

# Vaccine and Related Biologics Products Advisory Committee

December 14, 2005

## RotaTeq™



Rotavirus vaccine, live, oral, pentavalent  
k Merck & Co., Inc.

# RotaTeq™ Proposed Indication

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 P1a (e.g., G9)

RotaTeq™ may be administered to infants as young as 6 weeks of age

# RotaTeq™ Agenda

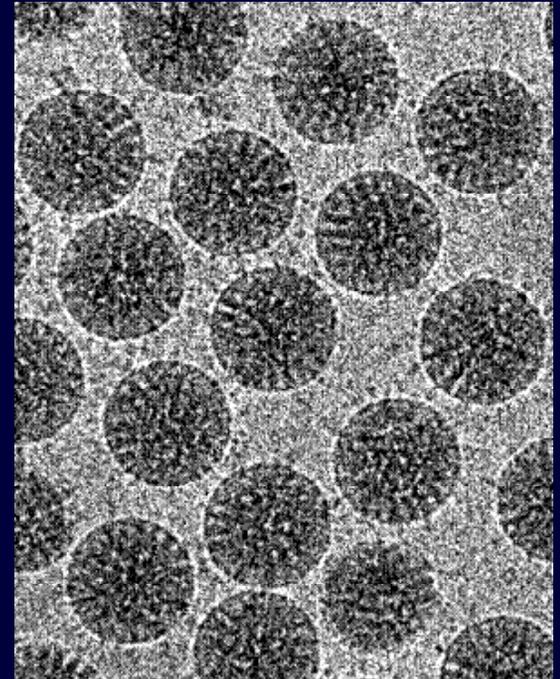
- Mark Bagarazzi, MD, FAAP
  - Global impact of rotavirus gastroenteritis
  - Overview of RotaTeq™ clinical development program

# RotaTeq™ Agenda

- Mark Bagarazzi, MD, FAAP
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  - Overview of RotaTeq™ clinical development program
- Penny Heaton, MD
  - Rotavirus gastroenteritis in the US
  - Clinical trial results
  - Overall benefit/risk profile

# Rotavirus: Leading Cause of Severe Diarrhea in Infants and Young Children Worldwide

- Virtually all children are infected by 5 years of age
- Worldwide, approximately 1,000 children die every day from rotavirus
- Rotavirus accounts for over 2 million hospitalizations worldwide annually (55,000-70,000 in US)
- Rotavirus affects all children equally
  - Regardless of socioeconomic status, environmental conditions, geographic area
  - Severe symptoms equally common in developed and developing world



Parashar et al., *Emerging Infect Dis.* 2003; 9:565-72.  
Parashar et al., 2005 IDSA; Abstract 579.

# RotaTeq™ Development



# RotaTeq™ Development

**Proof-of-  
Concept  
Study  
(G1-3, P1)  
(002)**

1993

1997

1998

1999

2000

2001

2002

2003

2004

2005

# RotaTeq™ Development

**Proof-of-  
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Study  
(G1-3, P1)  
(002)**

**Study of  
Different  
Buffers  
(G1-2)  
(003)**

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# RotaTeq™ Development

**Proof-of-Concept Study  
(G1-3, P1)  
(002)**

**Study of Different Buffers  
(G1-2)  
(003)**

**Dose-ranging Study,  
Monovalent (P1),  
Quadrivalent (G1-4),  
Pentavalent (G1-4, P1)  
(005)**

1993

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1998

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2000

2001

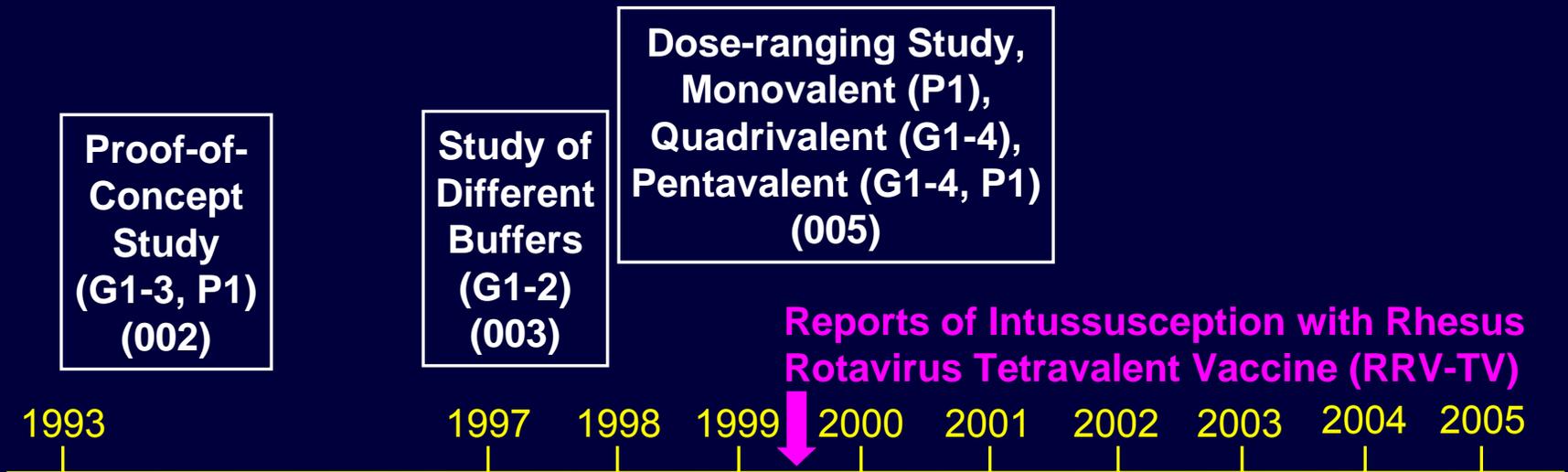
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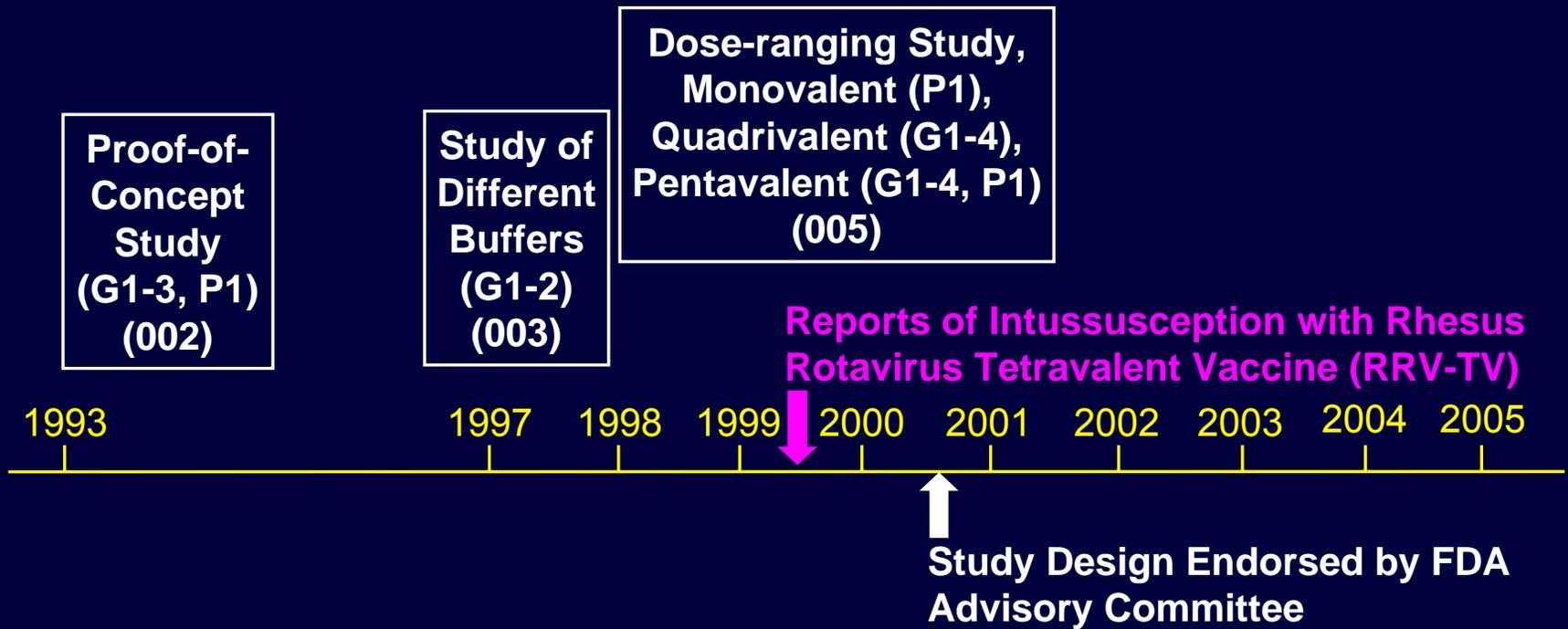
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2005

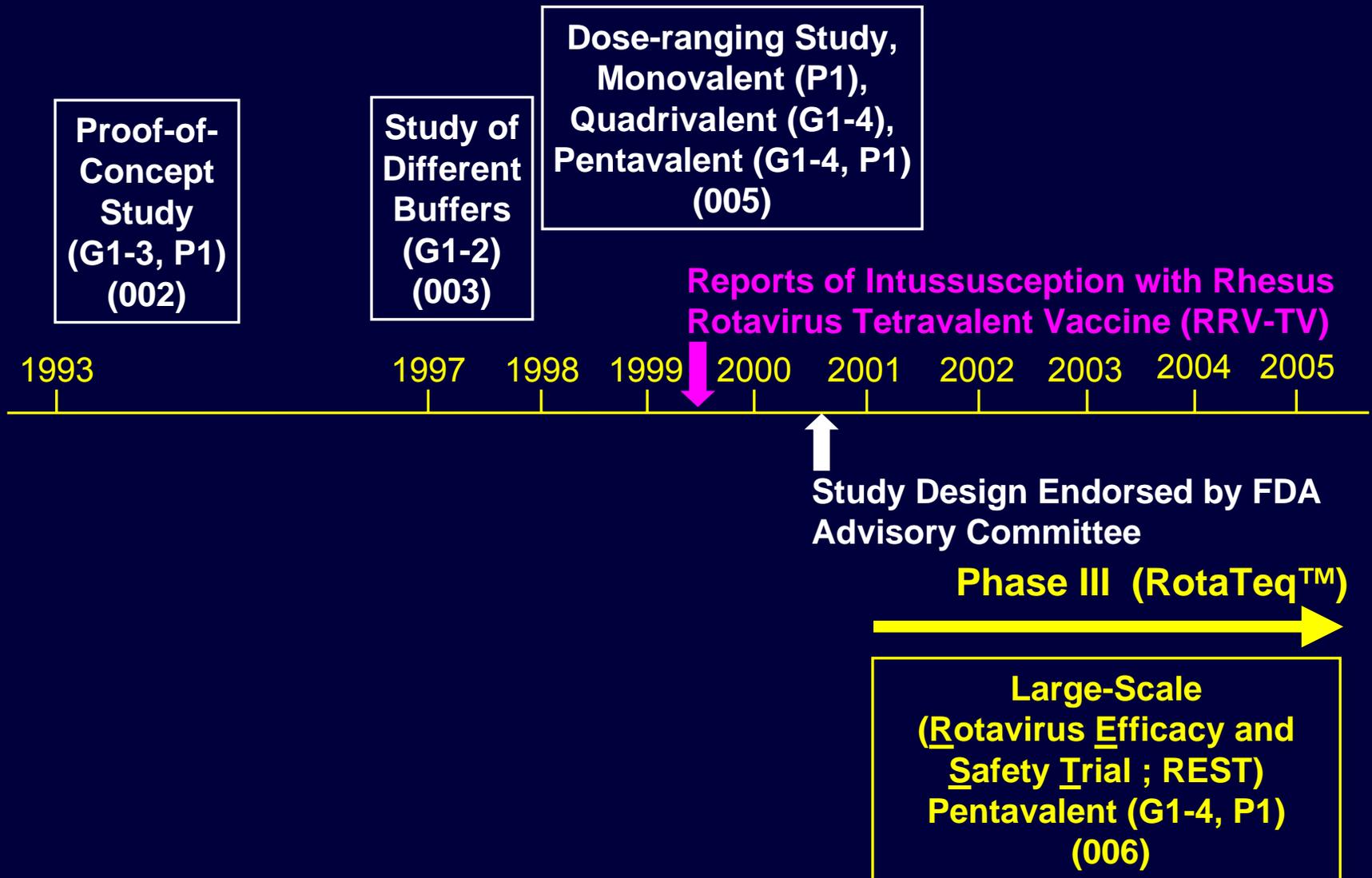
# RotaTeq™ Development



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# RotaTeq™ Phase III Program

- Safety
  - Intussusception (REST)

**Large-Scale  
(Rotavirus Efficacy and  
Safety Trial ; REST)  
(006)**

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**Dose  
Confirmation  
Efficacy  
(007)**

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- Safety
  - Intussusception (REST)

**Large-Scale  
(Rotavirus Efficacy and  
Safety Trial ; REST)  
(006)**

**Dose  
Confirmation  
Efficacy  
(007)**

**Consistency  
Lots Study  
(009)**

# RotaTeq™ Phase III Program

- Safety

- Intussusception (REST)
- Generally well tolerated
- AEs of special interest (Fever, vomiting, diarrhea, and irritability)

**Large-Scale  
(Rotavirus Efficacy and  
Safety Trial ; REST)  
(006)**

**Dose  
Confirmation  
Efficacy  
(007)**

**Consistency  
Lots Study  
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# RotaTeq™ Phase III Program

- Efficacy (REST, Protocol 007)

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    - Prevents 98% of severe disease
    - Prevents 74% of all disease

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- Efficacy (REST, Protocol 007)
  - RV gastroenteritis due to vaccine-virus serotypes
    - Prevents 98% of severe disease
    - Prevents 74% of all disease
  - Reduction in hospitalizations and emergency department visits by 94%

# RotaTeq™ Phase III Program

- Immunogenicity

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  - Consistency of manufacturing process (Protocol 009)

# RotaTeq™ Phase III Program

- Immunogenicity
  - Consistency of manufacturing process (Protocol 009)
  - Integration of RotaTeq™ into immunization schedule of 2- to 6-month olds (REST)

# Experts in Attendance

- H Fred Clark, DVM, PhD – Children’s Hospital of Philadelphia, University of Pennsylvania School of Medicine
- Paul Offit, MD - Children’s Hospital of Philadelphia, University of Pennsylvania School of Medicine
- King Holmes, MD, PhD - University of Washington School of Medicine, (Chairman REST DSMB)
- Janet Wittes, PhD – Statistics Collaborative (Statistician, REST DSMB)
- Gary S. Marshall, MD – University of Louisville
- David O. Matson, MD, PhD – Eastern Virginia Medical School (Principal Investigator, REST, US sites)

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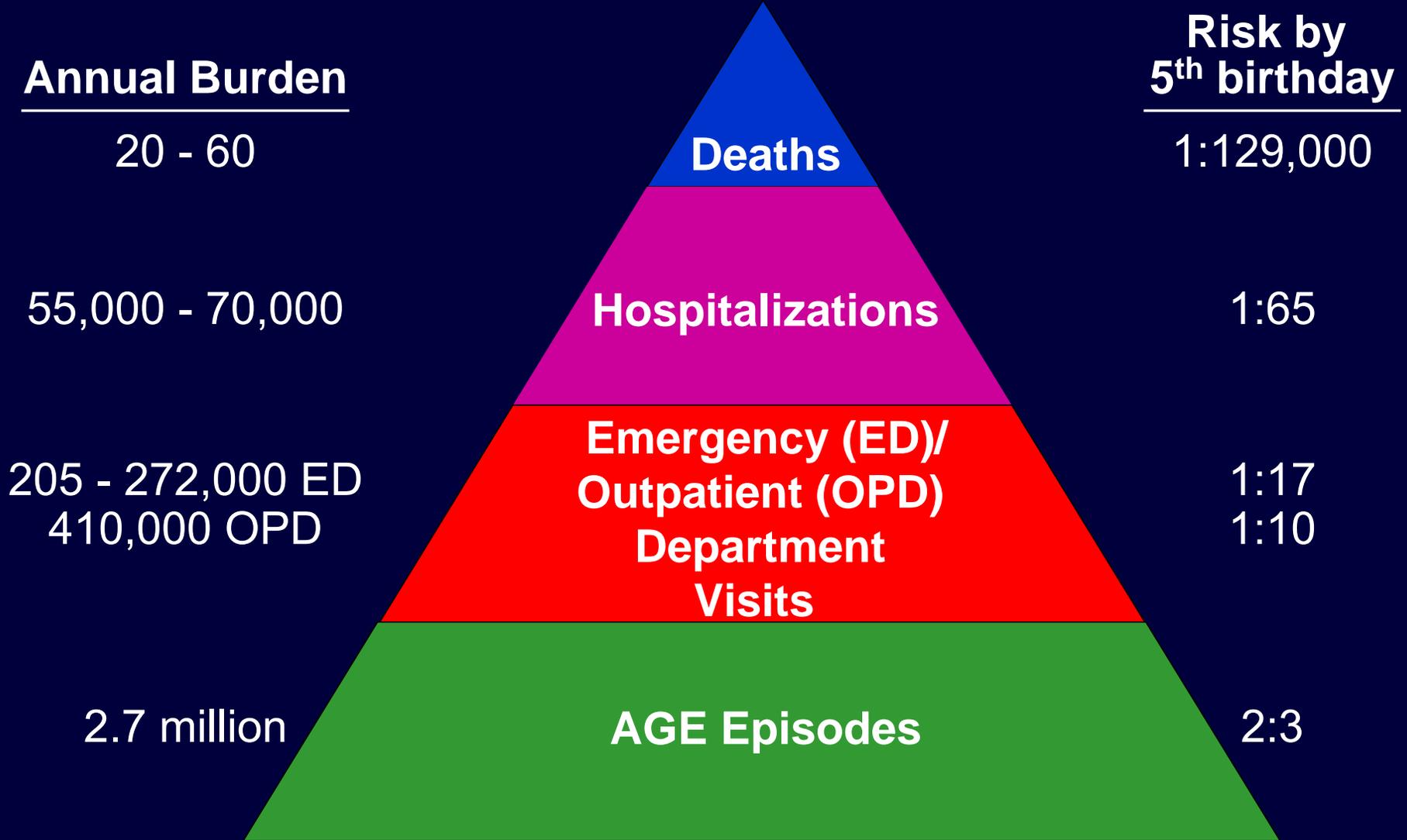
# Objectives

- Brief review of rotavirus epidemiology
- Description of the pentavalent human-bovine reassortant rotavirus vaccine, RotaTeq™
- Overview of Phase III clinical trials
- Results from Phase III clinical trials supporting licensure of RotaTeq™
  - Safety
  - Efficacy
  - Immunogenicity

# Public Health Burden of Rotavirus Disease in the United States

- Rotavirus accounts for 4% to 6% of all pediatric hospitalizations
  - Risk of developing rotavirus gastroenteritis and associated outcomes does not vary by geographic region
- Updated estimates of rotavirus morbidity and mortality show no change over the last decade

# US Annual Burden of Rotavirus Disease



Parashar et al., 2005 IDSA; Abstract 579.

# Structure of Rotavirus

- Nonenveloped icosahedral particle
  - 11 segments of double-stranded RNA enclosed in a triple layer capsid
- Outer layer consists of VP7 and VP4, which are important for immunity
  - Induce serotype-specific neutralizing antibodies
- Rotaviruses are classified by their G- and P-types
  - VP7 determines G-type
  - VP4 determines P-type

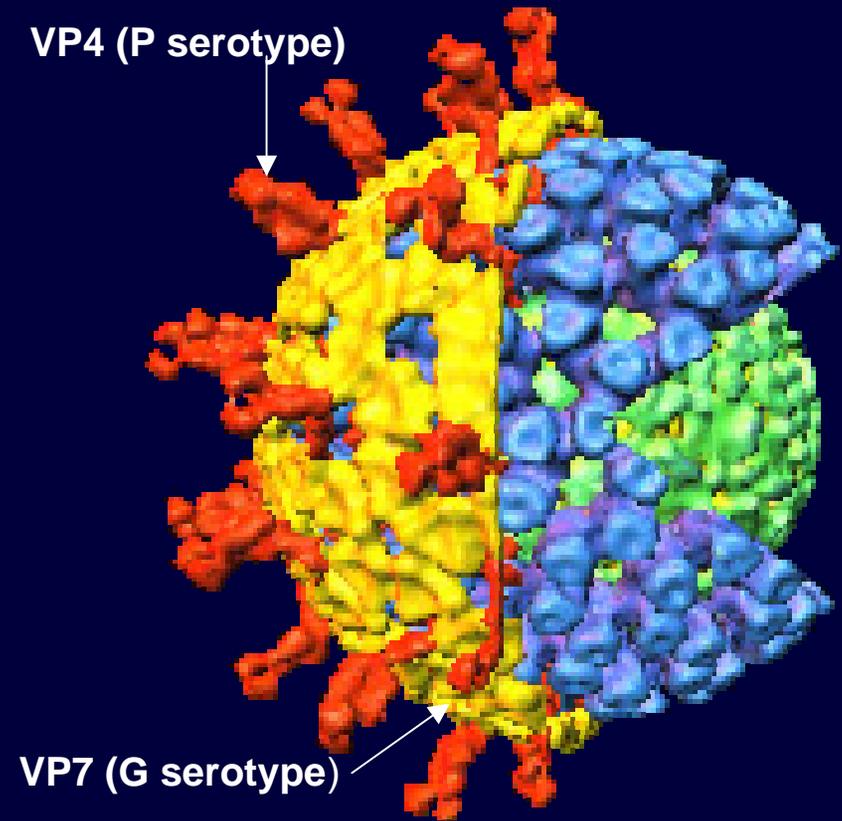
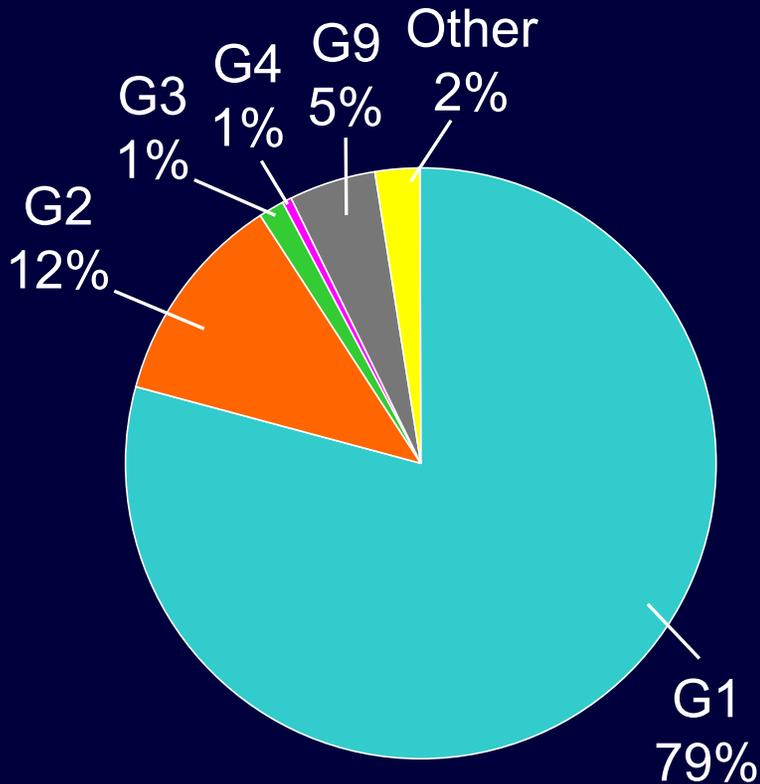
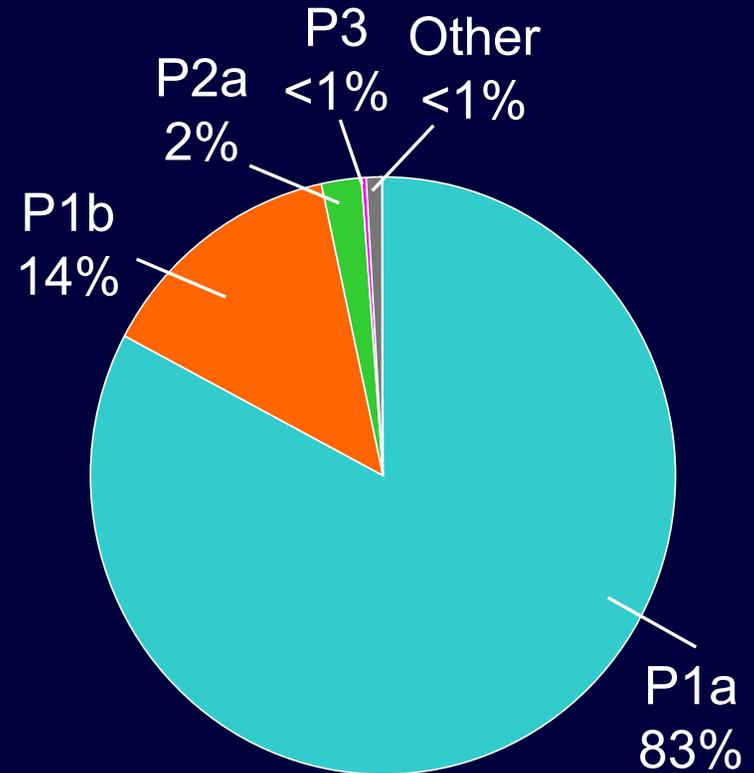


Figure adapted from Estes MK, *J Infect Dis.* 1996;174(Suppl 1):S37-S46.

# G1, G2, G3, and G4 Account for >90% of Rotavirus Cases\*



# P1a is Most Common P-Type



Prevalent G- and P-types in US, 1996-2002

\* Griffin et al., *J Clin Microbiol* 2000; 38:2784-7 and Santos et al., *Rev. Med. Virol.* 2005; 15:29-56.

# Rotavirus Gastroenteritis is Characterized by Fever, Vomiting, and Watery Diarrhea

- Average duration 6 days (3 to 9 days)
- Extended duration of vomiting with diarrhea may cause dehydration
  - Hospitalization may be required
  - Death may occur if supportive care unavailable

<u>Clinical Finding</u>	<u>Rotavirus Positive</u>	<u>Rotavirus Negative</u>
Vomiting*	96%	58%
Dehydration*	83%	40%
Fever	77%	61%
Diarrhea	100%	100%

Rodriguez et al., *J Pediatrics* 1977; 91(2):188-193 and Santos et al., *Rev. Med. Virol.* 2005; 15:29-56.  
\* Statistically significant.

# Basis for Prevention of Rotavirus Gastroenteritis Through Vaccination

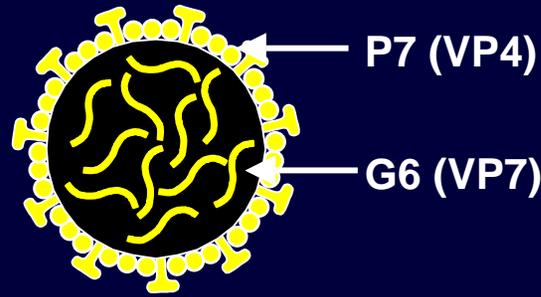
- Wild-type rotavirus infection induces immunity against subsequent rotavirus gastroenteritis
  - Greatest protection against severe disease
  - Substantial protection against mild gastroenteritis
- Natural immunity is largely serotype-specific
- We developed a multivalent rotavirus vaccine directed against the most prevalent rotavirus serotypes

# Characteristics of RotaTeq™

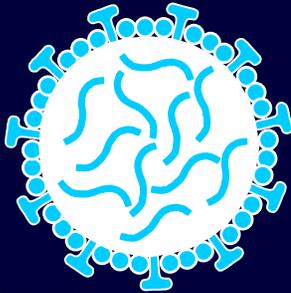
- Oral vaccine suspended in a liquid buffer/stabilizer
  - Protected from gastric acid
  - Stored refrigerated with 24-month shelf life
- Administered directly from tube
- 3-dose regimen that will integrate into pre-established immunization schedules
  - First dose age 6 to 12 weeks
  - Subsequent doses at 1- to 2-month intervals
- Contains 5 human-bovine rotavirus reassortants
  - Serotypes: Human G1, G2, G3, G4, and P1a  
Bovine G6, P7



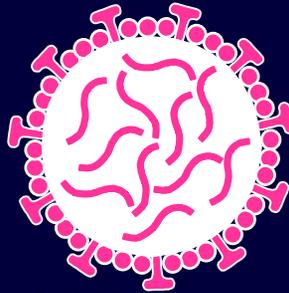
# Bovine (WC3) Rotavirus



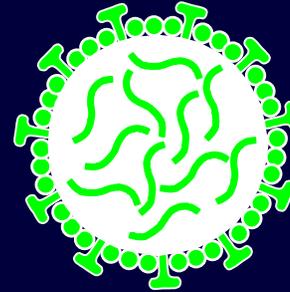
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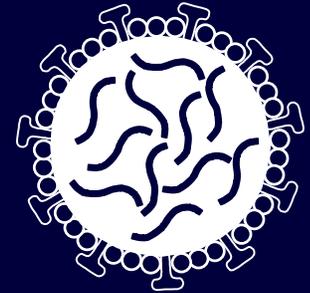
G1,P1 Human Rotavirus



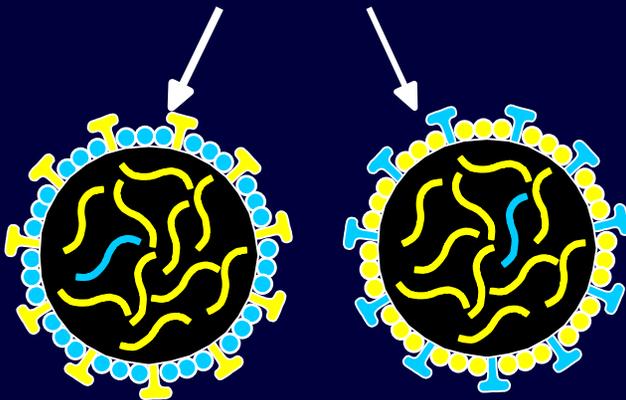
G2 Human Rotavirus



G3 Human Rotavirus

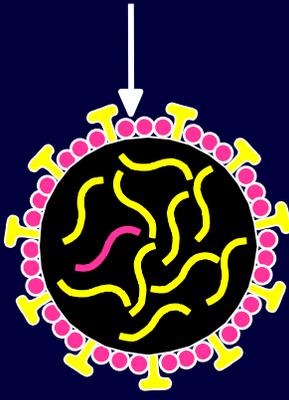


G4 Human Rotavirus

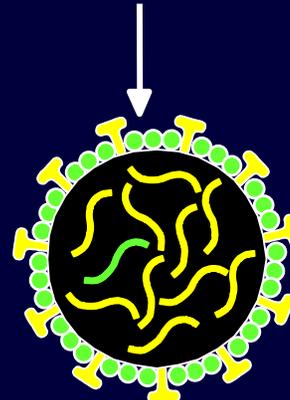


G1 (P7)

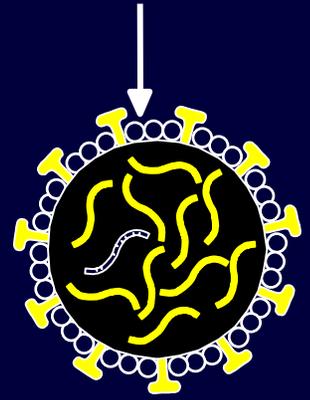
P1 (G6)



G2 (P7)



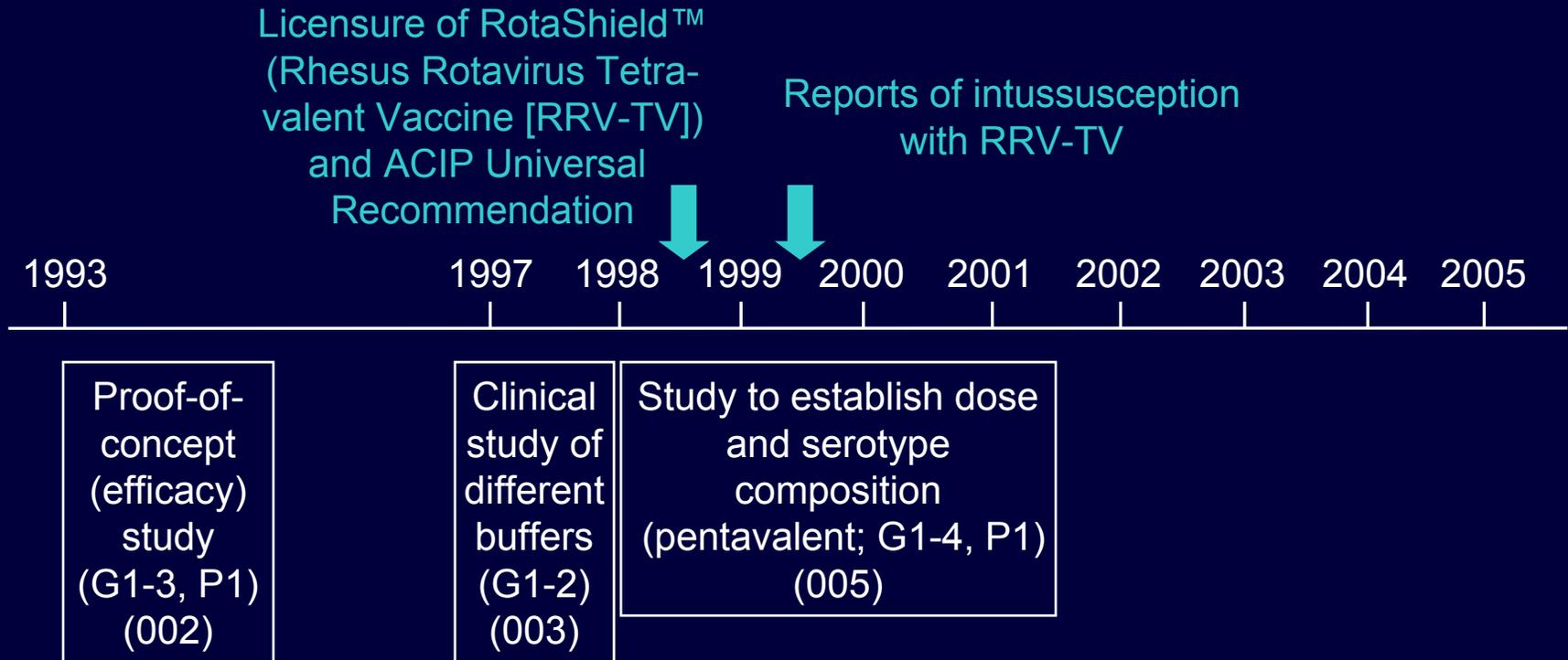
G3 (P7)



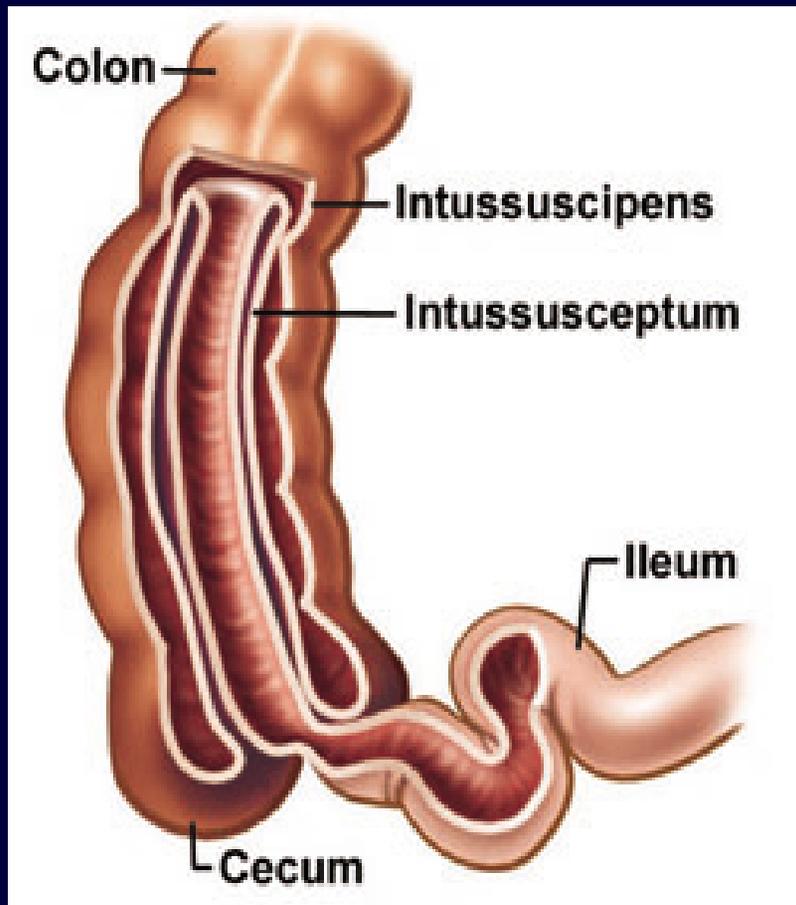
G4 (P7)

## Human-Bovine Reassortant Rotavirus Vaccine Strains

# Overview of Development of RotaTeq™

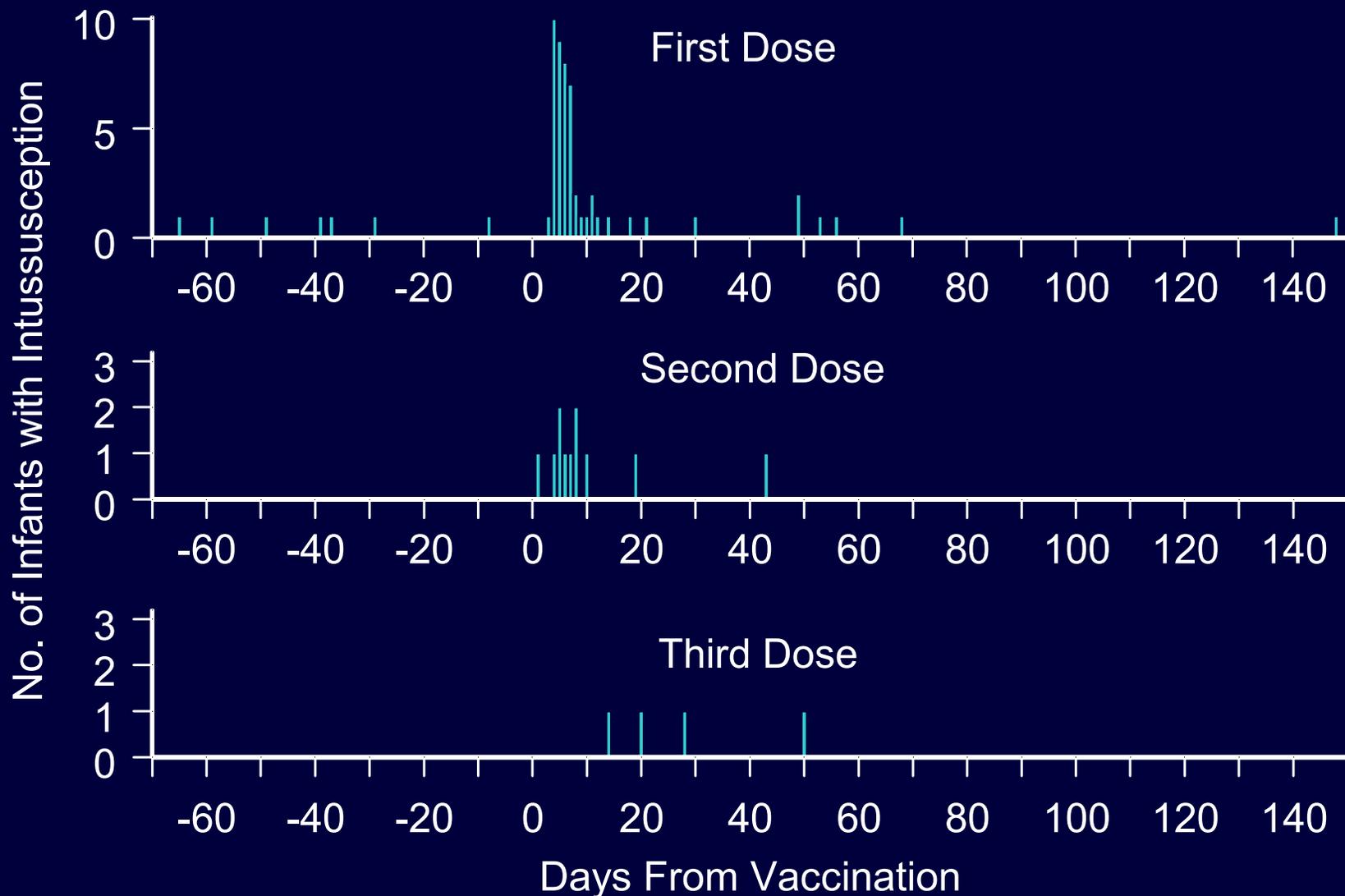


# Characteristics of Naturally-Occurring Intussusception



- Etiology not well defined
- Uncommon: Incidence  $\sim 1/2000$  infant-years
- Peak incidence is between 5 and 9 months of age
- Male to female case ratio = 1.5-4:1
- Treated with enema or surgery
- Morbidity and mortality low if treated early; however, delay in diagnosis may be fatal

# Cases of Intussusception Associated with RRV-TV Clustered During the 2 Weeks After Doses 1 and 2



Murphy et al., *New Engl J Med* 2001; 344:564-72.

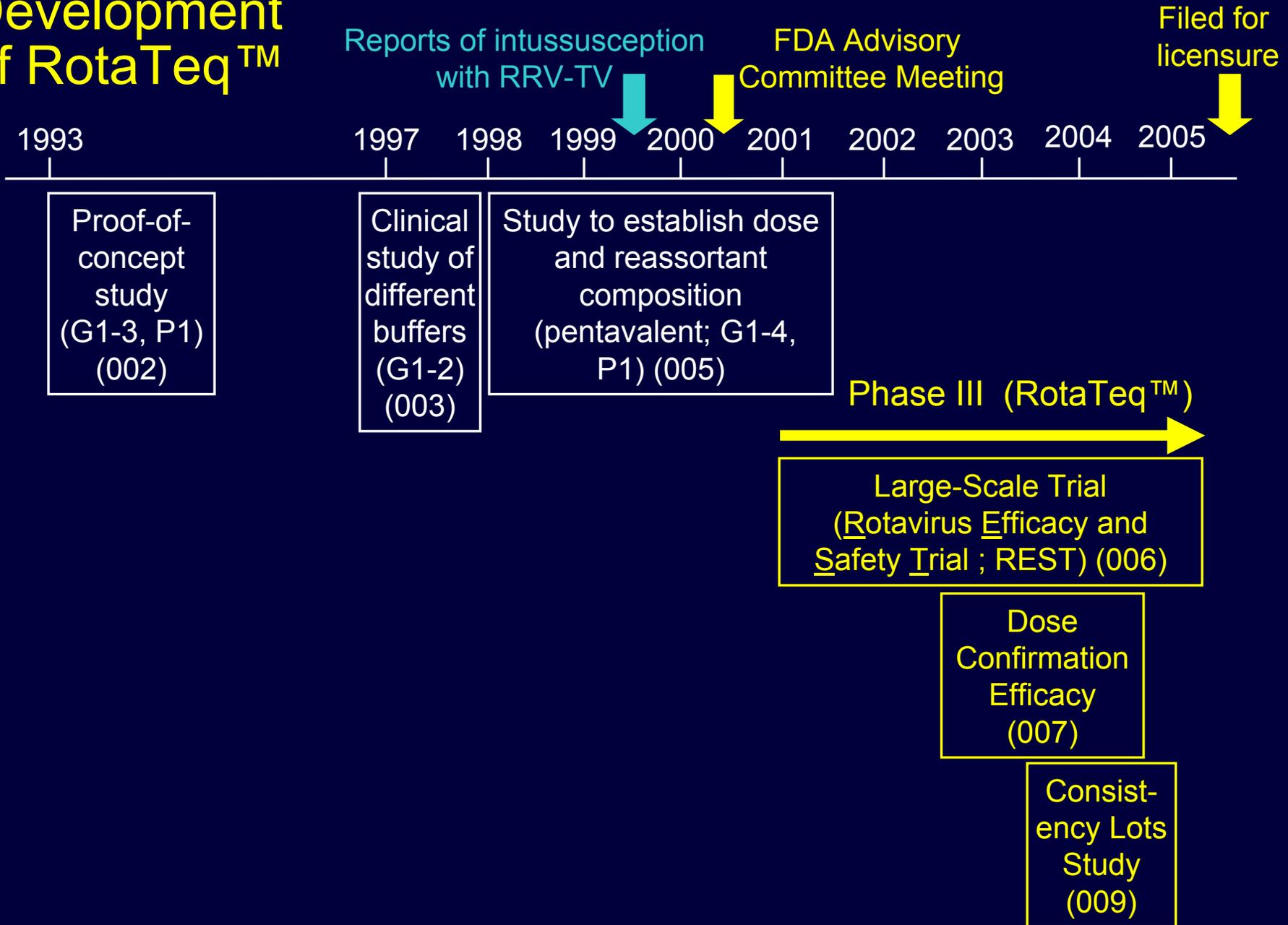
# Basis for Decision to Continue Development of RotaTeq™ in the Face of Concerns About Intussusception (IS)

- Public health need for a safe and effective rotavirus vaccine
- Phase II studies showing that the vaccine was well tolerated and prevented rotavirus gastroenteritis
  - Single case of IS in 2470 vaccine recipients
- RRV-TV associated with IS may be rhesus strain-specific
  - Wild-type rotavirus does not appear to cause IS
  - Pre-clinical/clinical differences between RotaTeq™ and RRV-TV

<u>Factor</u>	<u>RotaTeq™</u>	<u>RRV-TV</u>
Systemic disease in mice	No	Yes
Reactogenic in infants	No	Yes

- FDA Advisory Committee approved design for large-scale Rotavirus Efficacy and Safety Trial (REST) in May 2000

# Development of RotaTeq™



Evaluation of Safety with  
Respect to Intussusception:

Rotavirus Efficacy and Safety Trial  
(REST)

# REST Study Design

- Sample size:  $\geq 60,000$  (randomized 1V:1P)  
Additional groups of 10,000 subjects enrolled until primary safety criteria met or 100,000 subjects enrolled
- Age: 6 to 12 weeks at first dose
- Regimen: 3 oral doses, 1 every 4 to 10 weeks
- Sites: Areas with good standard of care for intussusception
- Duration: January 2001 to April 2005

# REST Primary Safety Hypothesis

- RotaTeq™ will not increase the risk of intussusception (IS) relative to placebo within 42 days of any dose
- To satisfy the primary safety hypothesis, 2 criteria must be met:
  1. Interim monitoring: No increased IS risk (LB 95% CI >1) in vaccine recipients following any dose
    - 1 to 7 days
    - 1 to 42 days
  2. End of study: Upper bound of the 95% CI estimate of the relative risk of IS  $\leq 10$ 
    - RR point estimates  $\leq 2$  would be needed to satisfy the safety criteria

# Comprehensive Interim Monitoring for Intussusception (IS)

## Active Surveillance at Study Sites

- Contacts on days 7, 14, and 42
- Up to 1 year after first dose

## Independent Safety Endpoint Adjudication Committee

- Adjudicated cases using specific case definition

## Independent Data and Safety Monitoring Board (DSMB)

- Unblinded each case and made recommendations for continuation
- Reviewed safety data every 6 months



Potential  
IS Case



Positively-  
Adjudicated  
IS Case

# Comments on Statistical Properties of REST Study Design

- Goals of REST study design and the extensive safety monitoring were to provide:
  - High probability that a study of a vaccine with increased intussusception risk would stop early; and simultaneously
  - High probability that a safe vaccine would meet the end-of-study criteria
- The statistical operating characteristics of REST were estimated using Monte Carlo simulation

# Statistical Operating Characteristics of REST

<u>Risk Scenario</u>	<u>Probability of Stopping Early Because Unsafe</u>	<u>Probability of Meeting End of Study Safety Criteria</u>
Safe Vaccine (RR=1)	6%	94%
RRV-TV Risk Profile*	~90%	~10%

\* Murphy et al., *New Engl J Med* 2001; 344: 564-72.  
Probabilities based on two different risk profiles reported by CDC.

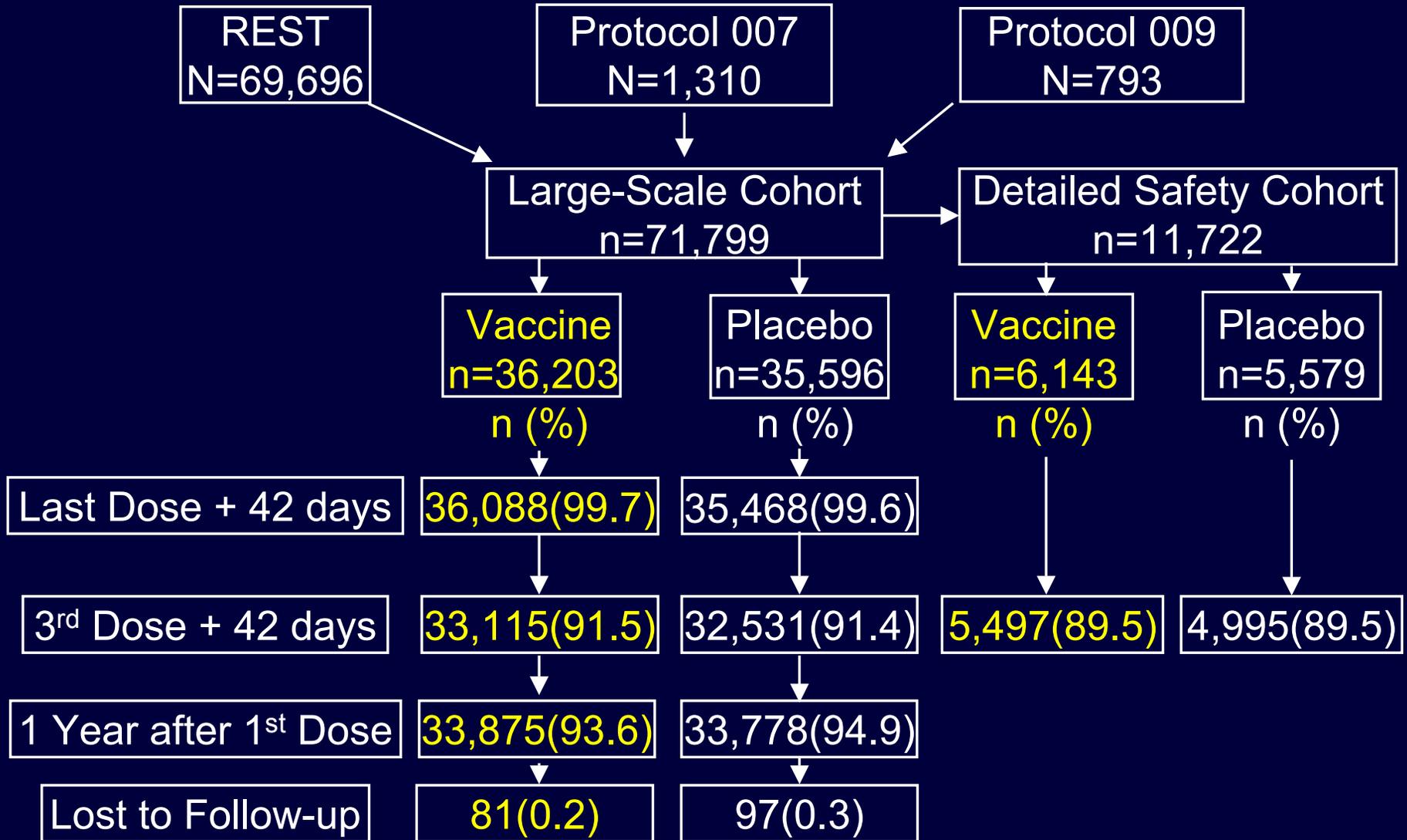
# 71,799 Subjects in 11 Countries Vaccinated

## 36,203 in RotaTeq™ Group

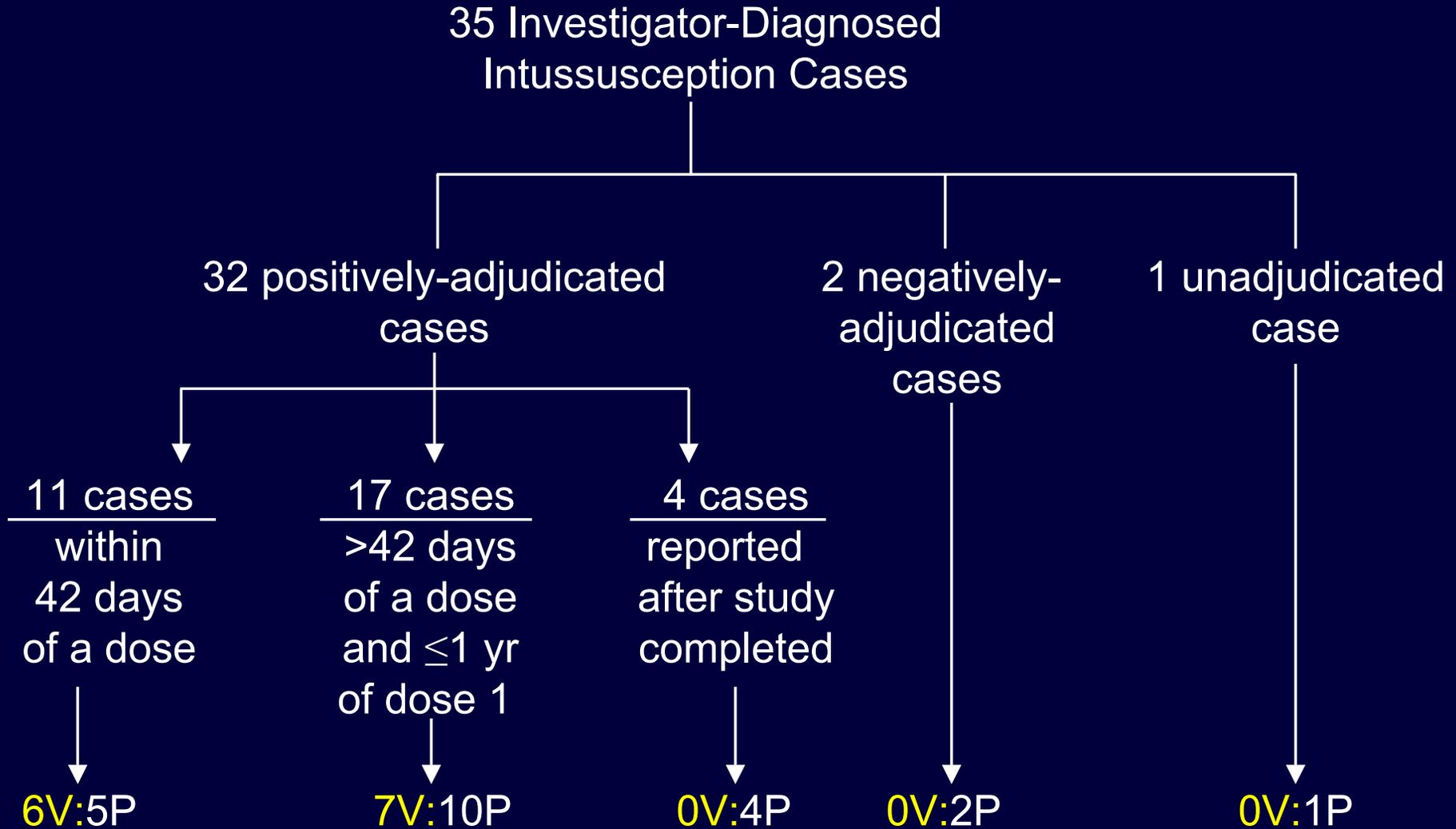
## 35,596 in Placebo Group



# Safety Follow-up: Phase III Trials



# REST Intussusception Results



No intussusception cases in Protocols 007 and 009

# Confirmed Intussusception Cases in REST Within 1 Year of Dose 1

13 Vaccine : 15 Placebo  
RR=0.9; 95% CI=0.4, 1.9

Dose 1



Dose 2



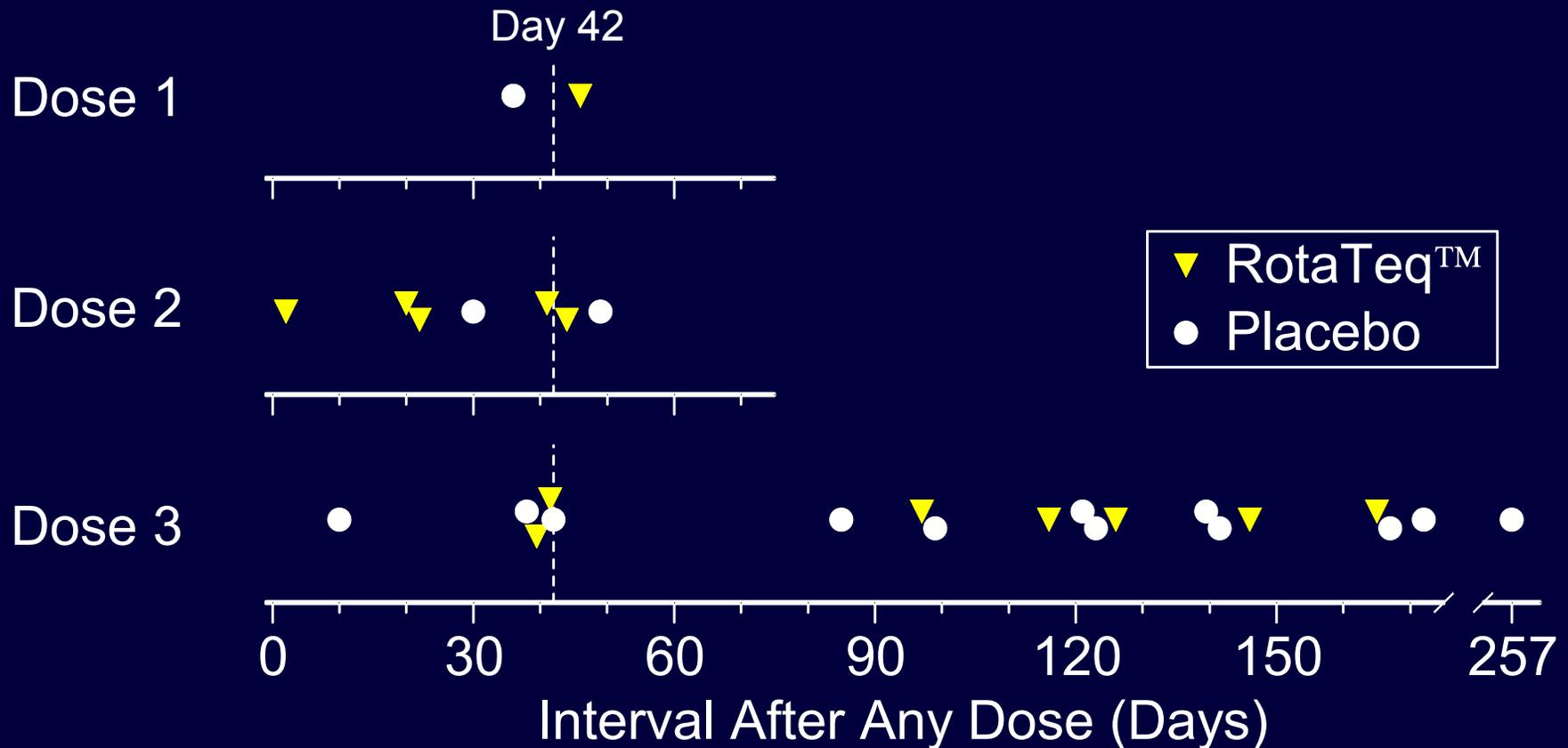
Dose 3



Interval After Any Dose (Days)

# Confirmed Intussusception Cases in REST Within 42 Days of Each Dose

6 Vaccine : 5 Placebo  
RR=1.2; 95% CI=0.3, 5.0\*



\* Unadjusted for multiplicity.

# Characteristics of Intussusception Cases Were Similar to Those of Naturally- Occurring Intussusception

- Incidence, gender, and age of cases were similar to naturally-occurring intussusception
  - Incidence (infant-years):
    - 1:2253 overall; 1:2101 in placebo recipients
  - Gender: 19 male, 13 female
  - Peak age at diagnosis: 5 to 9 months
- No shift of vaccine cases to younger infants 2 to 3 months old

# REST Data Provide a High Level of Confidence in the Safety of RotaTeq™

- Primary safety hypothesis was satisfied
  - Relative risk of intussusception met pre-specified statistical criteria for clinical acceptability
    - RR=1.6; 95% CI=0.4,6.4 (multiplicity adjusted)
- Intussusception cases occurred sporadically
  - No clinical evidence of an increased intussusception risk among vaccine recipients within 7 and 14 days of any dose
- Characteristics of cases in REST were similar to those of naturally-occurring intussusception

# Additional Safety Data from the Phase III Studies

(REST, Protocol 007, Protocol 009)

# Overview of Safety Evaluations in Phase III Studies

**Large-Scale Cohort**  
N=71,799  
(36,203V:35,596P)

**All serious adverse events (SAEs)  
including intussusception**

- Vaccine-related SAEs and deaths were to be reported until study's end

+

**Detailed Safety  
Cohort**  
N=11,722  
(6143V:5579P)

**All adverse events (AEs)**

- Other AEs of clinical interest
  - Fever (temp  $\geq 100.5^{\circ}\text{F}$  rectal equivalent), vomiting, diarrhea, irritability, and hematochezia

- Fecal vaccine-strain shedding was evaluated in 2 ways
  - Pre-specified time interval
  - All rotavirus-positive potential acute gastroenteritis cases

N=Number vaccinated.

# Summary of Serious Adverse Events (SAEs) Within 42 Days of Any Dose

## Large-Scale Cohort

	Number (%) of Subjects	
	RotaTeq™	Placebo
No SAEs	35,289 (97.6)	34,614 (97.4)
SAEs	861 (2.4)	922 (2.6)
Dose-related SAEs	49 (0.1)	79 (0.2)
Deaths	15 (<0.1)	13 (<0.1)
Discontinued due to an SAE	83 (0.2)	72 (0.2)

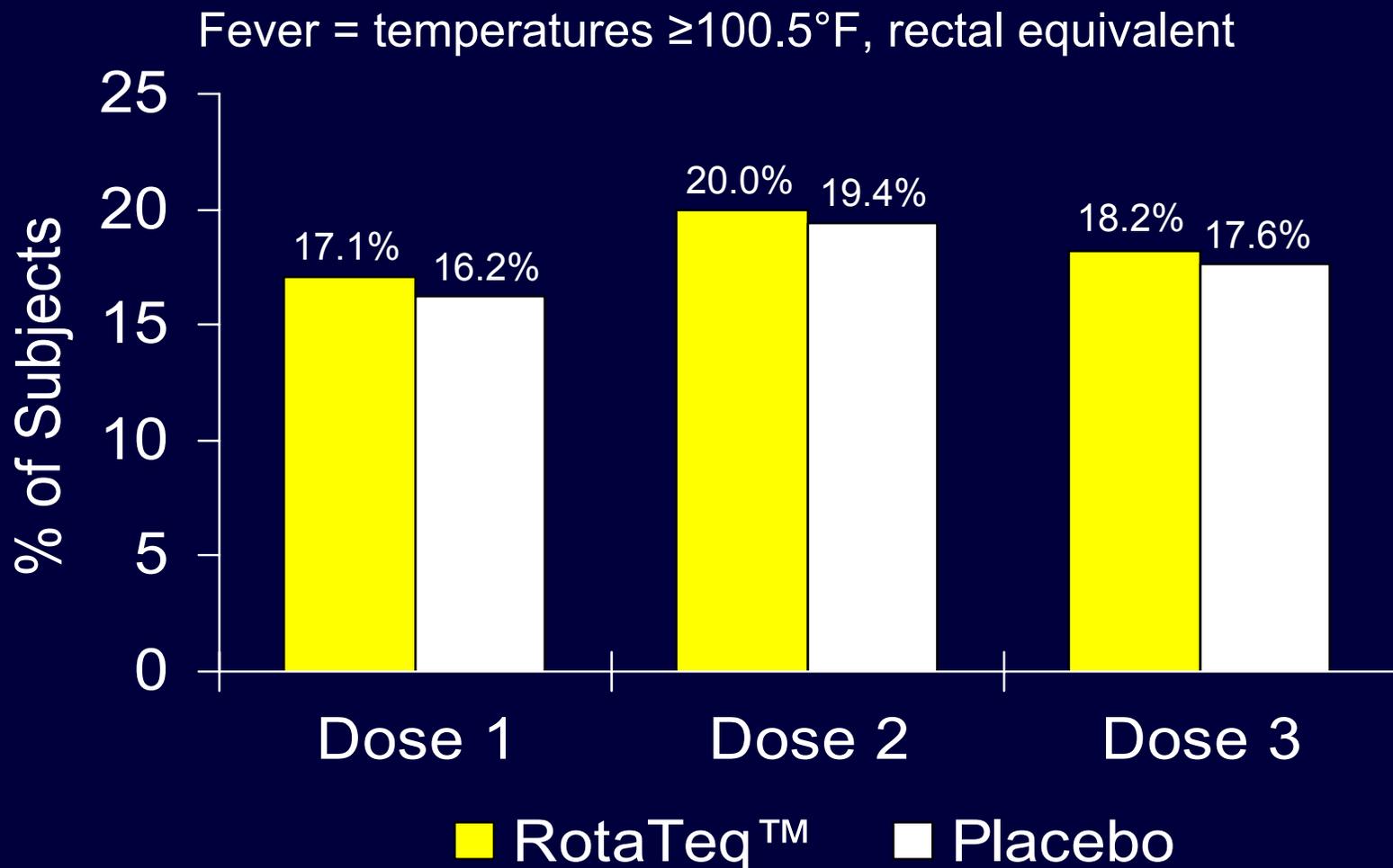
# Most Frequently Reported SAEs Within 42 Days of Any Dose

## Large-Scale Cohort

	Number (%) of Subjects	
	<u>RotaTeq™</u>	<u>Placebo</u>
Most frequent SAEs overall		
Bronchiolitis	226 (0.6)	257 (0.7)
Gastroenteritis	73 (0.2)	117 (0.3)
Most frequent dose-related SAEs (blinded investigator-assessment)		
Gastroenteritis	17 (<0.1)	33 (0.1)
Fever	8 (<0.1)	12 (<0.1)
Dehydration	3 (<0.1)	13 (<0.1)

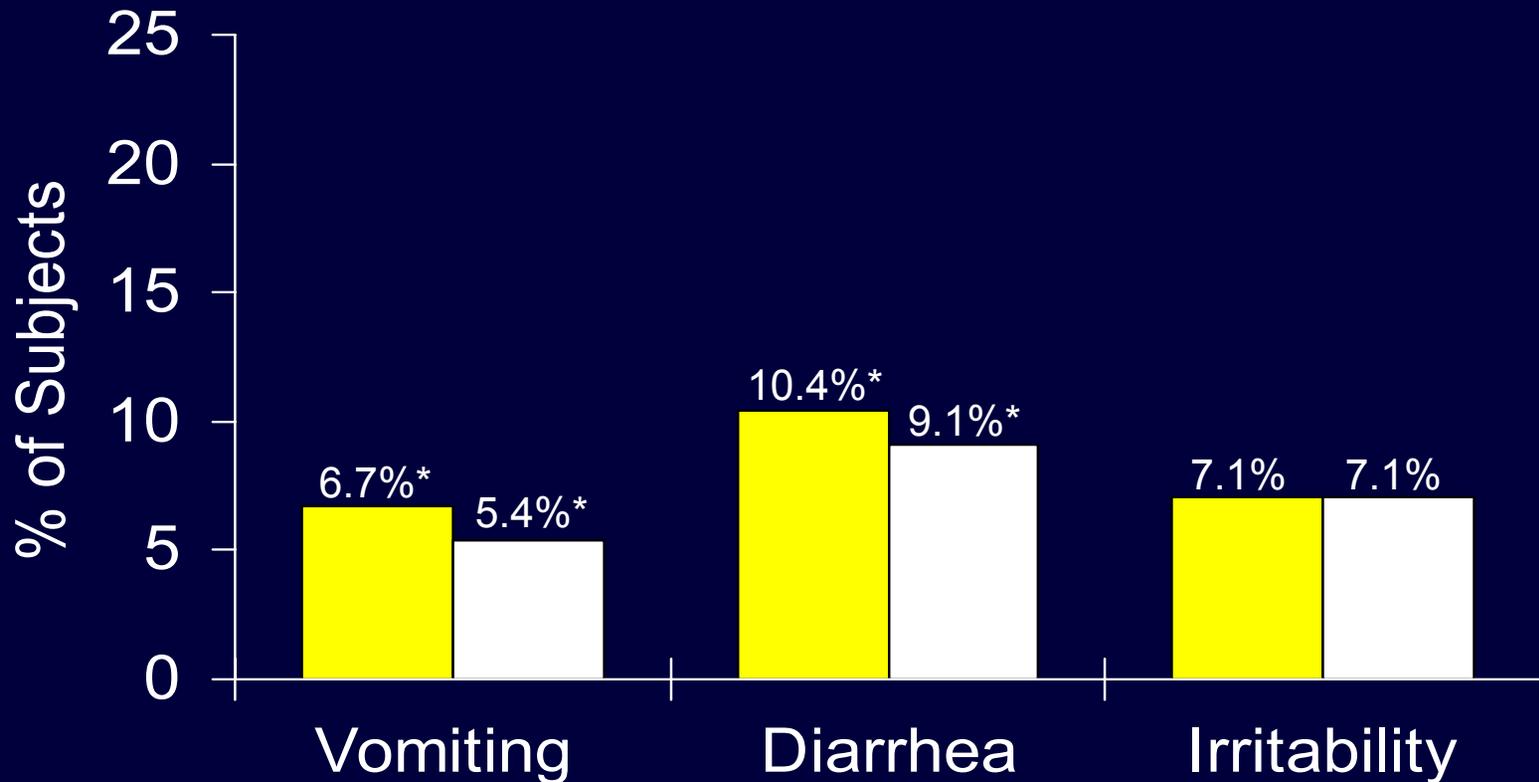
# Percent of Infants with Fever Within Week of Dose by Vaccination Group and Dose Number

## Detailed Safety Cohort



# Percent of Infants with Vomiting, Diarrhea, and Irritability Within Week of First Dose by Vaccination Group

## Detailed Safety Cohort

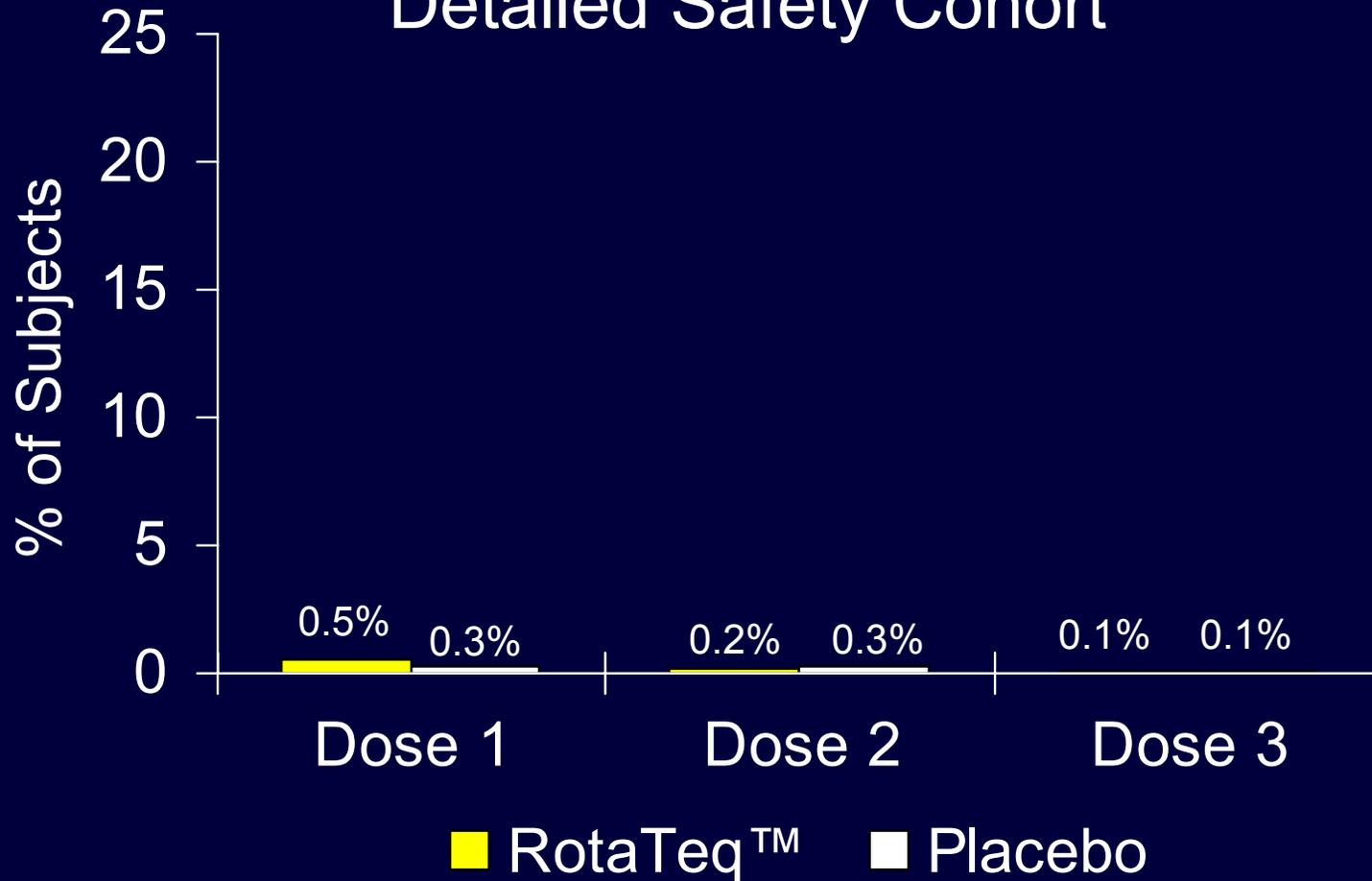


\* p-Value (2 sided) <0.05.

■ RotaTeq™ ■ Placebo

# Percent of Infants with Hematochezia\* Within 6 Weeks of Dose by Vaccination Group and Dose Number

Detailed Safety Cohort



\* Includes bloody stools, melena, and procedures for hematochezia.

# Evaluation of Fecal Shedding of Vaccine-Virus Strains

- Phase II studies of fecal shedding of vaccine-virus strains:
  - Low (<10%) proportion of subjects
  - Low (<10<sup>3</sup> PFU/mL) quantities
  - Almost exclusively after dose 1
- Vaccine-virus strain fecal shedding peaked during 4- to 6-day period after the first dose
- Fecal shedding of vaccine-virus strains evaluated in REST and Protocol 007
  - Prospectively defined subset of ~300 subjects 4 to 6 days after each dose (REST)
  - Potential acute gastroenteritis episodes that were rotavirus EIA-positive (REST and Protocol 007)

# Fecal Shedding of Vaccine-Virus Strains in REST and Protocol 007 Occurred Almost Exclusively After Dose 1

<u>Dose Number</u>	<u>Number of Shedders/ Number Tested (%)</u>	
	<u>RotaTeq™</u>	<u>Placebo</u>
One	32/360 (8.9)	2/287 (0.7)
Two	0/249 (0)	0/282 (0)
Three	1/385 (0.3)	0/962 (0)

- Latest shedding postdose was 15 days from dose 1
- One subject shed 4 days from dose 3
- Low quantities ( $5 \times 10^1$  to  $1.88 \times 10^4$  PFU/mL)

# Summary of General Safety

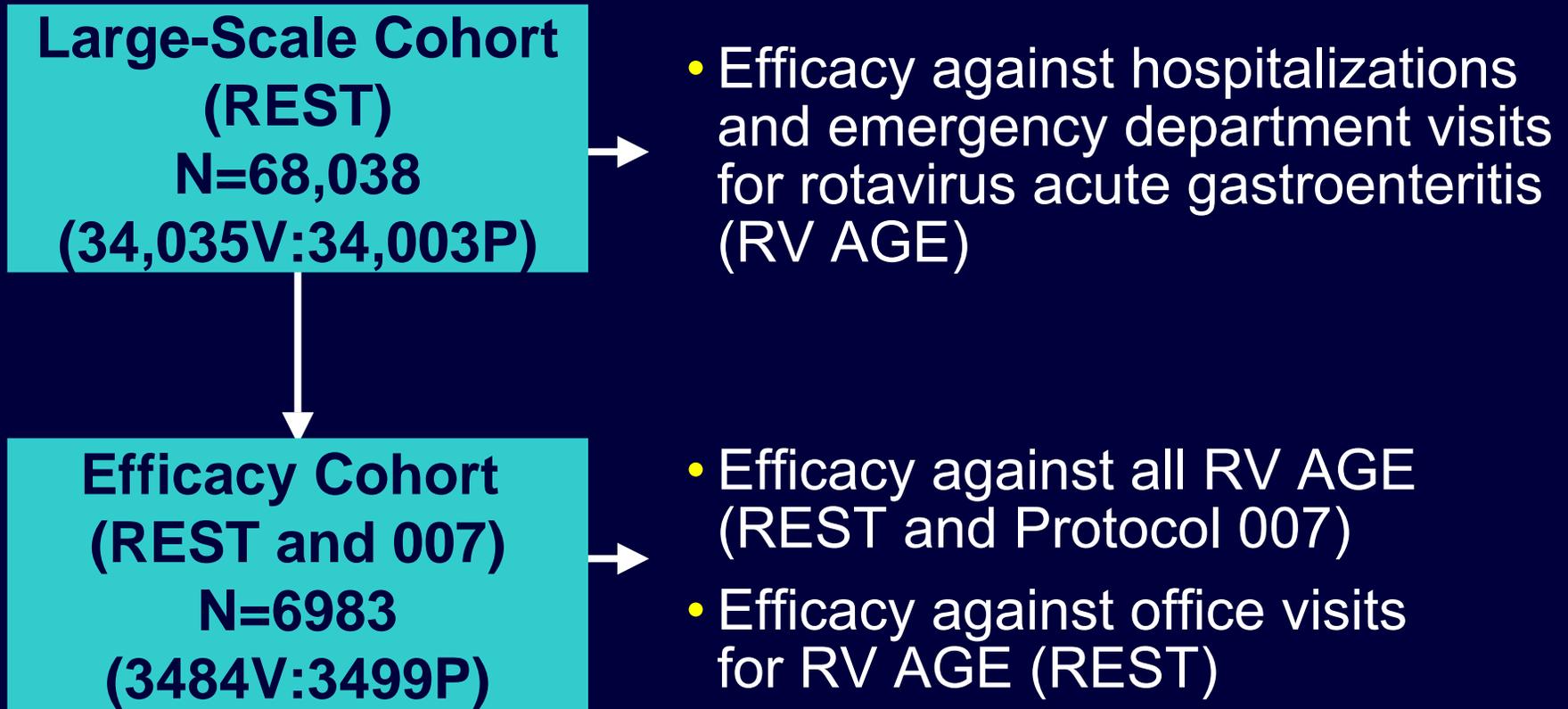
- RotaTeq™ was generally well tolerated
- RotaTeq™ was well tolerated with respect to the adverse events of special clinical interest (fever, vomiting, diarrhea, irritability, and hematochezia)
  - Small risk (1.3%) of mild diarrhea and vomiting after vaccination
- Vaccine-virus strain fecal shedding occurred infrequently and almost exclusively during the week after the first dose
  - Suggests that risk of transmission of vaccine-virus strains is low

# Efficacy Objectives and Results from the Phase III Studies

(REST and Protocol 007)

# Efficacy Evaluations in the Phase III Studies

## REST, Protocol 007



N=Number vaccinated.

# Primary Efficacy Hypotheses

## REST and Protocol 007

- Oral RotaTeq™ will be efficacious against rotavirus disease caused by serotypes G1, G2, G3, and G4 that occurs following a 3-dose regimen

## Other Efficacy Objectives

- Efficacy against moderate and severe rotavirus disease caused by G1-4 serotypes (REST and 007)
- Efficacy against rotavirus gastroenteritis caused by the individual G serotypes in the vaccine (G1, G2, G3, G4) and not in the vaccine (e.g., G9) (REST and 007)
- Efficacy during a second rotavirus season postvaccination (REST)

# Case Definition for Rotavirus Gastroenteritis

## Clinical and Laboratory Criteria

- Clinical Case Definition
  - Forceful vomiting and/or  $\geq 3$  loose stools in 24 hours
  - Severity of cases assigned using a clinical scoring system
    - Based on intensity and duration of fever, vomiting, diarrhea, and behavioral changes:  
 $\leq 8$ =mild;  $>8 \leq 16$ =moderate;  $>16$ =severe
- Laboratory Case Definition
  - Rotavirus detection by EIA
  - Serotype identification by PCR
  - Vaccine-virus strain identification by plaque and electropherotyping

# Efficacy Endpoints

- Primary efficacy analysis
- Efficacy against hospitalizations, emergency department visits, and office visits for rotavirus gastroenteritis
- Intention-to-treat (ITT) efficacy analyses
- Serotype-specific efficacy
- Second season efficacy

# Primary Efficacy Hypotheses Were Met RotaTeq™ Was Efficacious Against G1-4 Rotavirus Gastroenteritis

## Efficacy Cohort

<u>Disease Severity</u>	<u>Number of Cases</u>		<u>% Efficacy</u>	<u>95% CI</u>
	<u>Vaccine (N=3484)</u>	<u>Placebo (N=3499)</u>		
Any	97	369	73.8	67.2,79.3
Severe	1	57	98.2	89.6,100.0

N=number vaccinated.

# RotaTeq™ Was Efficacious Against Hospitalizations, Emergency Department Visits & Office Visits for G1-4 Rotavirus Gastroenteritis

## REST

<u>Type of Health Care Encounter</u>	<u>Number of Cases</u>		<u>% Rate Reduction</u>	<u>95% CI</u>
	<u>Vaccine</u>	<u>Placebo</u>		
Hospitalizations†	6	144	95.8	90.5, 98.2
Emerg. Dept. Visits†	14	213	93.4	88.1, 96.3
Office Visits‡	13	99	86.1	74.2, 92.6

† N=34,035 vaccinated in vaccine group and 34,003 vaccinated in placebo group.

‡ N=2834 vaccinated in vaccine group and 2839 vaccinated in placebo group.

# Intention-to-Treat Analysis: Efficacy of RotaTeq™ Against G1-4 Rotavirus Gastroenteritis

From First Day of Vaccination Among All Subjects  
Who Received at Least One Dose  
Efficacy Cohort

<u>Disease Severity</u>	<u>Number of Cases</u>		<u>% Efficacy</u>	<u>95% CI</u>
	<u>Vaccine (N=3484)</u>	<u>Placebo (N=3499)</u>		
Any	177	435	59.7	51.9,66.4
Severe	2	62	96.8	88.1,99.6

N=number vaccinated.

# Intention-to-Treat Analysis: Efficacy of RotaTeq™ Against Hospitalizations, Emergency Department Visits, and Office Visits for G1-4 Rotavirus Gastroenteritis

From First Day of Vaccination Among All Subjects  
Who Received at Least One Dose  
REST

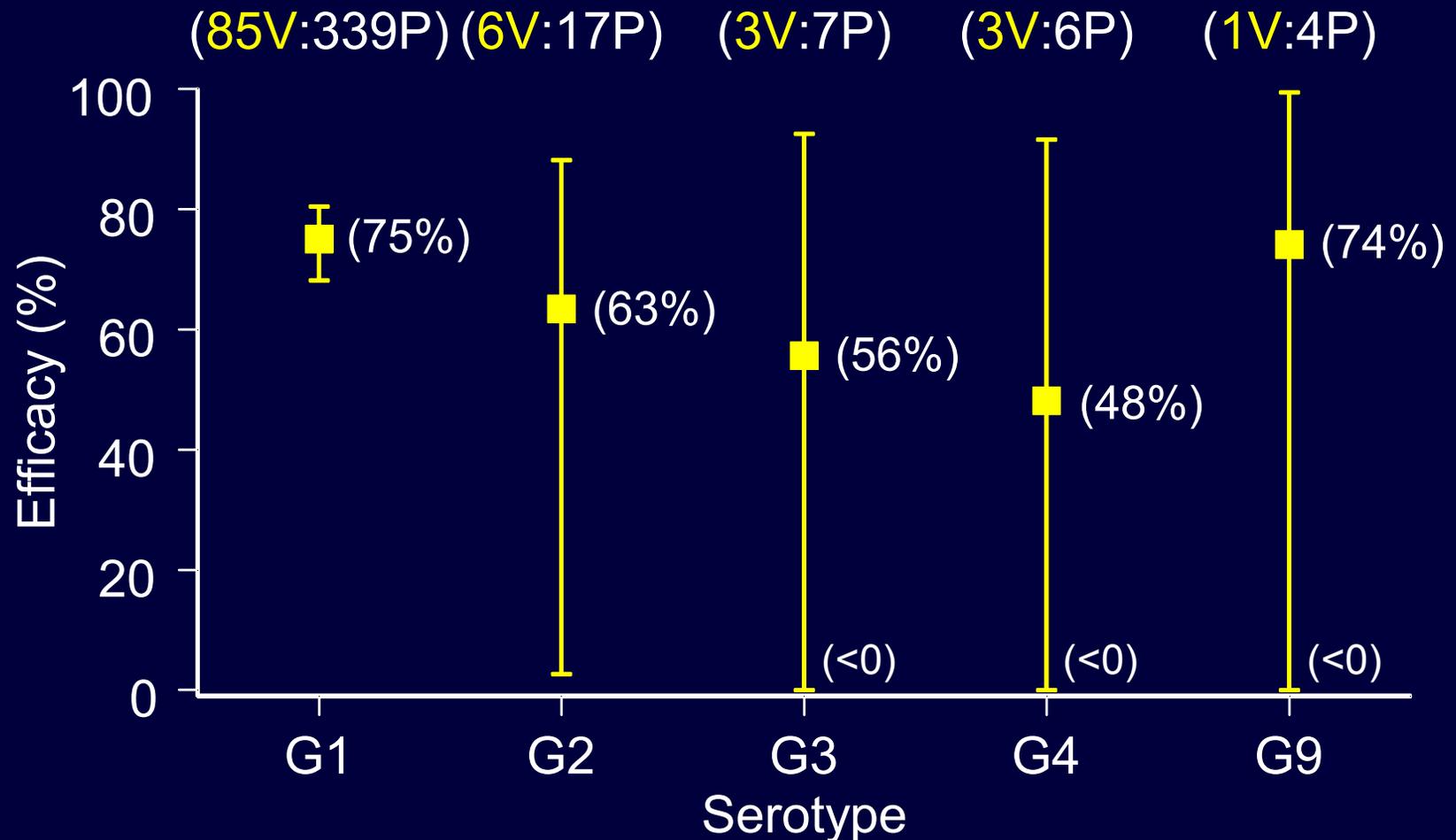
<u>Type of Health Care Encounter</u>	<u>Number of Cases</u>		<u>% Rate Reduction</u>	<u>95% CI</u>
	<u>Vaccine</u>	<u>Placebo</u>		
Hospitalizations <sup>†</sup>	10	187	94.7	89.3, 97.3
Emerg. Dept. Visits <sup>†</sup>	28	279	90.0	84.4, 93.6
Office Visits <sup>‡</sup>	18	118	84.3	73.5, 90.7

<sup>†</sup> N=34,035 vaccinated in vaccine group and 34,003 vaccinated in placebo group.

<sup>‡</sup> N=2834 vaccinated in vaccine group and 2839 vaccinated in placebo group.

# RotaTeq™ Was Efficacious Against Rotavirus Gastroenteritis Caused by Serotypes G1-4 & G9

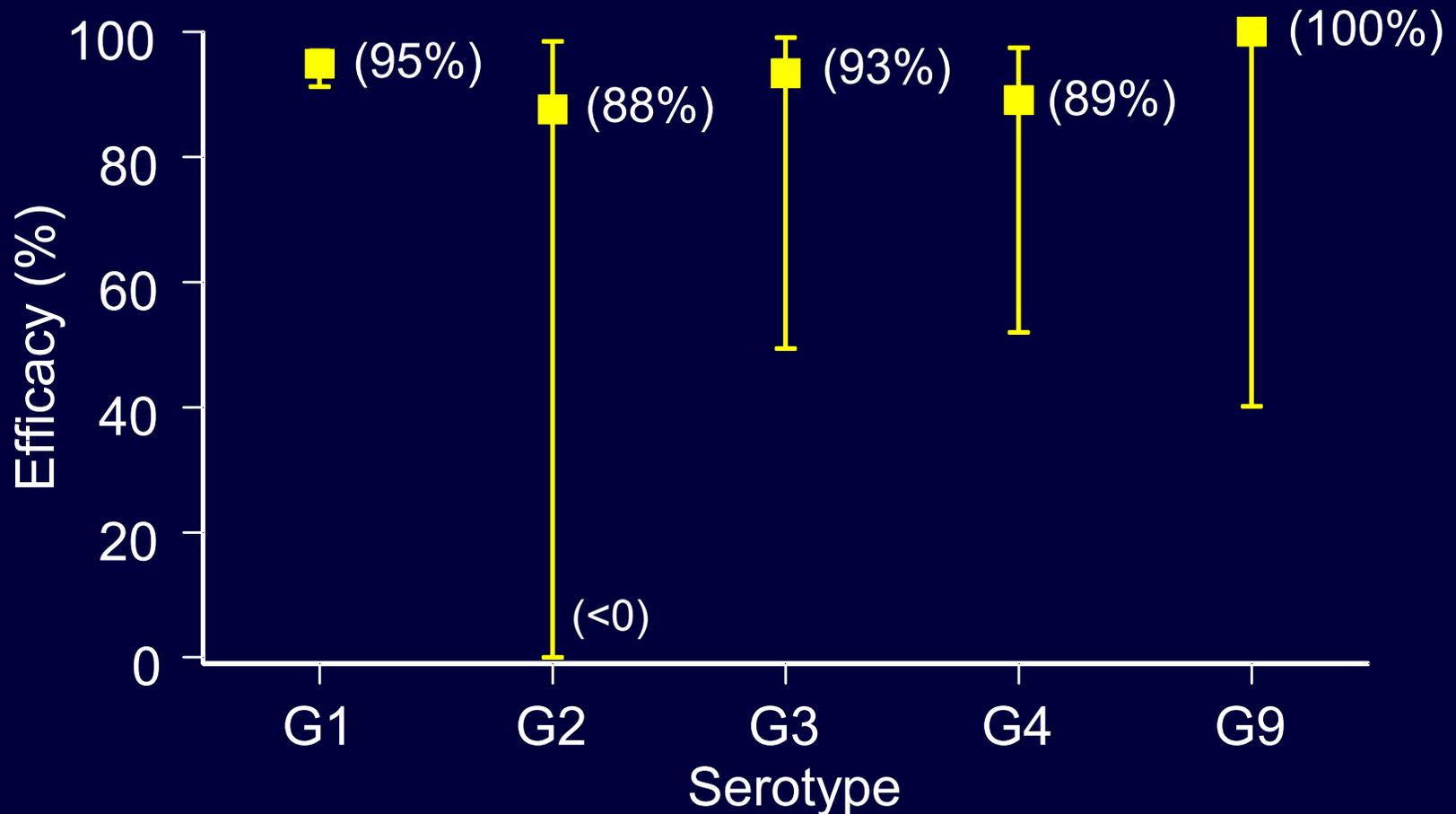
## Efficacy Cohort



# RotaTeq™ Was Efficacious Against Hospitalizations and Emergency Department Visits for Rotavirus Gastroenteritis Caused by G1-4 & G9

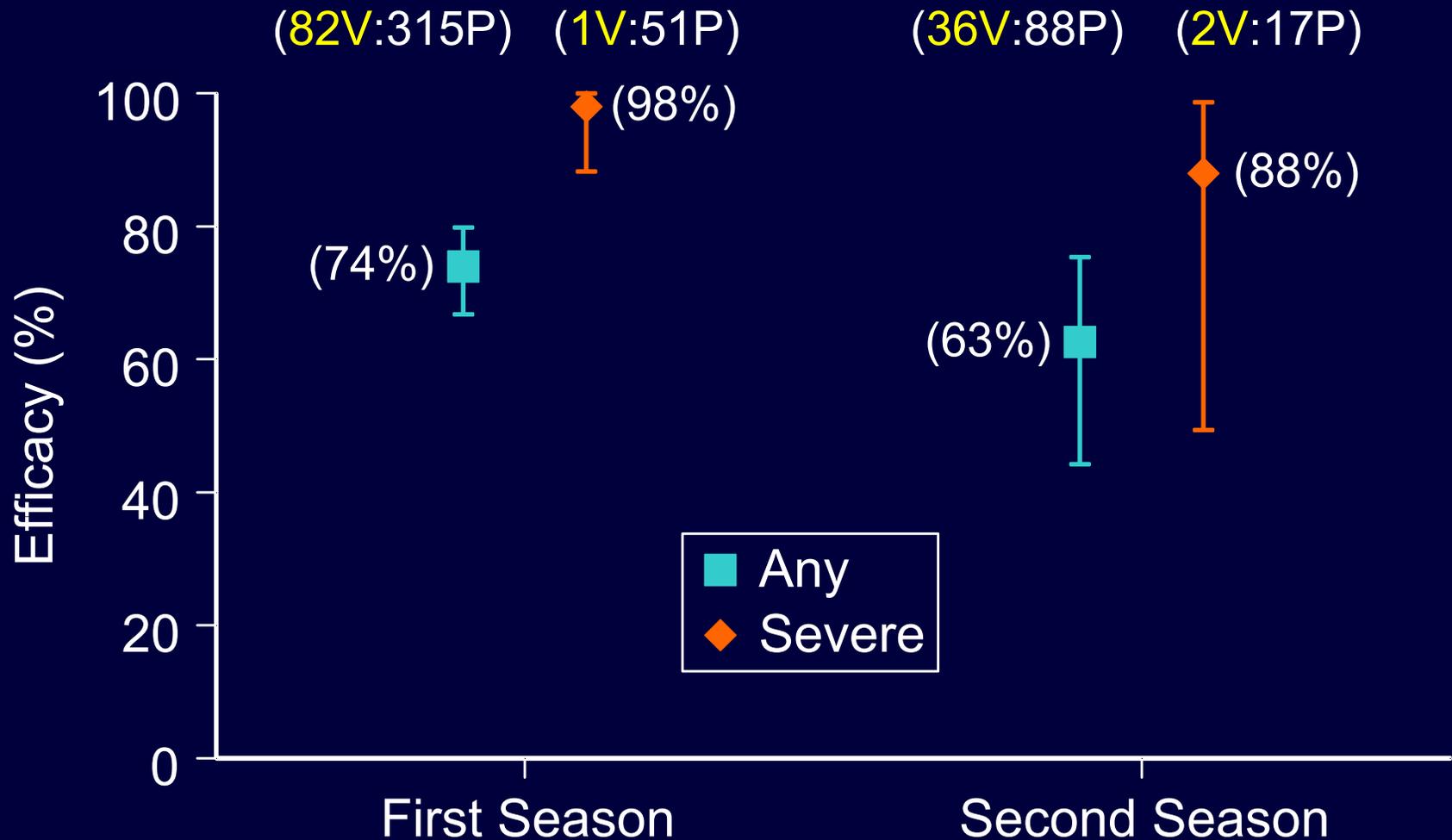
REST

(16V:316P) (1V:8P) (1V:15P) (2V:18P) (0V:13P)



# Efficacy of RotaTeq™ Persisted During the Second Rotavirus Season Postvaccination

REST



# Summary of Efficacy

- RotaTeq™ prevented G1-4 rotavirus gastroenteritis of any severity (74%) and severe disease (98%)
- RotaTeq™ prevented healthcare encounters for rotavirus gastroenteritis
  - 96% reduction in hospitalizations
  - 93% reduction in emergency department visits
  - 86% reduction in office visits
- Serotype-specific data indicate that RotaTeq™ is efficacious against the G serotypes in the vaccine and against G9 strains containing P1
- Efficacy persisted during the second rotavirus season postvaccination

# Immunogenicity Objectives and Results from the Phase III Studies

(REST, Protocol 007, and Protocol 009)

- Immunogenicity of RotaTeq™
- Immunogenicity of Concomitant Vaccines

# Immunogenicity of RotaTeq™

- No definitive immunologic surrogate for efficacy identified
  - Studies of wild-type rotavirus suggest that serum and fecal anti-rotavirus IgA and G1 SNA titers correlate with protection
- Magnitude of antibody responses to RotaTeq™ correlates with potency (viral titer) but not efficacy
- Immunogenicity data from Phase III studies have been utilized for comparisons
  - Demonstration of consistency of manufacturing process
  - Concomitant use studies
- Pattern of antibody responses to RotaTeq™ has been consistent across different populations and studies
  - High proportion (>90%) have significant rise in anti-rotavirus IgA
  - Magnitude of serum neutralizing antibody responses to G and P types vary

Velazquez et al., *J Infect Dis* 2000; 182:1602-9 and Matson DO et al., *J Infect Dis* 1993; 167:577-83 and O’Ryan et al., *J Infect Dis* 1994; 169:504-11.

# Evaluation of Immunogenicity of Licensed Vaccines Given Concomitantly with RotaTeq™

## (662V:696P)

- Evaluated antibody responses to DTaP, IPV, Hib, Hep B, and pneumococcal conjugate vaccines
- Compared antibody responses to these vaccines when given with RotaTeq™ with the responses when given with placebo
- Statistical criteria for demonstrating noninferiority
  - DT, IPV, Hib, and Hep B: 95% confident no more than a 10 percentage point decrease among vaccinees compared with placebo recipients for the proportion who achieve seroprotection
  - Pertussis and pneumococcus: 95% confident no more than a 2-fold decrease among vaccinees compared with placebo recipients for the ratio of GMT

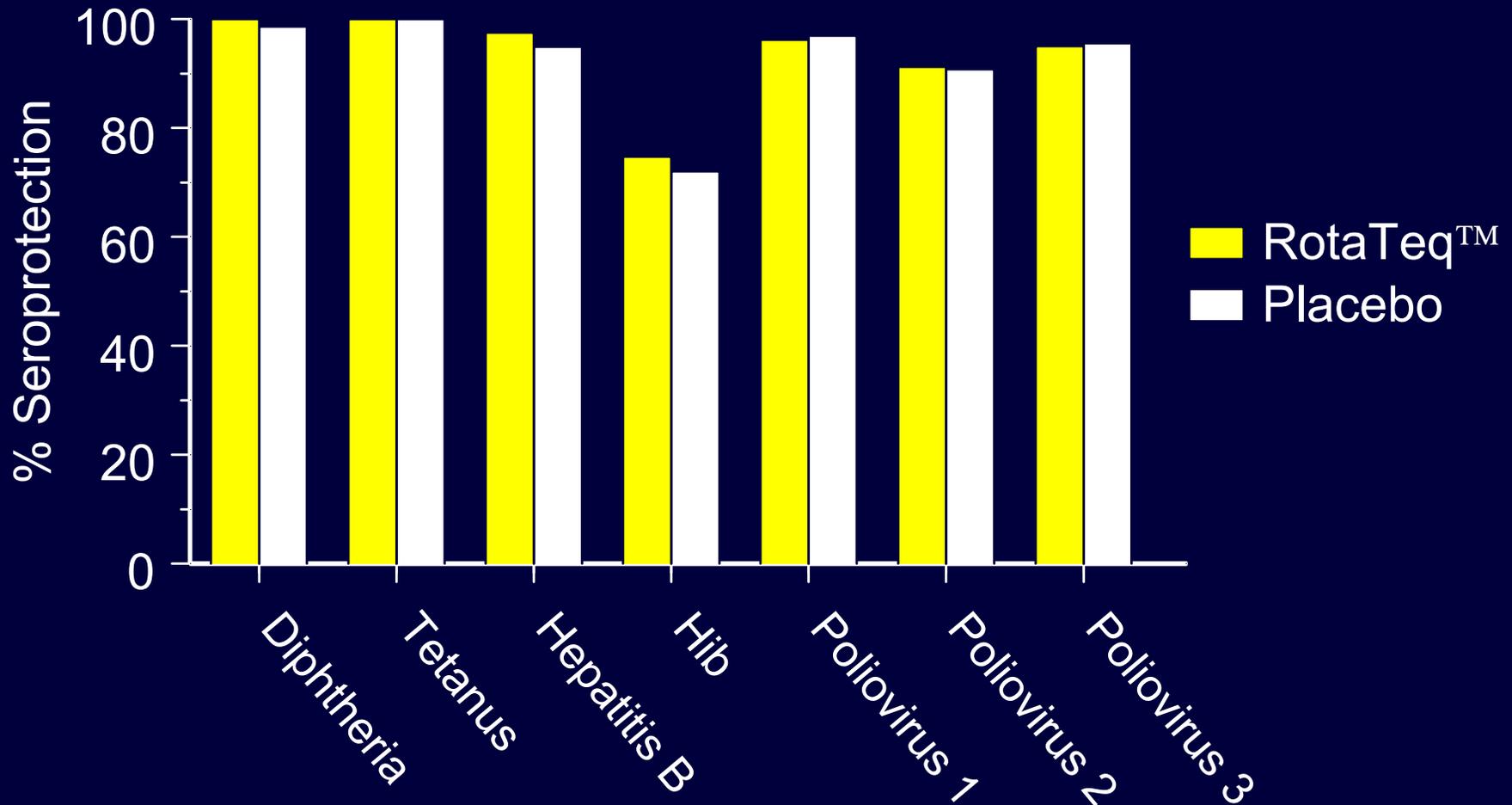
N= Number vaccinated

# Concomitant Vaccination Schedule

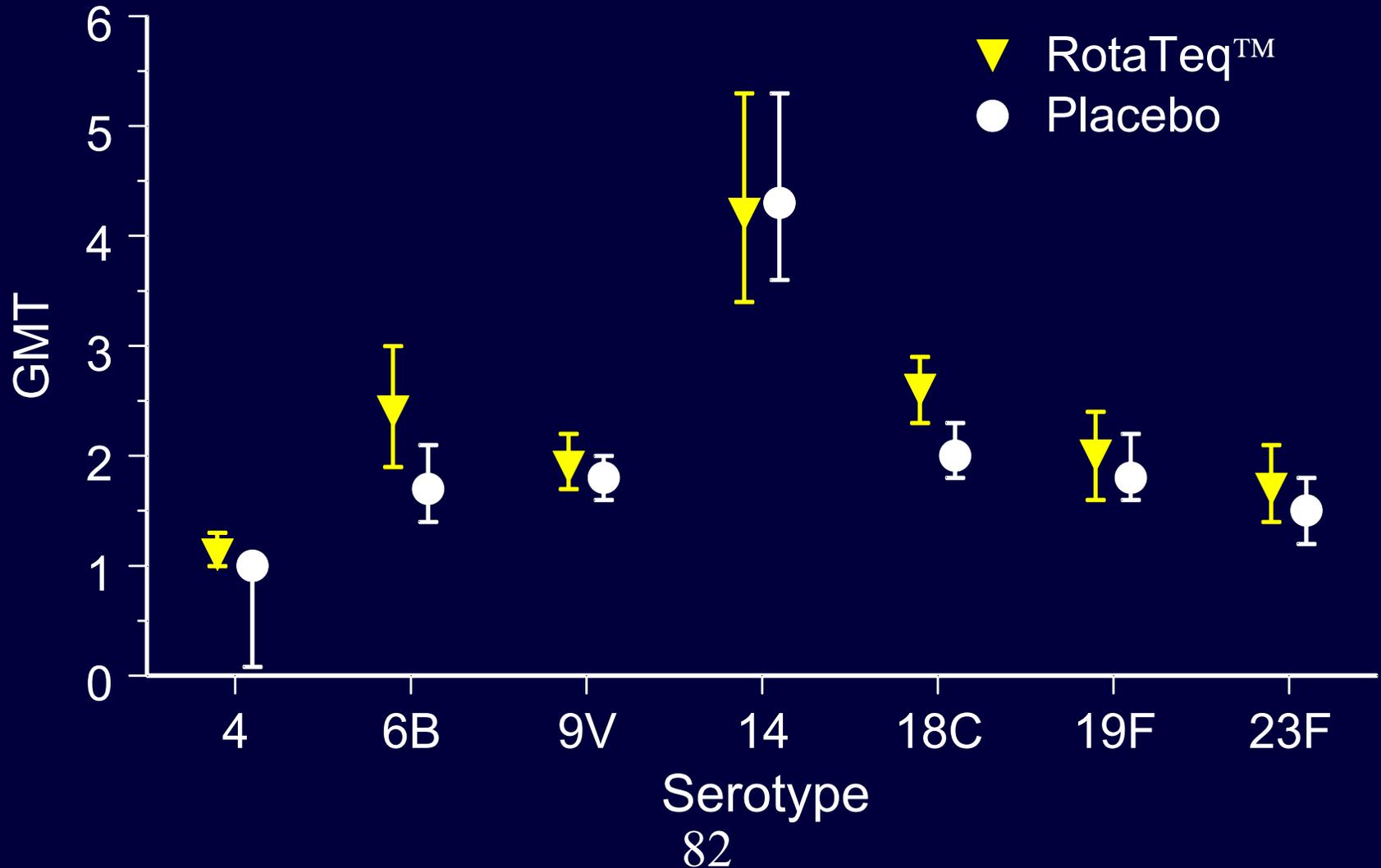
- 3 doses of DTaP and pneumococcal conjugate vaccine
  - GMT measured ~42 days postdose 3 at 7 to 8 months of age
- 2 doses of COMVAX<sup>®</sup> (Hib/Hep B) and IPV
  - Subjects were required to receive a neonatal dose of hepatitis B within 2 weeks of birth
  - Seroprotection measured on day of dose 3 at 5 to 6 months of age

<u>Antigen</u>	<u>Seroprotection Criteria</u>
Diphtheria/Tetanus	≥0.01 IU/mL
Hib	>1.0 mcg/mL
Hep B	≥10 mIU/mL
Polio	NA ≥1:8

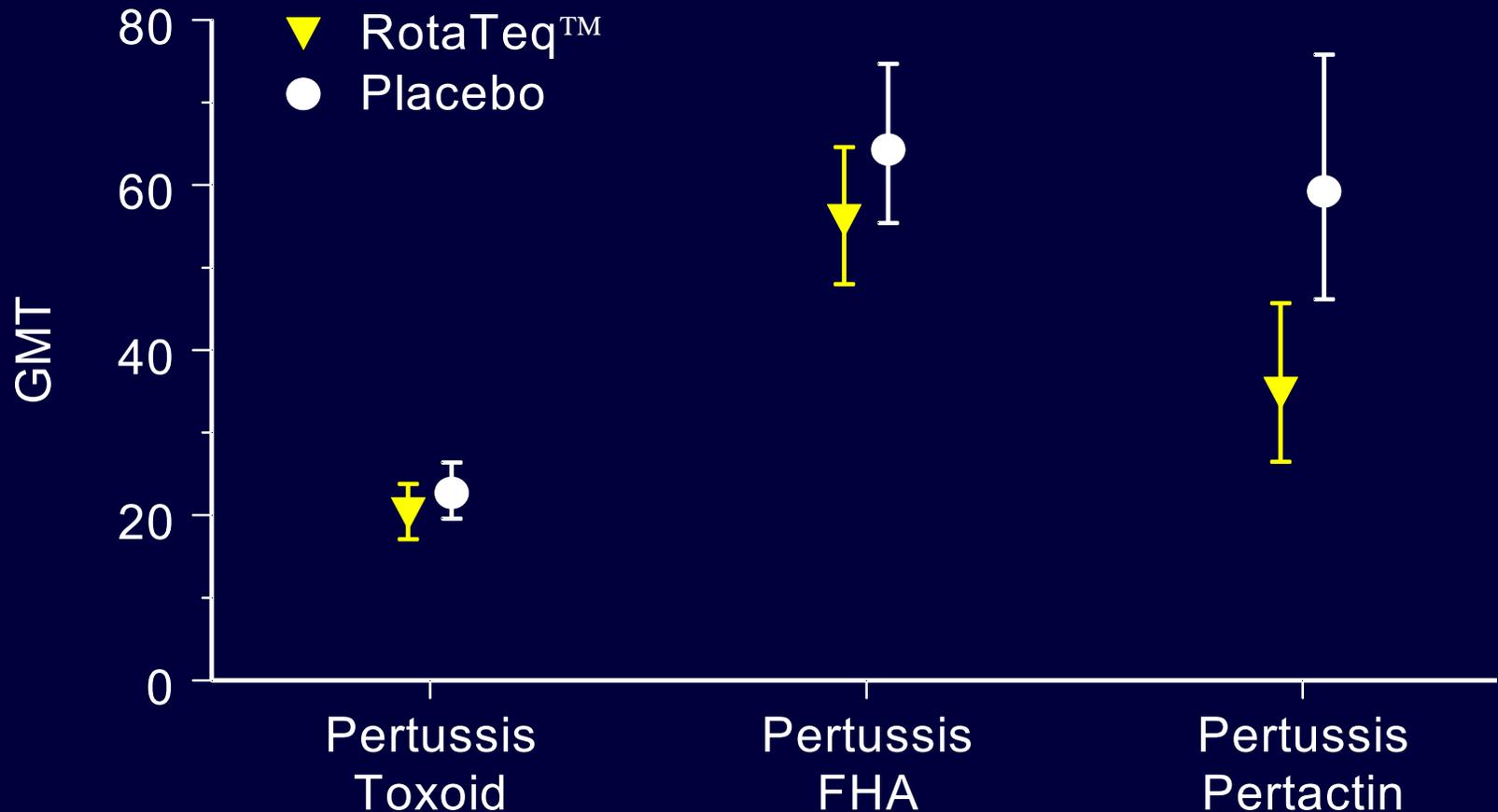
# Antibody Responses to Diphtheria, Tetanus, Hep B, Hib, and Polio Were Similar in RotaTeq™ and Placebo Recipients



# Antibody Responses to Pneumococcal Conjugate Vaccine Were Similar in RotaTeq™ and Placebo Recipients



# Antibody Responses to Pertussis Toxoid, FHA, and Pertactin in RotaTeq™ and Placebo Recipients



Note: Pertactin level >5 Eu/mL.

95% RotaTeq™ recipients vs. 96% placebo recipients.

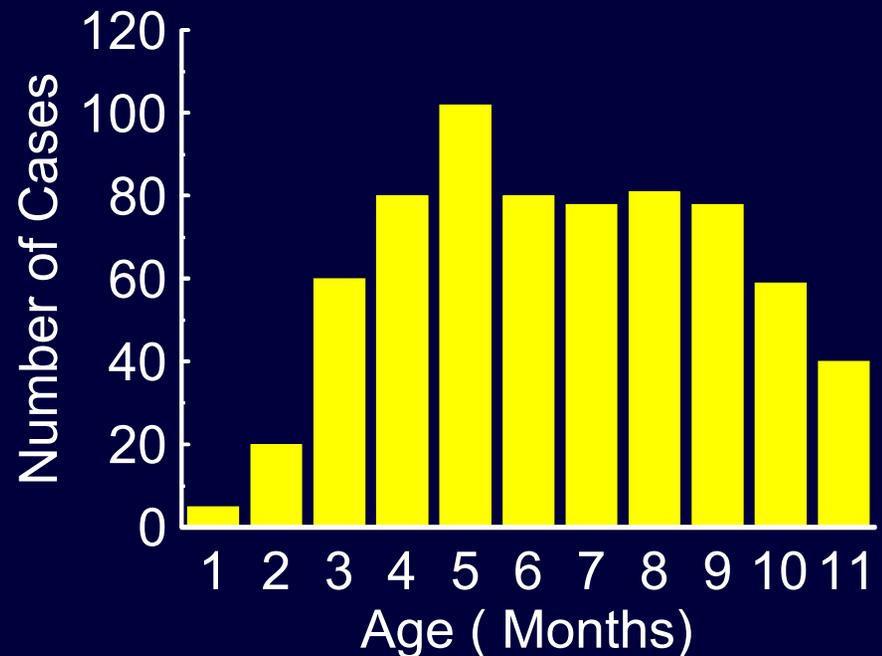
# Summary of Immunogenicity

- RotaTeq™ was generally immunogenic
- No definitive immunologic surrogate for efficacy identified
- Administration of RotaTeq™ with licensed pediatric vaccines induced acceptable antibody responses to the concomitant vaccines

# Post-Licensure Plan to Monitor the Safety of RotaTeq™

- Post-licensure surveillance is planned to monitor intussusception (IS) cases temporally associated with vaccination
  - RotaTeq™ will be given on a 2-, 4-, 6-month schedule
  - This schedule overlaps with the peak age of naturally-occurring IS

Hospitalizations for Intussusception by Age in Months  
New York State, 1991 to 1995\*



\* Rennels et al., *Ped Infect Dis J* 1998; 17: 924-5.

# Post-Licensure Plan to Monitor the Safety of RotaTeq™

- Clinical studies
  - Phase III studies (REST, 007, 009)
  - Future clinical studies
- Merck-sponsored pharmacovigilance activities
- Active surveillance
  - Prospective population-based study to assess IS and general safety
  - Study design allows rapid detection of IS
- Enhanced passive surveillance
  - IS: Telephone follow-up of all cases and prompt reporting to FDA
  - All adverse events: Reporting to FDA on a monthly (vs. quarterly) basis
- Coordination and communication with public health agencies
  - FDA / CDC (VAERS )
  - CDC (VSD)

# Overall Assessment and Conclusions from Studies of RotaTeq™

# Overall Assessment and Conclusions

- Rotavirus is a significant cause of childhood morbidity in the US
  - 55,000 to 70,000 hospitalizations/year
  - Causes similar outcomes regardless of geography
- Only available therapy for rotavirus gastroenteritis in the US is supportive care
- Results of REST and other Phase III studies provide a high level of confidence in the safety of RotaTeq™
  - Well tolerated with respect to all AEs
  - No signal of a safety concern with regard to IS

# Overall Assessment and Conclusions (Cont'd)

- RotaTeq™ prevents 74% of any severity of rotavirus gastroenteritis and 98% of severe disease
- RotaTeq™ reduces healthcare encounters for rotavirus gastroenteritis
  - 96% ↓ hospitalizations
  - 93% ↓ emergency department visits
  - 86% ↓ physician office visits
- RotaTeq™ can be concomitantly administered with the licensed pediatric vaccines evaluated
- Given the absence of identified risk factors for severe rotavirus gastroenteritis and the universal nature of this disease, this vaccine is an important public health priority