusception. The preestablished statistical criteria for demonstrating a clinically acceptable safety profile were satisfied. Other clinical features of the intussusception cases were reassuring, including the absence of clustering of cases after the first dose, and the similarity of the cases to background intussusception. These data coupled with the overall favorable safety profile as will be discussed in the sections that follow, and the excellent efficacy data already discussed support the use of RotaTeq™ for prevention of rotavirus gastroenteritis and associated health care encounters.

Figure 6-5

Age at Diagnosis of Infants With Intussusception



†Rennels, *et al*. PIDJ Vol. 17, No. 10, Oct. 1998,

6.4 Other Serious Adverse Experiences

All subjects enrolled in Protocol 006 (REST), Protocol 007, and Protocol 009 were followed for all serious clinical adverse experiences including death that occurred within 42 days following any vaccination, whether or not related to the study vaccine/placebo. In addition, deaths and vaccine-related serious adverse experiences were to be reported until the end of the studies.

6.4.1 Deaths

The number of deaths and the associated adverse experiences reported in the 3 Phase III studies were comparable to what was expected based on the large sample size and the age range of subjects enrolled. Overall, there were 52 deaths reported among the subjects in the Phase III studies. Twenty-five (25) deaths occurred among recipients of RotaTeq™ and 27 deaths occurred among placebo recipients. None of the deaths was assessed to be vaccine related by the investigator. The most common cause of death at any time was sudden infant death syndrome (SIDS), which is not unexpected given the age of infants in these studies. There were 17 cases of SIDS; 8 occurred among vaccine recipients and 9 occurred among placebo recipients. Of the 17 cases of SIDS that were reported, 16 cases were diagnosed by the investigator as SIDS with an autopsy result confirming this diagnosis.

6.4.2 Serious Adverse Experiences (SAEs)

In the 3 Phase III studies, 1,783 subjects reported one or more serious adverse experiences within 42 days of any dose (see Table 6-4); 861 vaccine recipients and 922 placebo recipients. Of these, 128 subjects had at least one serious adverse experience that was assessed by the investigator to be vaccine or placebo related, including 49 (0.1%) among vaccine recipients and 79 (0.2%) among placebo recipients. The proportion of subjects who discontinued from the study due to a serious adverse experience was comparable among recipients of vaccine and placebo recipients (0.2% versus 0.2%). The most common serious adverse experiences were bronchiolitis and gastroenteritis, both of which were more frequent among placebo recipients than vaccine recipients. These findings are consistent with the most common reasons for hospitalizations in children who are the same age as the study subjects. The 3 most common vaccine- or placebo-related serious adverse experiences were gastroenteritis, pyrexia, and dehydration, all of which were more common in the placebo group than the group that received RotaTeq™. The incidence of serious adverse experiences that are manifestations of childhood gastroenteritis were low and were generally similar among recipients of vaccine and placebo recipients, including the following events expressed as absolute numbers per group: diarrhea (9 vaccine/19 placebo), hematochezia (4 vaccine/7 placebo), vomiting (23 vaccine/18 placebo), pyrexia (44 vaccine/49 placebo) and dehydration (21 vaccine/25 placebo). Table 6-5 displays these most common serious adverse experiences for all subjects in the 3 Phase III studies (Protocol 006 [REST], Protocol 007, and Protocol 009).

Table 6-4

Accounting of All Serious Adverse Experiences in the Large-Scale Study
(Within 42 Days Following Vaccination)
(Protocol 006 [REST], Protocol 007, and Protocol 009)

	Number (%) of Subjects	
	RotaTeq™	Placebo
	N = 36,165	N = 35,560
No serious adverse experiences	35,289 (97.6)	34,614 (97.4)
One or more serious adverse experiences	861 (2.4)	922 (2.6)
Vaccine-related serious adverse experiences	49 (0.1)	79 (0.2)
Deaths	15 (<0.1)	13 (<0.1)
Discontinued due to a serious adverse experience	83 (0.2)	72 (0.2)
N = Number vaccinated.		

Table 6-5

Number (%) of the Most Frequent Serious Adverse Experiences Among Subjects in the Large-Scale Study
(Within 42 Days Following Vaccination)
(Protocol 006 [REST], Protocol 007, and Protocol 009)

Serious Adverse Experiences (SAEs)	RotaTeq™ (N=36,165)	Placebo N=35,560
	Number (%) of Subjects	Number (%) of Subjects
Most Frequent SAEs		
Bronchiolitis	226 (0.6)	257 (0.7)
Gastroenteritis	73 (0.2)	117 (0.3)
Most Frequent SAEs (manifestations of childhood gastroenteritis)		
Diarrhea	9 (0.0)	19 (0.1)
Hematochezia	4 (0.0)	7 (0.0)
Vomiting	23 (0.1)	18 (0.1)
Pyrexia	44 (0.1)	49 (0.1)
Dehydration	21 (0.1)	25 (0.1)
Most Frequent VR SAEs (blinded-investigator assessment)		
Gastroenteritis	17 (<0.1)	33 (0.1)
Pyrexia	8 (<0.1)	12 (<0.1)
Dehydration	3 (<0.1)	13 (<0.1)
N = Number vaccinated; VR = Vaccine related.		

6.5 Common Adverse Experiences

As previously mentioned in Section 6.3, a subset of subjects enrolled in Protocol 006 (REST), and all subjects enrolled in Protocol 007 and Protocol 009, were followed for all clinical adverse experiences, regardless of severity, from the time the consent form was signed through 42 days following the first study vaccination, and from the time of any subsequent study vaccination(s) through 42 days thereafter (i.e., Detailed Safety Substudy). As displayed in Figure 6-1, 11,722 subjects were vaccinated in the Detailed Safety Substudy of the 3 Phase III studies (Protocol 006 [REST], Protocol 007, and Protocol 009) with 6,143 subjects receiving RotaTeq™ and 5,579 subjects receiving placebo.

The proportions of subjects in the Phase III studies who had one or more adverse experiences within 42 days of any dose were generally similar among vaccine recipients (86%) and placebo recipients (87%). The most frequently reported common adverse experiences (incidence =10%) in both the group that received RotaTeq™ and the placebo group were diarrhea, vomiting, gastroenteritis, pyrexia, otitis media, upper respiratory tract infection, irritability, and cough. The 3 most frequently reported vaccine-related or placebo-related (as determined by the investigator) adverse experiences were pyrexia, diarrhea, and vomiting.

The adverse experiences regardless of causality that were reported within the 42 days after any dose at a statistically higher rate among recipients of RotaTeq™ as compared with placebo recipients were diarrhea (24% versus 21%), vomiting (15% versus 14%), nasopharyngitis (7% versus 6%), otitis media (15% versus 13%), and bronchospasm (1.1% versus 0.7%). The adverse experience of crying was reported at a statistically higher rate in the placebo group than the vaccine group (3.6% versus 4.4%). These differences are only evident when the data are combined across the 3 Phase III studies; this was not observed in the individual studies. The risk differences observed for these adverse experiences when combining the data across studies are small and, not unexpected given that RotaTeq™ is a live vaccine and given the multiple comparisons that were done. In addition, the majority of diarrhea and vomiting episodes were categorized to be of mild intensity as assessed by the investigator. The most frequent adverse experiences are presented in Table 6-6.

A similar safety profile was observed during the evaluation of adverse events among infants in the U.S. Concomitant Use Substudy in Protocol 006 (REST). The incidence of fever and other adverse events were comparable among the vaccine and placebo groups, confirming that RotaTeq™ is well tolerated when administered with the other licensed childhood vaccines evaluated in Protocol 006 (REST).

Table 6-6

Number (%) of the Most Frequent Adverse Experiences Among Subjects in the Detailed Safety Substudy
(Within 42 Days Following Vaccination)
(Protocol 006 [REST], Protocol 007, and Protocol 009)

Adverse Experiences (AEs)	RotaTeq™ N=6,143	Placebo N=5,579
	Number (%) of Subjects	Number (%) of Subjects
Most Frequent Adverse Experiences †		
Diarrhea	1479 (24)	1186 (21)
Vomiting	929 (15)	758 (14)
Nasopharyngitis	422 (7)	325 (6)
Otitis Media	887 (15)	724 (13)
Bronchospasm	66 (1)	40 (0.7)
Most Frequent VR SAEs (blinded investigator-assessment)		
Pyrexia	1279 (21)	1037 (19)
Diarrhea	1077 (18)	840 (15)
Vomiting	622 (10)	465 (8)

† Statistically Higher Rate in RotaTeq™ when compared with placebo.
N = Number vaccinated; VR = Vaccine related.

6.6 Safety With Respect to Adverse Experiences of Clinical Interest

The subjects in the Detailed Safety Substudy were also followed for other adverse experiences of special clinical interest for a live rotavirus vaccine, including diarrhea, elevated temperatures (=38.1ºC [=100.5ºF], rectal equivalent), behavioral changes (irritability), and vomiting within 7 days of vaccination. These were considered to be adverse experiences of special clinical interest for the clinical development program for RotaTeq™, because these are clinical symptoms that are normally associated with naturally occurring wild-type rotavirus infection. Hematochezia within 42 days of vaccination was also considered an adverse experience of special clinical interest in the 3 Phase III studies (Protocol 006 [REST], Protocol 007, and Protocol 009), given the reports of bloody stools among recipients of RRV-TV (Wyeth-Lederle) [27].

6.6.1 Elevated Temperature, Vomiting, Diarrhea, Irritability, Hematochezia

Analyses of the combined data from the 3 Phase III studies for the adverse experiences of special clinical interest showed that the incidence of diarrhea during the 7 days after Dose 1, Dose 2, and any dose was statistically higher in recipients of RotaTeq™ (10%, 9%, 18%, respectively) as compared with placebo recipients (9%, 6%, 15%, respectively). The incidence of vomiting was statistically higher during the 7 days after Dose 1 and any dose in recipients of RotaTeq™ (7% and 12%, respectively) as compared with placebo recipients (5% and 10%, respectively). These differences were only evident when the data were combined across the 3 Phase III studies; this was not observed for these adverse experiences of special clinical interest in the individual studies. The differences

in the incidence of these adverse experiences between the 2 treatment groups are small, and the majority of the episodes of diarrhea and vomiting were assessed by the investigator to be of mild intensity. Mild symptoms of these clinical adverse experiences are not unexpected given that RotaTeq™ is a live, oral vaccine. Furthermore, the incidences of serious adverse experiences that are manifestations of childhood gastroenteritis were low and comparable in the group that received RotaTeq™ and the placebo group. Figure 6-6 displays the percent of subjects with vomiting, diarrhea, and irritability during the 7 days after vaccination Visit 1.

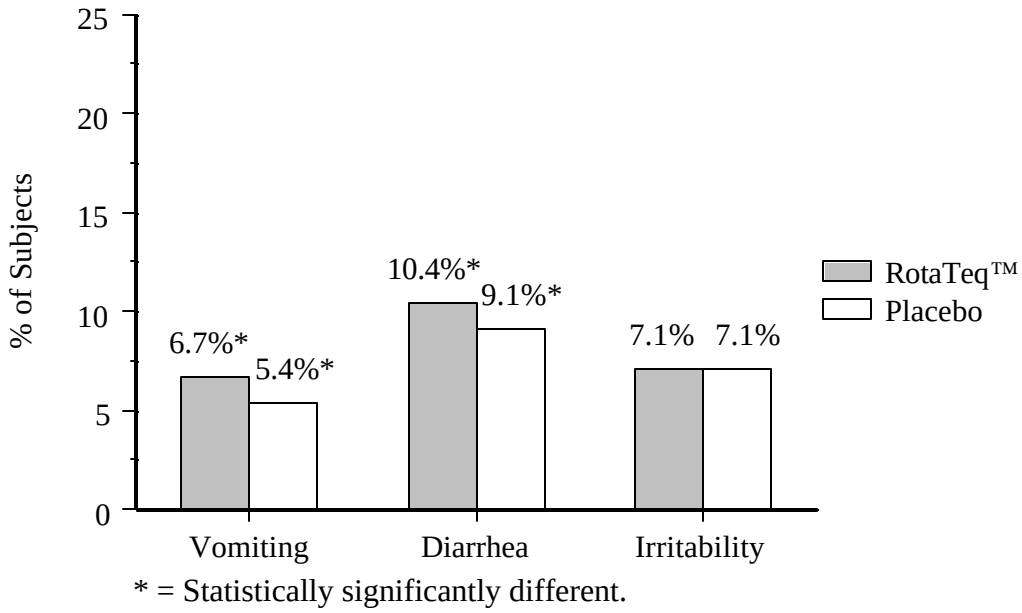
The incidences of elevated temperature (=100.5°F [=38.1°C], rectal equivalent), and behavioral changes (irritability) were generally similar among recipients of RotaTeq™ and placebo recipients during the week after each dose and the week after any dose based on the analyses of the integrated data from the 3 Phase III studies. Figure 6-7 displays the percent of subjects with elevated temperatures (=100.5°F [=38.1°C], rectal equivalent) during 7 days after any vaccination.

The incidence of hematochezia among subjects in the 3 Phase III studies during the 42-day period after each dose and any dose was low and comparable among vaccine recipients as compared with placebo recipients. Figure 6-8 displays the percent of subjects with hematochezia during 42 days after any vaccination.

These summaries of the adverse experiences of special clinical interest indicate that RotaTeq™ is generally well tolerated. There is a small increase in mild diarrhea and mild vomiting within the week following vaccination Visit 1; the vaccine does not appear to be associated with excess fever or bloody stools.

Figure 6-6

Percent of Subjects With Vomiting, Diarrhea, and Irritability During 7 Days After Vaccination Visit 1 by Treatment Group
(Protocol 006 [REST], Protocol 007, and Protocol 009)



* = Statistically significantly different.

Figure 6-7

Percent of Subjects With Elevated Temperatures (=100.5°F [=38.1°C], Rectal Equivalent) During 7 Days After Vaccination by Treatment Group and Dose Number (Protocol 006 [REST], Protocol 007, and Protocol 009)

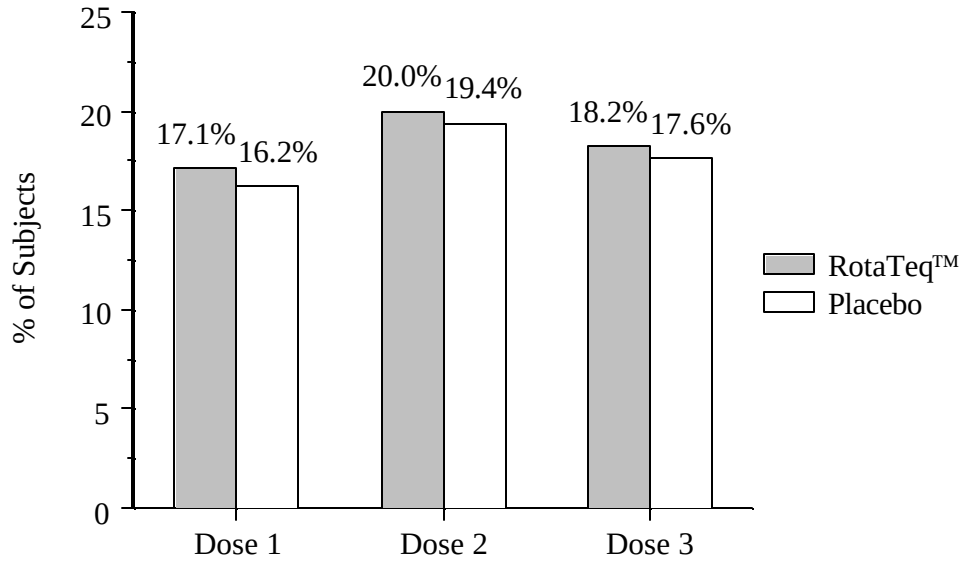
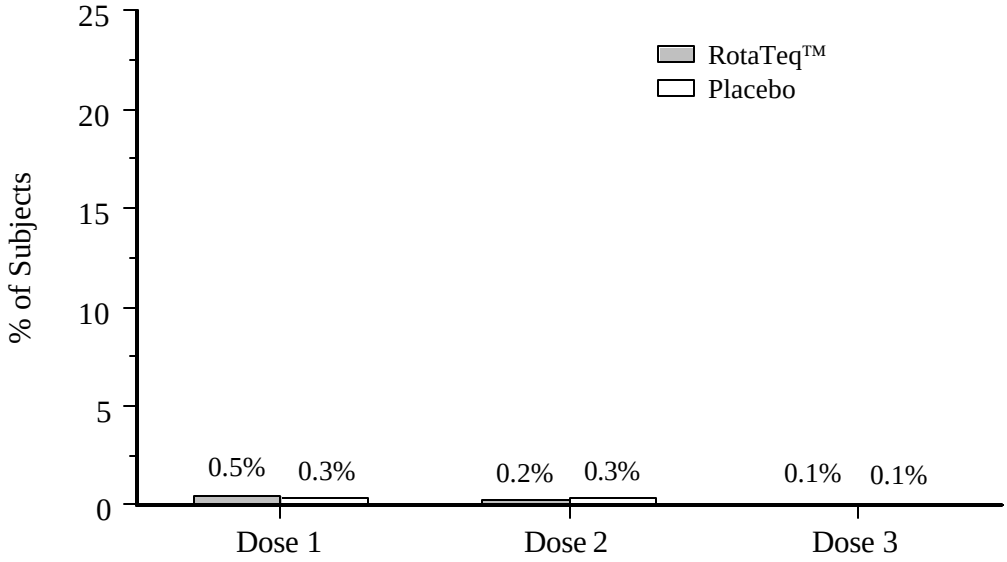


Figure 6-8

Percent of Subjects With Hematochezia During 42 Days After Vaccination by Treatment Group and Dose Number
(Protocol 006 [REST], Protocol 007, and Protocol 009)



6.7 Fecal Shedding of Vaccine-Virus Strains

Because RotaTeq™ is a live human-bovine rotavirus reassortant vaccine that is administered orally, the vaccine-virus strains could theoretically be shed in the feces of vaccine recipients. Vaccine-virus replication in the intestinal tract peaks during the 4- to 6-day period after a dose, with minimal, if any, replication occurring after a week, as was demonstrated in a Phase II study, Protocol 002.

Results of Fecal Shedding of Vaccine-Virus Strains in Clinical Trials

In Protocol 006 (REST), fecal shedding of vaccine-virus strains was to be evaluated among a subset of approximately 300 subjects (the first 150 subjects randomized in Finland and the first 150 subjects randomized in the United States). A stool sample was to be collected from each subject in this subset during Days 4 to 6 following vaccination Visits 1, 2, and 3. Shedding was evaluated using plaque assay with electrophenotyping.

The percent of subjects who shed vaccine-virus strains in the stool Days 4 to 6 following vaccination Visit 1 was 13% in the group that received RotaTeq™, and there was no fecal shedding of vaccine-virus strains in the group that received placebo. There was no shedding of vaccine-virus strains reported 4 to 6 days following vaccination Visits 2 and Visits 3. The vaccine-virus strains shed were either from the vaccine or from reassortants

of the vaccine. These data are consistent with previous studies with regard to the proportion of infants with fecal shedding of vaccine-virus strains.

Fecal shedding of vaccine-virus strains was also evaluated for all potential AGEs for which the stools tested positive for rotavirus by EIA in Protocol 006 (REST) and Protocol 007. Fecal shedding of vaccine-virus strains at any time (i.e., samples scheduled 4 to 6 days postvaccination or samples from potential AGEs that were rotavirus EIA-positive) during these 2 Phase III studies, was detected in 32 (9%) subjects following Dose 1 and in only 1 (0.3%) subject 4 days following Dose 3. The longest postdose time point at which shedding of vaccine-virus strains was detected was 15 days following Dose 1. The most commonly shed strains were G1 and P1 reassortants.

In Protocol 006 (REST), there were 2 subjects who had vaccine-virus shedding detected in a stool sample following the first dose of placebo. A thorough investigation was conducted to determine why these subjects had vaccine-virus strains detected in the stool samples. These subjects did not live with or attend daycare with a vaccine recipient and did not have a caretaker in come with a vaccine recipient. The conclusion of the investigation was that the most likely explanation fort his study was mislabeling of samples.

The potential for horizontal transmission of vaccine viruses was not evaluated. Fecal shedding of vaccine-virus strains has been observed in a low proportion of subjects in the clinical studies and almost exclusively following Dose 1. When considering vaccination of infants with immunocompromised household members, it is important to remember that nearly all children will be infected with natural rotavirus by 5 years of age. RotaTeq™ has the potential to decrease the risk of exposure to wild-type rotavirus infection among the household members of vaccinated infants. The benefit of this protection may outweigh the very small theoretical risk of horizontal transmission of reassortant vaccine viruses, which are not pathogenic for humans.

6.8 Conclusions Regarding Clinical Safety

RotaTeq™ was generally well tolerated in the 3 Phase III studies (Protocol 006 [REST], Protocol 007, and Protocol 009). The prespecified criteria for an acceptable safety profile with regard to intussusception during the 42-day period following vaccination was satisfied. The random timing of the cases after vaccination, the overall profile of the cases, and the similarity of the cases to background intussusception cases provide a high level of confidence in the safety of the vaccine.

RotaTeq™ was also well tolerated with regard to the other adverse experiences of clinical interest for this vaccine. There was a small (1.3%) statistically significant increase in mild diarrhea and vomiting following the first dose of RotaTeq™, which would not be unexpected given that this is a live virus vaccine. The incidences of elevated temperature and irritability during the week following vaccination, and the incidences of hematochezia were comparable in the vaccine group and the placebo group.

RotaTeq™ was also well tolerated when administered concomitantly with other licensed pediatric vaccines including DTaP, IPV, Hib, Hep B, and PREVNAR™. These data indicate that RotaTeq™ can be safely added to the routine childhood immunization schedule with no expected increase in fever or other serious adverse experiences.

RotaTeq™ is also unlikely to be associated with adverse experiences in immunocompromised household members of infants receiving the vaccine. The vaccine-virus strains, which consist of a bovine rotavirus background that replicates poorly in humans, are shed in a small proportion of subjects (<10%) and in low quantities; thus, the opportunity for transmission is limited. Vaccination of infants with immunocompromised household members should be evaluated on a case-by-case basis given that the benefits of preventing exposure to wild-type rotavirus may outweigh the theoretical risk, if any, from horizontal transmission of vaccine-virus strains.

7. Post-Licensure Surveillance Study for Intussusception

RotaTeq™ has been shown in clinical trials to have an acceptable safety profile. Merck will continue to monitor the safety of the vaccine after licensure and with increasing use. Monitoring will be accomplished by a combination of routine passive pharmacovigilance and a postlicensure observational surveillance study.

Despite having seen no signal that would indicate an association of RotaTeq™ with intussusception, further postlicensure monitoring of this uncommon event is planned. A 2-component plan is proposed consisting of passive surveillance and a postlicensure surveillance study.

Because one can anticipate high awareness of the issue of intussusception on the part of health care practitioners, it is expected that passive reporting of this adverse experience will be high. Intussusception in temporal association with RotaTeq™ will be subject to expedited review and reporting. In addition, reports of intussusception will be analyzed in the periodic (every 6 months) safety reviews for RotaTeq™ for 3 years from the international birthdate of vaccine licensure.

In order to obtain additional data regarding any temporal association of intussusception and RotaTeq™, an observational post-licensure study is proposed. This study is designed to assess safety data collected prospectively in a cohort of infants vaccinated in a routine pediatric healthcare setting in order to evaluate the vaccine in routine use. This post-licensure study will be conducted in one or more managed care organizations and will: (1) Evaluate the safety of RotaTeq™ with respect to intussusception, and (2) Describe the general short-term safety profile RotaTeq™.

8. Overall Summary and Conclusions: Benefits Versus Risks

Rotavirus infects nearly all children by 5 years of age regardless of socioeconomic status or environmental conditions, resulting in 25 million clinic visits, 2 million hospitalizations, and 325,000 to 592,000 deaths worldwide, and 1.8 million clinic visits and 223,000 hospitalizations in industrialized nations annually [2]. Recent studies suggest that the burden of rotavirus disease may be greater than current estimates, which have been based on the assumption that rotavirus is responsible for approximately one third of all diarrhea-associated hospitalizations. Hospital-based studies utilizing active surveillance have found that rotavirus is responsible for 40 to 60% of all diarrhea-associated hospitalizations among children less than 5 years of age [70; 71; 72; 73; 74]. If these proportions were applied to the average number of yearly hospitalizations for acute gastroenteritis, the estimate of annual rotavirus-associated hospitalizations would be substantially higher [72].

Currently, the only available therapy for rotavirus gastroenteritis is supportive care; although there are 2 licensed rotavirus vaccines outside of the United States, their availability is limited. These Phase III studies have demonstrated that RotaTeq™ is clinically efficacious in preventing 74% of rotavirus gastroenteritis against any severity and 98% of severe rotavirus gastroenteritis caused by the serotypes responsible for over 88% of rotavirus disease worldwide (G1, G2, G3, and G4). Furthermore, Protocol 006 (REST) also showed the persistence of efficacy; RotaTeq™ prevented 88% of severe rotavirus disease during the second rotavirus season postvaccination. The large sample size of Protocol 006 (REST) provided a unique opportunity to quantify the impact of vaccination on health care encounters for rotavirus gastroenteritis in a prelicensure setting. RotaTeq™ reduced the rate of hospitalizations for rotavirus gastroenteritis by 96%, reduced the rate of emergency department visits by 93%, and reduced the rate of office visits for rotavirus gastroenteritis by 86% as compared with placebo.

The Phase III trials also confirmed that RotaTeq™ is well tolerated as demonstrated by the overall clinical safety profile. Although there was a statistical difference in the incidence of diarrhea (during the week following Dose 1 and Dose 2) and the incidence of vomiting (during the week following Dose 1) among recipients of RotaTeq™ as compared with placebo recipients, these differences were small and the majority of episodes were assessed by the investigator as mild. In addition, the incidences of serious adverse experiences during the 42-day period following vaccination that are manifestations of childhood gastroenteritis were low and were comparable among the group that received vaccine and the placebo group. With respect to intussusception, the results of the Large-Scale Safety Study provide a high level of confidence in the safety of RotaTeq™. The preestablished criteria for acceptable safety were met; there was little

difference in the incidence of intussusception between the vaccine and placebo groups within 42 days after vaccination. There was also no clinical evidence of excess risk of intussusception associated with RotaTeq™ within 7 and 14 days following vaccination or within 365 days following vaccination Visit 1.

The clinical development program for RotaTeq™ is exceptional with regard to the scope of the safety and efficacy databases pre-licensure. The results of the clinical trials strongly support the licensure of RotaTeq ™. While it is not possible to prove the absence of risk, the studies show no signal of a safety concern with regard to intussusception. Alternatively, the studies demonstrate the potential benefit of the vaccine to virtually eliminate hospitalizations and other health care encounters for rotavirus gastroenteritis. In light of the absence of any signal of a safety concern and the clear demonstration of efficacy, the risk-benefit assessment of RotaTeq™ support use of this vaccine in infants and young children in the United States.

9. List of References

1. Brandt CD, Kim HW, Rodriguez WJ, Arrobio JO, Jefferies BC, Stallings EP, et al. Pediatric viral gastroenteristis during eight years of study. J Clin Microbio 1983;18(1):71-8.

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

3. Fischer TK, Bresee JS, Glass RI. Rotavirus vaccines and the prevention of hospital-acquired diarrhea in children. Vaccine 2004;22S:S49-S54.

4. Kapikian AZ, Chanock RM. Rotaviruses. In: Fields BN, Knipe DM, Howley PM, et al., eds. Fields Virology. 3rd ed. Philadelphia: Lippincott - Raven Publishers, 1996:1657-708.

5. Kapikian AZ, Wyatt RG. Viral gastrointestinal infections. In: Kapikian AZ, Wyatt RG, eds. Textbook of Pediatric Infectious Diseases. 3rd ed. Philadelphia (PA): Philadelphia: Saunders, 1992, 1992:655-76.

6. Rodriguez WJ, Kim HW, Arrobio JO, Brandt CD, Chanock RM, Kapikian AZ, et al. Clinical features of acute gastroenteritis associated with human reovirus-like agent in infants and young children. J Pediatr 1977;91(2):188-93.

7. Ciarlet M, Estes MK. In: Bitton G, ed. Encyclopedia of environmental microbiology. Rotaviruses. New York (NY): John Wiley & Sons, 2002:2753-73.

8. Santos N, Hoshino Y. Global distribution of rotavirus serotypes/genotypes and its implication for the development and implementation of an effective rotavirus vaccine. Rev Med Virol 2005;15:29-56.

9. Velázquez FR, Matson DO, Calva JJ, Guerrero ML, Morrow AL, Carter-Campbell S. Rotavirus infection in infants as protection against subsequent infections. N Engl J Med 1996;335(14):1022-8.

10. Moulton LH, Staat MA, Santosham M, Ward RL. The protective effectiveness of natural rotavirus infection in an American Indian population. J Infect Dis 1998;178:1562-6.

11. Vethanayagam RR, Babu MA, Nagalaxmi KS, Maiya PP, Venkatesh HA, Purohit S, et al. Possible role of neonatal infection with the asymptomatic reassortant rotavirus (RV) strain I321 in the decrease in hospital admissions for RV diarrhea, Bangalore, India, 1988-1999. J Infect Dis 2004;189:2282-9.

12. Bishop RF, Barnes GL, Cipriani E, Lund JS. Clinical immunity after neonatal rotavirus infection: a prospective longitudinal study in young children. N Engl J Med 1983;309(2):72-6.

13. Velázquez FR, Matson DO, Guerrero ML, Shults J, Calva JJ, Morrow AL, et al. Serum antibody as a marker of protection against natural rotavirus infection and disease. J Infect Dis 2000;182:1602-9.

14. Matson DO, O'Ryan ML, Herrera I, Pickering LK, Estes MK. Fecal antibody responses to symptomatic and asymptomatic rotavirus infections. J Infect Dis 1993;167:577-83.

15. O'Ryan ML, Matson DO, Estes MK, Pickering LK. Anti-rotavirus G type-specific and isotype-specific antibodies in children with natural rotavirus infections. J Infect Dis 1994;169:504-11.

16. Bern C, Unicomb L, Gentsch JR, Banul N, Yunus M, Sask RB, et al. Rotavirus diarrhea in Bangladeshi children: correlation of disease severity with serotypes [Abstract]. J Clin Microbiol 1992;30(12):3234-8.

17. Clark HF, Furukawa T, Bell LM, Offit PA, Perrella PA, Plotkin SA. Immune response of infants and children to low-passage bovine rotavirus (strain WC3). AJDC 1986;140:350-6.

18. Clark HF, Offit PA, Krah, D, Shaw AR, Eiden JJ, Pichichero M, et al. WC3 reassortant vaccines in children. Arch Virol 1996; 12(suppl); 187-98.

19. Clark HF, Offit PA, Ellis RW, Eiden JJ, Krah D, Shaw AR, et al. The development of multivalent bovine rotavirus (strain WC3) reassortant vaccine for infants. J Infect Dis 1996;174(suppl 1):S73-S80.

20. Gorziglia M, Larralde G, Kapikian AZ, Chanock RM. Antigenic relationships among human rotaviruses as determined by outer capsid protein VP4. PNAS 1990;87:7155-9.

21. Clark HF, Lawley D, Shrager D, Jean-Guillaume D, Offit PA, Whang SY, et al. Infant immune response to human rotavirus serotype G1 vaccine candidate reassortant WI79-9: different dose response patterns to virus surface proteins VP7 and VP4. Pediatr Infect Dis J 2004;23(3):206-11.

22. Centers for Disease Control and Prevention. Intussusception among recipients of rotavirus vaccine-United States, 1998-1999. MMWR 1999;48(27):577-81.

23. Murphy TV, Gargiullo PM, Massoudi MS, Nelson DB, Jumaan AO, Okoro CA, et al. Intussusception among infants given an oral rotavirus vaccine. N Engl J Med 2001;344(8):564-72.

24. Murphy BR, Morens DM, Simonsen L, Chanock RM, La Montagne JR, Kapikian AZ. Reappraisal of the association of intussusception with the licensed live rotavirus vaccine challenges initial conclusions. J Infect Dis 2003;187:1301-8.

25. O'Ryan M, Lucero Y, Peña A, Valenzuela MT. Two-year review of intestinal intussusception in six large public hospitals of Santiago, Chile. Pediatr Infect Dis J 2003;22(8):717-21.

26. Parashar UD, Holman RC, Cummings KC, Staggs NW, Curns AT, Zimmerman CM, et al. Trends in intussusception-associated hospitalizations and deaths among US infants. Pediatrics 2000;106(6):1413-21.

27. Gay N, Ramsay M, Waight P. Rotavirus vaccination and intussusception [correspondence]. Lancet 1999;354:956.

28. Staat MA, Roberts NE, Bernstein DI. Epidemiology and clinical features of intussusception (IS) in children <24 months of age in Hamilton County, Ohio [Abstract]. Infectious Diseases 2001;242A.

29. Rennels MB, Parashar UD, Holman RC, Le CT, Chang H-G, Glass RI. Lack of an apparent association between intussusception and wild or vaccine rotavirus infection. Pediatr Infect Dis J 1998;17(10):924-5.

30. Ravitch MM. Intussusception in infants and children. Springfield (IL): Charles C. Thomas, 1959:3-27.

31. Pang L-C. Intussusception revisited: Clinicopathologic analysis of 261 cases, with emphasis on pathogenesis. South Med J 1989;82(2):215-28.

32. Orenstein J. Update on intussusception. Contemp Pediatr 2000;17(3):180, 185-86, 188-91.

33. Eshel G, Barr J, Heyman E, Tauber T, Klin B, Vinograd I, et al. Intussusception: A 9-year survey (1986-1995). J Pediatr Gastroenterol Nutr 1997;24(3):253-6.

34. Daneman A, Alton DJ. Intussusception: Issues and controversies related to diagnosis and reduction. Pediatric Gastrointestinal Radiology 1996;34(4):743-56.

35. del-Pozo G, Albillos JC, Tejedor D, Calero R, Rasero M, de-la-Calle U, et al. Intussusception in children: Current concepts in diagnosis and enema reduction. Radiographics 1999;19(2):299-319.

36. Ein SH, Alton D, Palder SB, Shandling B, Stringer D. Intussusception in the 1990s: has 25 years made a difference? Pediatr Surg Int 1997;12:374-6.

37. Haubrich WS, Schaffner F. In: Berk JE, ed. Gastroenterology. Volume 1. 5th ed. Philadelphia (PA): W.B. Saunders Company, 1995:192-7.

38. Kornecki A, Daneman A, Navarro O, Connolly B, Manson D, Alton DJ. Spontaneous reduction of intussusception: clinical spectrum, management and outcome. Pediatr Radiol 2000;30:58-63.

39. Montgomery EA, Popek EJ. Intussusception, adenovirus, and children: A brief reaffirmation. Hum Pathol 1994;25(2):169-74.

40. Porter HJ, Padfield CJH, Peres LC, Hirschowitz L, Berry PJ. Adenovirus and intranuclear inclusions in appendices in intussusception. J Clin Pathol 1993;46:154-8.

41. Hsu H-Y, Kao C-L, Huang L-M, Ni Y-H, Lai H-S, Lin F-Y, et al. Viral etiology of intussusception in Taiwanese childhood. Pediatr Infect Dis J 1998;17(10):893-8.

42. Nicolas JC, Ingrand D, Fortier B, Bricout F. A one-year virological survey of acute intussusception in childhood. J Med Virol 1982;9:267-71.

43. Mulcahy DL, Kamath KR, de Silva LM, Hodges S, Carter IW, Cloonan MJ. A two-part study of the aetiological role of rotavirus in intussusception. J Med Virol 1982;9:51-5.

44. Konno T, Suzuki H, Kutsuzawa T, Imai A, Katsushima N, Sakamoto M, et al. Human rotavirus infection in infants and young children with intussusception. J Med Virol 1978;2:265-9.

45. Chang EJ, Zangwill KM, Lee H, Ward JI. Lack of association between rotavirus infection and intussusception: implications for use of attenuated rotavirus vaccines. Pediatr Infect Dis J 2002;21(2):97-102.

46. MRL Report: Genetic and biologic differences between the bovine rotavirus strain WC3 of RotaTeq® and the simian RRV strain of RotaShield®, 28-Jan-2005.

47. Uhnoo I, Riepenhoff-Talty M, Dharakul T, Chegas P, Fisher JE, Greenberg HB, et al. Extramucosal spread and development of hepatitis in immunodeficient and normal mice infected with rhesus rotavirus. J Virol 1990;64(1):361-8.

48. Qiao H, Clark HF, DiVietro M, Riepenhoff-Talty M. A comparison of the effects of oral inoculation with rotashield and pentavalent reassortant rotavirus vaccine (WC3-PV) on suckline $CB17_{scid}$ mice. J Gen Virol 2004;85:2245-53.

49. Parashar UD, Holman RC, Clarke MJ, Bresee JS, Glass RI. Hospitalizations associated with rotavirus diarrhea in the united states, 1993 through 1995: surveillance based on the new ICD-9-CM rotavirus-specific diagnostic code. Int J Infect Dis 1998;177:13-7.

50. Clark HF, Offit PA. Vaccines for rotavirus gastroenteritis universally needed for infants. Pediatr Ann 2004;33(8):537-44.

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

52. MRL Report: Acute gastroenteritis report card validation report, 2003.

53. U.S. Department of Health and Human Services. Reference for historical data or rotavirus season: World AIDS day December 1, 1997. MMWR1197; 46(46): 1085-108.

54. Memo to Drummond JE from Chen J: Statistical report on the characterization of the human anti-rotavirus (G3) serum neutralization assay using strain OSU 78-8, 16-Oct-2001.

55. Memo to Drummond J from Chen J: Characterization of the human antirotavirus serum IgA enzyme immunoassay, 21-Jul-1999.

56. Memo to Kniskern P, Shaw A from Chen J: Statistical report on the characterization of the rotavirus neutralization assay, 14-Jan-1998.

57. Memo to Drummond JE from Chen J: Statistical report on the characterization of the human anti-rotavirus serum neutralization assay for type G4 rotavirus, 11-Dec-1998.

58. Nissan A, Zhang JM, Lin Z, Haskel Y, Freund HR, Hanani M. The contribution of inflammatory mediators and nitric oxide to lipopolysaccharide-induced intussusception in mice. J Surg Res 1997;69:205-7.

59. Lin Z, Cohen P, Nissan A, Allweis TM, Freund HR, Hanani M. Bacterial wall lipopolysaccharide as a cause of intussusception in mice. J Pediatr Gastroenterol Nutr 1998;27(3):301-5.

60. Freund H, Hurvitz H, Schiller M. Etiologic and therapeutic aspects of intussusception in childhood. Am J Surg 1977;134:272-4.

61. Nissan S, Levy E. Intussusception in infancy caused by hypertrophic Peyer's patches. Surgery 1966;59(6):1108-11.

62. Orr KB. Mesenteric adenitis and intussusception in childhood. Med J Aust 1969;1(11):579-81.

63. Bines JE, Kohl KS, Forster J, Zanardi LR, Davis RL, Hansen J, et al. Acute intussusception in infants and children as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation. Vaccine 2004;22:569-74.

64. Anderson EL, Belshe RB, Bartram J, Crookshanks-Newman F, Chanock RM, Kapikian AZ. Evaluation of rhesus rotavirus vaccine (MMU 18006) in infants and young children. J Infect Dis 1986;153(5):823-31.

65. Wright PF, King J, Araki K, Kondo Y, Thompson J, Tollefson SJ, et al. Simultaneous administration of two human-rhesus rotavirus reassortant strains of VP7serotype 1 and 2 specificity to infants and young children. J Infect Dis 1991;164:271-6.

66. Ward RL, Dinsmore AM, Goldberg G, Sander DS, Rappaport RS, Zito ET. Shedding of rotavirus after administration of the tetravalent rhesus rotavirus vaccine. Pediatr Infect Dis J 1998;17(5):386-90.

67. Bernstein DI, Glass RI, Rodgers G, Davidson BL, Sack DA. Evaluation of rhesus rotavirus monovalent and tetravalent reassortant vaccines in US children. JAMA 1995;273(15):1191-6.

68. Joensuu J, Koskenniemi E, Vesikari T. Symptoms associated with rhesus-human reassortant rotavirus vaccine in infants. Pediatr Infect Dis J 1998;17(4):334-40.

69. Rennels MB, Glass RI, Dennehy PH, Bernstein DI, Pichichero M, Zito ET, et al. Safety and efficacy of high-dose rhesus-human reassortant rotavirus vaccines - report of the national multicenter trial. Pediatrics 1996;97(1):7-13.

70. Ford-Jones EL, Wang E, Petric M, Corey P, Moineddin R, Fearon M. Hospitalization for community-acquired rotavirus-associated diarrhea: a prospective, longitudinal, population-based study during the seasonal outbreak. Arch Pediatr Adolesc Med 2000;154:578-85.

71. Hsu VP, Staat MA, Roberts N, Thieman C, Bernstein DI, Bresee J, et al. Use of active surveillance to validate *international classification of diseases* code estimates of rotavirus hospitalizations in children. Pediatrics 2005;115(1):78-82.

72. Bresee J, Fang Z-Y, Wang B, Nelson EAS, Tam J, Soenarto Y, et al. First report from the Asian rotavirus surveillance network. Emerg Infect Dis 2004;10(6):988-95.

73. Carlin JB, Chondros P, Masendycz P, Bugg H, Bishop RF, Barnes GL. Rotavirus infection and rates of hospitalisation for acute gastroenteritis in young children in Australia, 1993-1996. Med J Aust 1998;169:252-6.

74. O'Ryan M, Pérez-Schael I, Mamani N, Peña A, Salinas B, González G, et al. Rotavirus-associated medical visits and hospitalizations in South America: a prospective study at three large sentinel hospitals. Pediatr Infect Dis J 2001;20(7):685-93.

75. Griffin DD, Kirkwood CD, Parashar UD, Woods PA, Bresee JS, Glass RI, et al. Surveillance of rotavirus strains in the United States: identification of unusual strains. J Clin Microbio 2000;38(7):2784-7.

76. Trollfors B, Taranger J, Lagergård T, Lind L, Sundh V, Zackrisson G, et al. A placebo-controlled trial of a pertussis-toxoid vaccine. N Engl J Med 1995;333:1045-50.

77. Taranger J, Trollfors B, Lagergård T, Lind L, Sundh V, Bryla DA, Schneerson R, et al. Correlation between pertussis toxin IgG antibodies in postvaccination sera and subsequent protection against pertussis. J Infect Dis 2000;181:1010-3.

78. Taranger J, Trollfors B, Bergfors E, Knutsson N, Lagergård T, Schneerson R, et al. Immunologic and epidemiologic experience of vaccination with a monocomponent pertussis toxoid vaccine. Pediatrics 2001; 108(6):1-6.