

ROTAVIRUS

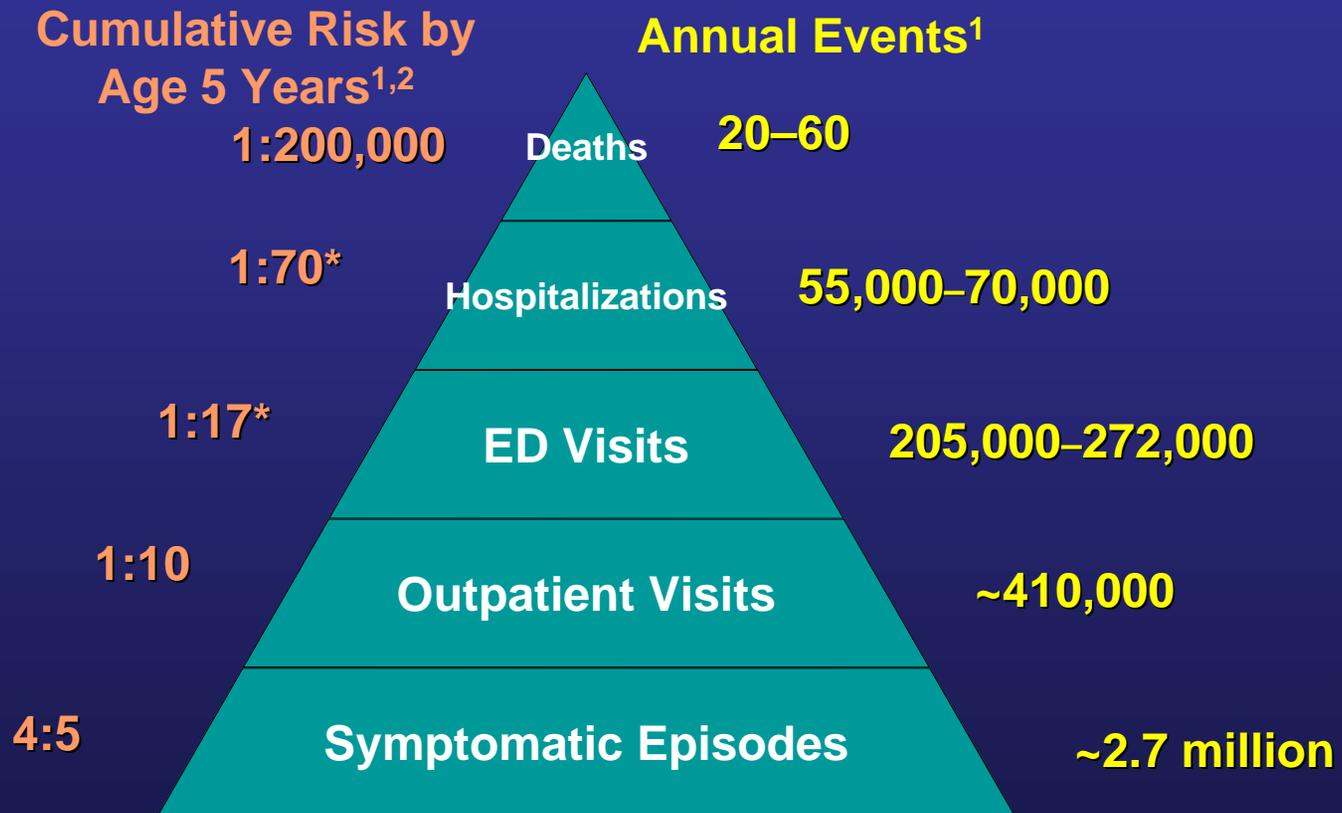
Epidemiology and Vaccine

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Overview

- I. Epidemiology of Rotavirus
- II. Impact and Transmission of Rotavirus Gastroenteritis
- III. Rotavirus Vaccine
- IV. Ongoing Studies on the Effectiveness of Rotavirus Vaccines

Rotavirus Gastroenteritis: Estimated Burden of Disease in US Children Younger Than 5 Years of Age



***1 in 14 require either an ED visit or hospitalization by age 5 years.**

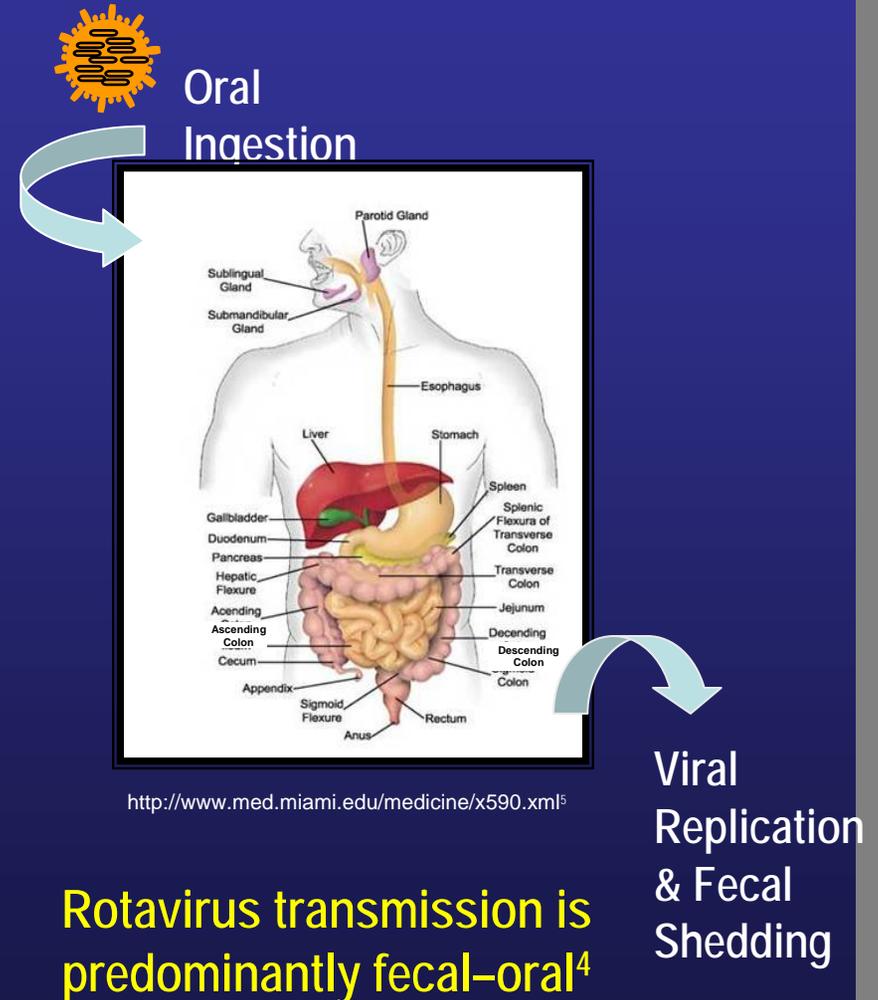
ED = emergency department

1. Parashar UD, Alexander JP, Glass RI, for the Centers for Disease Control and Prevention. *MMWR*. 2006;55:(RR-12):1–13. 2. Data available on request from Merck & Co., Inc., Professional Services-DAP, WP1-27, PO Box 4, West Point, PA 19486-0004. Please specify information package 20652084(1)-RTQ.

What Is Rotavirus Gastroenteritis (RGE)?

RGE is a potentially serious disease

- Leading cause of severe acute gastroenteritis
- Highly contagious, infecting virtually all children by 5 years of age^{1,2}
- The severity of rotavirus infection ranges from asymptomatic infection to severe dehydrating gastroenteritis, which can be life-threatening²
- Symptoms typically include vomiting, fever, abdominal pain, and watery diarrhea, which can persist for 3–9 days²
- Multiple infections are common in childhood³



1. Parashar UD, et al. *MMWR Morb Mortal Wkly Rep* 2006;55(No. RR-12):1–13.

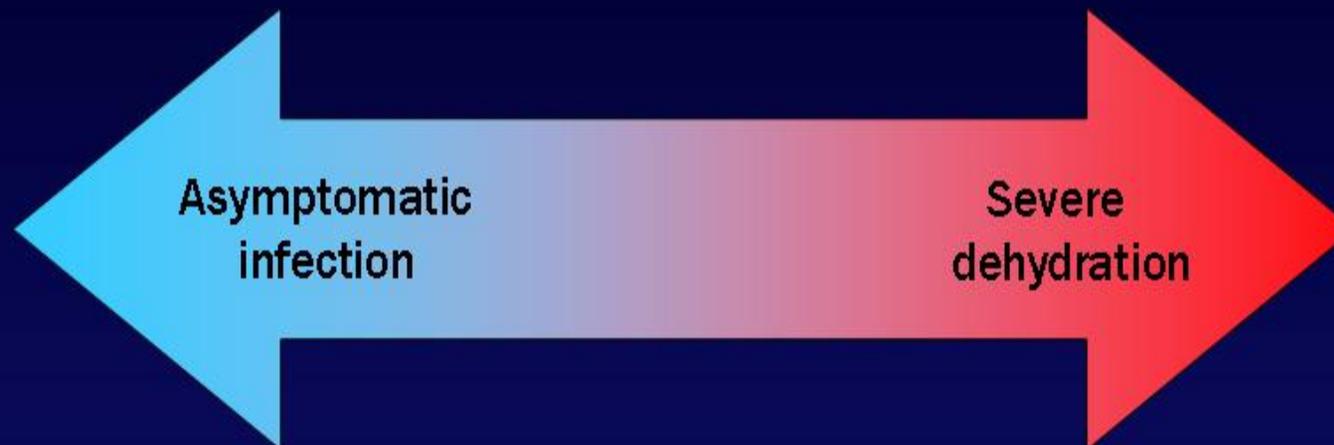
2. Rebel MS, Ou BS. *Pharmacotherapy*. 1999;19:1279–1295.

3. Velázquez FR, et al. *N Engl J Med*. 1996;335:1022–1028.

4. Anderson EJ, Weber SG. *Lancet*. 2004;4:91–99.

5. From Anatomy of digestive system. Available at <http://www.med.miami.edu/medicine/x590.xml>. Reprinted with permission.

Spectrum of Rotavirus Symptoms¹



- Most severe disease typically occurs in children 4–36 months of age.²
- Rotavirus infection occasionally causes illness in parents of children with rotavirus diarrhea, immunocompromised patients, the elderly, and travelers to developing countries.²
- Subsequent infections are generally less severe than first infections.³

1. Staat MA, Azimi PH, Berke T, et al. *Pediatr Infect Dis J.* 2002;21:221-227. 2. Parashar UD, Bresee JS, Gentsch JR, et al. *Emerg Infect Dis.* 1998;4:561-570.
3. Velazquez FR, Matson DO, Calva JJ, et al. *N Engl J Med.* 1996;335:1022-1028.

Rotavirus Epidemiology

- Reservoir Human- gastrointestinal tract
- Incubation Short < 2 days (range 1-7d.)
- Temporal pattern Fall & Winter temperate areas
- Transmission Fecal-oral, fomites
- Communicability 2 d. before to 10 d. after onset
- Diagnostics EIA, EM, PCR

Circulating Rotavirus Strains and Infection

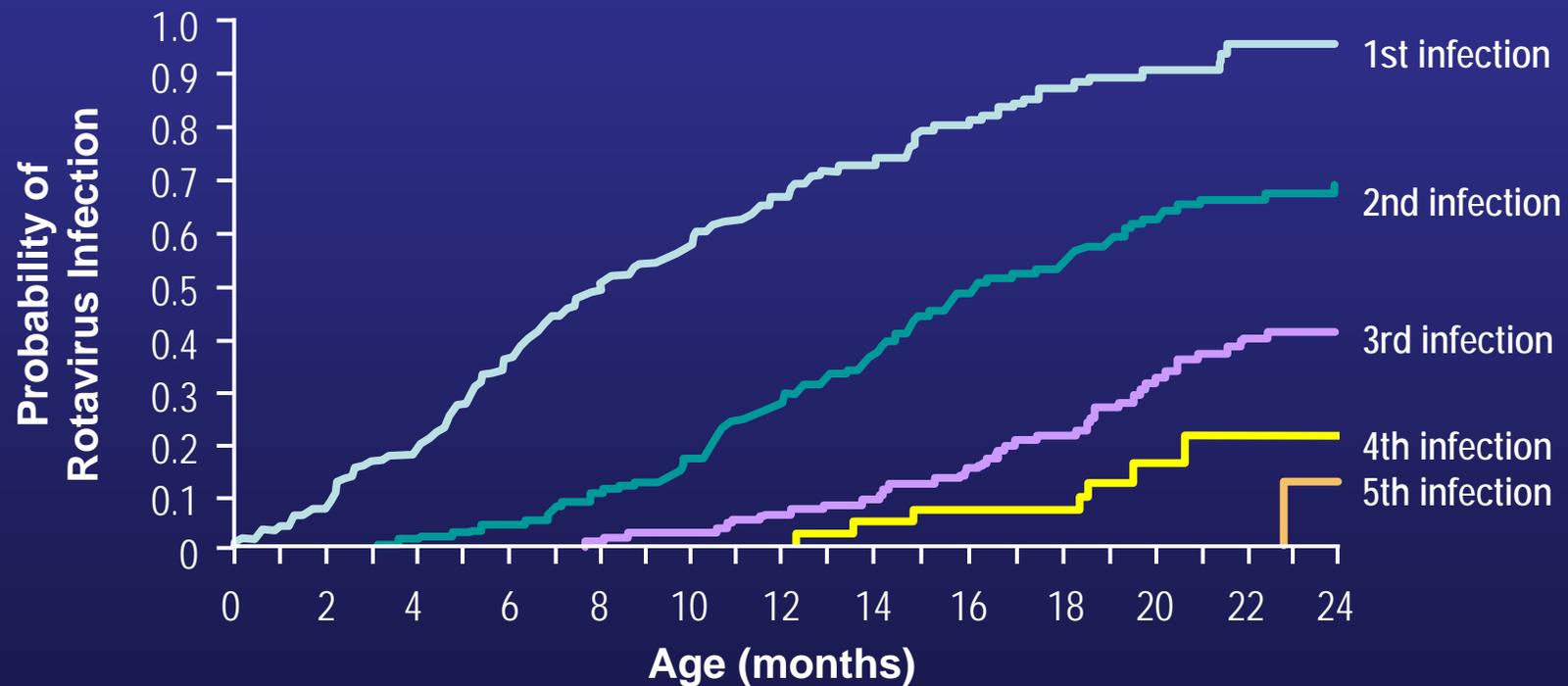
- Circulating strains can vary from year to year and region to region^{1,2}
- Multiple infections can occur in childhood³
- Protection against disease is thought to increase with each subsequent infection³
- Immunity following primary infection is thought to be predominantly serotype-specific³

1. Griffin DD, et al. *J Clin Microbiol.* 2000;38:2784–2787.

2. Santos N, Hoshino Y. *Rev Med Virol.* 2005;15:29–56.

3. Velázquez FR, et al. *N Engl J Med.* 1996;335:1022–1028.

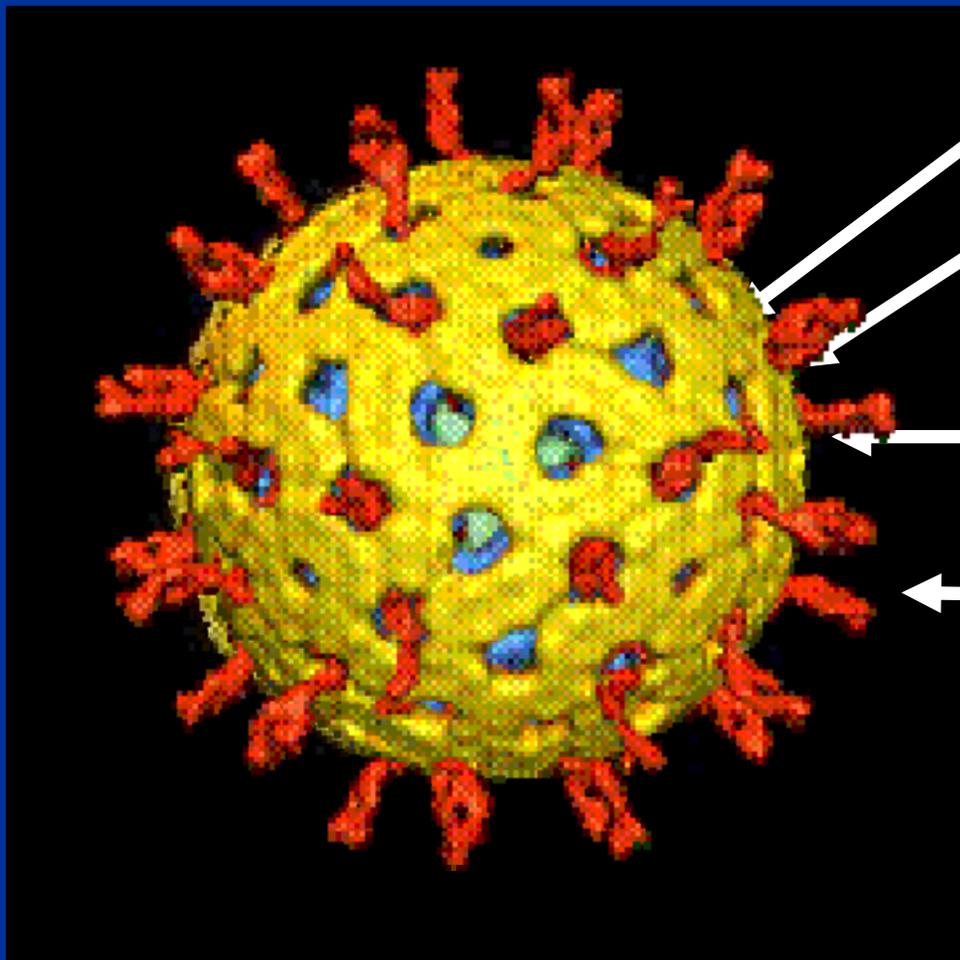
Rotavirus Infection: Cumulative Probability by 24 Months of Age



N=200

Reprinted with permission from Velázquez FR, et al. *N Engl J Med.* 1996;335:1022-1028.

Rotavirus Structure: Neutralization Proteins



Core

Inner capsid

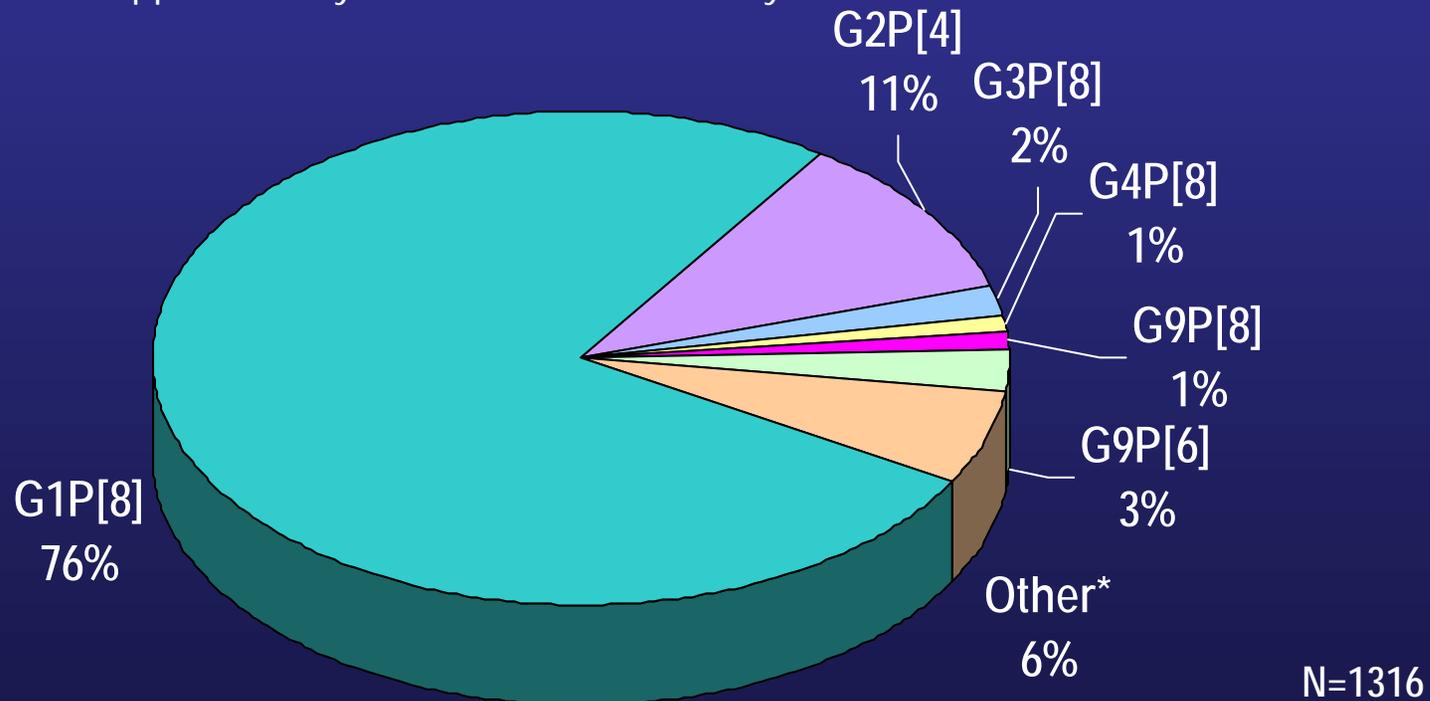
Outer capsid:

G surface protein (VP7)

P surface protein (VP4)

Distribution of Rotavirus Serotypes in the United States (1996–1999)

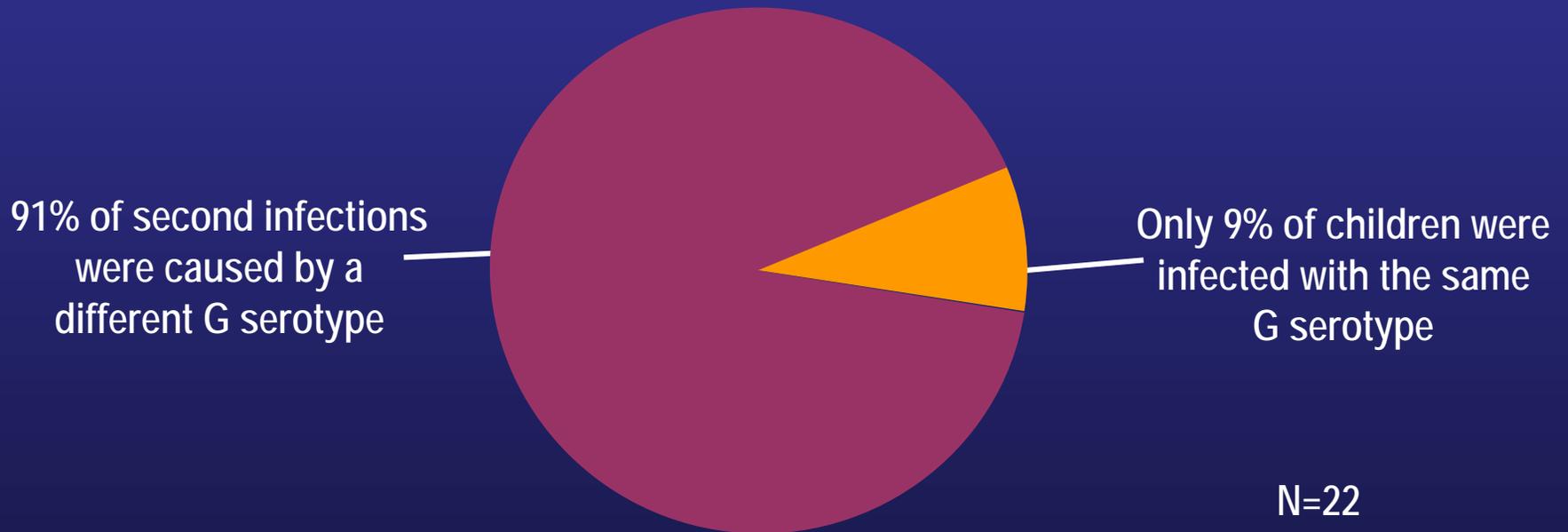
Serotypes G1, G3, and G4 with genotype P[8] and serotype G2 with genotype P[4] represented approximately 90% of the strains analyzed.



*Other includes typed uncommon strains, mixed infections, and nontypeable infections.

Type-Specific Exposure and Rotavirus Immunity

Percentage of Second Rotavirus Infections Caused by a Different G Serotype Than First Infections, Based on 22 Pairs of Isolated Rotavirus Strains in Mexico



First infections: G3 (50%), G1 (41%), G2 (9%), and G4 (0%)
Second infections: G2 (50%), G3 (27%), G1 (14%), and G4 (9%)

Rotavirus

- Most children will develop rotavirus GE by 5 years, many more than once
- It can be difficult to predict which serotype will predominate in a given year
- Antibodies to initial exposure are predominantly serotype specific

Prevention of Rotavirus
Rotavirus vaccines in the US

ACIP^a and AAP^b Recommendations – February, 2009^{1,2}

RotaTeq[®] (RV5) and Rotarix[®] (RV1) differ in composition and schedule of administration

- The ACIP and AAP did not express a preference for either vaccine

Routine Administration

- 1st dose: 6 weeks of age – 14 weeks, 6 days (max. age for 1st dose)
- Minimum interval between doses: 4 weeks
- All doses administered by: 8 months, 0 days

(Note: according to Prescribing Information, the first dose of RotaTeq should be administered between 6-12 weeks of age)

Interchangeability of Rotavirus Vaccines

- Vaccination should be completed with the same product whenever possible
- If the product used for previous doses is not available or unknown, the series should be completed with the available product
- A total of 3 doses of rotavirus vaccine should be administered if:
 - any dose in the series was RotaTeq, or if the product is unknown for any dose in the series
- No studies on the interchangeability of vaccines have been conducted

1. Centers for Disease Control and Prevention. *MMWR Morb. Mortal. Wkly. Rep.* 2009;58(no. RR-2):1–25.

2. Prevention of rotavirus disease: updated guidelines for use of rotavirus vaccine. American Academy of Pediatrics policy statement, February 11, 2009.

a ACIP=Advisory Committee on Immunization Practices. b AAP=American Academy of Pediatrics.

Rotarix is a trademark of GlaxoSmithKline.

General Description of a new Oral Pentavalent Rotavirus Vaccine (PRV)

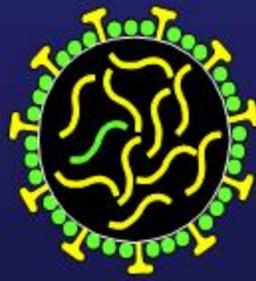
- Manufactured by Merck & Co., Inc. under the trade name RotaTeq[®] (Rotavirus Vaccine, Live, Oral, Pentavalent)
- Live, oral pentavalent vaccine containing 5 reassortant rotaviruses
- Reassortants propagated in Vero cells using standard cell culture techniques
- Reassortants suspended in a buffered stabilizer solution



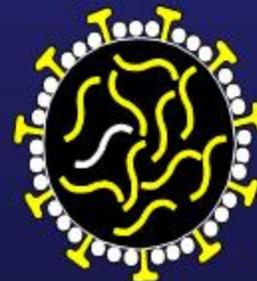
G1 WI79-9



G2 SC2-9



G3 WI78-8

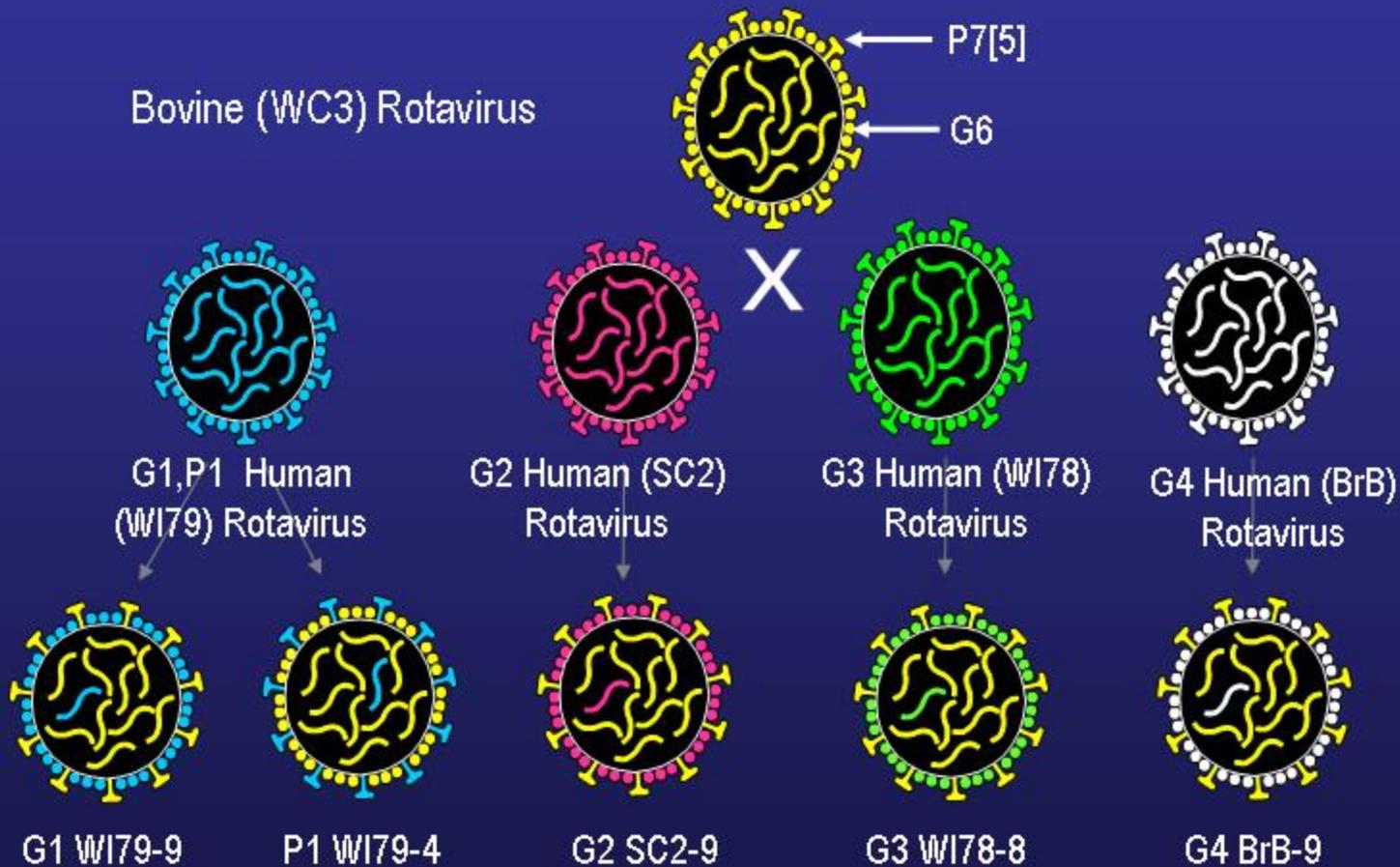


G4 BrB-9



P1A WI79-4

Description of Reassortants



Human-Bovine Reassortant Rotavirus Vaccine Strains

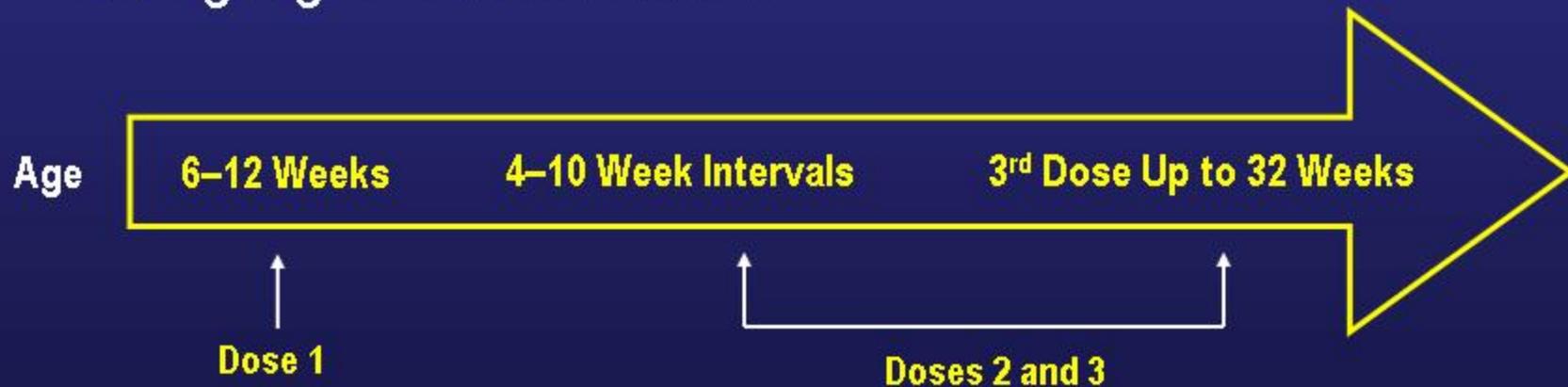
Rotavirus Vaccine Recommendations

- Administer simultaneously with all other indicated vaccines
- Breastfeeding infants should be vaccinated on usual schedule
- Vaccinate infants who have recovered from documented rotavirus infection
- Do not repeat dose if infant spits out or regurgitates vaccine -- administer remaining doses on schedule

MMWR 2006;55:(RR-12):1-13.

Clinical Studies: REST* Design

- Large scale clinical trial enrolling more than 70,000 infants¹
- Double-blind (with sponsor blinding), randomized, placebo-controlled study¹
- Dosing regimen and schedule:



*REST=Rotavirus Efficacy and Safety Trial

1. Vesikari T, Matson D O, Dennehy P, et al. *N Engl J Med.* 2006;354:23-33.

RotaTeq[®] (Rotavirus Vaccine, Live, Oral, Pentavalent) Demonstrated Substantial Efficacy Against G1, G2, G3, or G4 RGE^a in REST^b

Through the first rotavirus season after vaccination:

98% efficacy

against severe RGE (N=5,673)

74% efficacy

against any severity of RGE (N=5,673)

Up to 2 years after vaccination:

~95% reduction

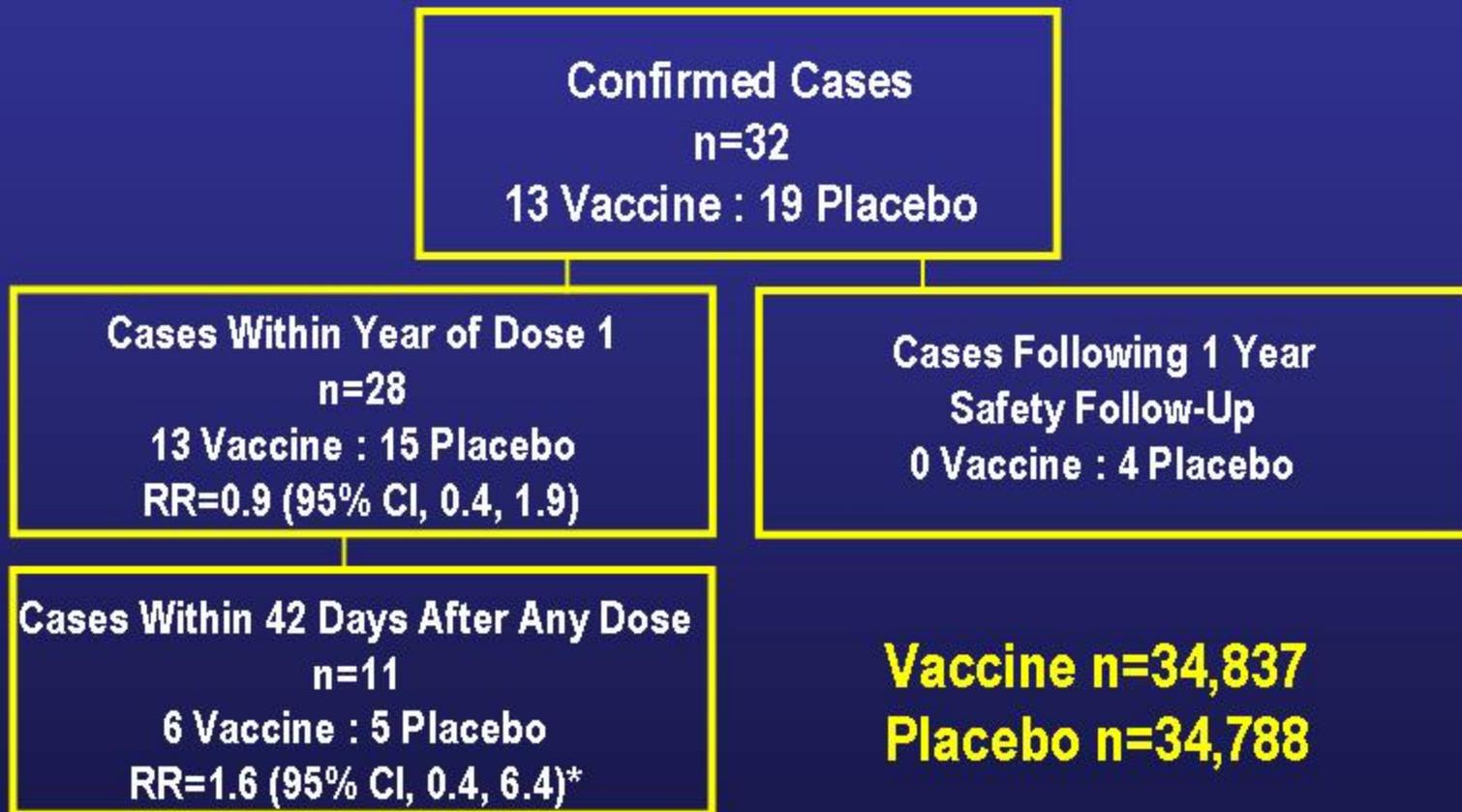
in the combined incidence of hospitalizations/ED^c visits for RGE (N=68,038)

In clinical trials, the most common adverse events included diarrhea, vomiting, irritability, otitis media, nasopharyngitis, and bronchospasm.

^aRGE=rotavirus gastroenteritis; ^bREST=Rotavirus Efficacy and Safety Trial; ^cED=emergency department.

Vesikari T, Matson DO, Dennehy P, et al. *N Engl J Med.* 2006;354:23–33.

Adverse Reactions: REST Intussusception Results



*RR and 95% CI based on group sequential design stopping criteria employed in REST.

Data available on request from Merck & Co., Inc., Professional Services-DAP, WP1-27, PO Box 4, West Point, PA 19486-0004. Please specify information package 20603902(1)-RTQ.

Dosage and Administration

- RotaTeq® (Rotavirus Vaccine, Live, Oral, Pentavalent) is an oral, ready-to-use, liquid vaccine given in a 3-dose series
 - First dose given at 6 to 12 weeks of age
 - Second and third doses given at 4- to 10-week intervals
 - Third dose should not be given after 32 weeks of age
- No restrictions on infant's consumption of food or liquid, including breast milk, before or after vaccination
- *Instructions for Use:* If for any reason an incomplete dose is administered (eg, infant spits or regurgitates the vaccine), a replacement dose is not recommended. Infants should continue to receive any remaining doses in the recommended series.

Rotarix[®] Rotavirus Vaccine (RV1)

- Monovalent attenuated human strain vaccine manufactured by GlaxoSmithKline
- Administered in two oral doses 1-2 mo apart
- Similar to natural infection, shed by >50% of recipients after first dose
- Provides cross protection against other serotypes
- Evaluated in safety and efficacy trial involving >60,000 infants aged 6 wks to 6 yrs in 11 Latin American countries and Finland¹
 - 84.7% efficacy against severe rotavirus gastroenteritis
 - 85% effective in preventing rotavirus related hospitalization
 - Excellent safety profile
- No increased risk for intussusception

1. Ruiz-Palacios, Perez-Schael, Velazquez et al. NEJM 2006;354

Effectiveness of Rotavirus Vaccine
*Assessing the Public Health Impact of the
US Rotavirus Vaccination Program*

Rotavirus Vaccine Evaluation Objectives

- Primary
 - Assess vaccine effectiveness against hospitalization/ED visits for rotavirus gastroenteritis over three rotavirus seasons (Dec 2006 – June 2009)
- Secondary
 - Assess trends in rotavirus disease by comparing data on gastroenteritis- and rotavirus-associated hospitalizations/ED visits in children <5 years of age

Rotavirus Vaccine Evaluation Study Sites

- Five Emerging Infections Program (EIP) sites are participating
 - Connecticut EIP
 - Georgia EIP
 - Minnesota EIP
 - New York EIP
 - Oregon EIP
- CT EIP activities limited to YNHH
 - Work began in May 2009; data collection and analysis will continue through December 2009.

CT EIP Rotavirus Evaluation

- Cases = children with gastroenteritis who tested positive for rotavirus
 - Must meet appropriate age criteria for vaccination and reside in New Haven County
- Controls = children with gastroenteritis who tested negative for rotavirus
 - Must meet appropriate age criteria for vaccination and reside in New Haven County

CT EIP Rotavirus Evaluation

- Obtained hospital discharge data of all children <5 years old with gastroenteritis ICD-9 code.
- Obtained laboratory line list of all children <5 years old tested for rotavirus.
- Will merge data sets to identify:
 - case children (rotavirus +)
 - control children (rotavirus -)
- Will request rotavirus vaccination history for all cases and control children from CT DPH immunization registry.
 - If unavailable through registry will contact primary care providers.

Additional Activities

- Other EIP sites are participating in additional study activities:
 - Multiple control groups
 - Registry controls – use immunization registry to identify controls (matched by case DOB and zip code of case birth residence) – [Dr. Guh]
 - Strain characterization of rotavirus positive stool specimens from cases
 - Residual stool from rotavirus testing of cases sent to CDC for typing [Dr. Vazquez' study is testing stool in CT]

EIP Rotavirus Evaluation

- Data from all 5 EIP sites will be combined at CDC to evaluate public health impact of the rotavirus vaccine program.
- Hope to have final results early next year (2010).