Moving a New Vaccine from Bench to Bedside: Rotavirus Vaccine as a Model

Penelope H. Dennehy, M.D.

Professor and Vice Chair for Academic Affairs

Alpert Medical School of Brown University

Director, Division of Pediatric Infectious Diseases

Hasbro Children's Hospital

BROWN
Alpert Medical School

Moving a New Vaccine from Bench to Bedside

- Research – basic and clinical
- Product development
- Clinical trials
- FDA review and licensure – regulation
- Recommendations for use
  - Universal vs selective
  - Advisory committees – public and private sectors
  - Economic assessment

Vaccine Development

- Preclinical development and testing
  - Laboratory
  - Animals
- Clinical trials – FDA IND application
  - Immunogenicity
  - Efficacy
  - Safety

Phases in Development of a Vaccine

Phase	Studies	No. of Persons Usually Studied	Rate of Detectable Adverse Events
1*	Safety, immunogenicity	10-100	10-20%
2*	Dose, ranging, immunogenicity, safety	100-1000	1-10%
3*	Efficacy, safety, immunogenicity	500-20,000	0.5-5%
4	Postlicensure studies, postmarketing surveillance	10,000-100,000 Millions	____

*Prelicensure

BROWN
Alpert Medical School

Prelicensure Human Studies

- Numbers of subjects are usually limited
- Common reactions are identified
- Poorly detected reactions:
  - Rare
  - Delayed onset
  - Subpopulations

Licensing of Vaccines in the US

- Food and Drug Administration (FDA) licenses vaccines
    - FDA Advisory Committee (VRBPAC)
- Licensure based on results of clinical trials
- Vaccines are not available for use in the US until licensed

Postlicensure Surveillance

- Identify rare reactions
- Monitor increases in known reactions
- Identify risk factors for reactions
- Identify vaccine lots with increased rates of reactions
- Identify signals

Postlicensure Vaccine Safety Activities

- Phase IV Trials
  - ~10,000 participants
  - limited
- Large-Linked Databases
- VAERS

Vaccine Adverse Event Reporting System (VAERS)

- Jointly administered by CDC and FDA
- National reporting system
- Passive (depends on healthcare providers and others to report)
- Receives ~10,000 reports per year

- Detects
  - new or rare events
  - increases in rates of known events
  - patient risk factors
- Additional studies required to confirm VAERS signals
- Not all reports of adverse events are causally related to vaccine

Recommendations for New Vaccines

- Advisory Committee on Immunization Practices (ACIP)
- Committee on Infectious Diseases of the American Academy of Pediatrics

Advisory Committee on Immunization Practices (ACIP)

- Consists of 15 experts in fields associated with immunization
  - Non-voting liaison representatives from many organizations
- Develops written recommendations for the routine administration of vaccines to the pediatric and adult populations
  - ACIP is the only entity in the federal government which makes such recommendations

ACIP Process for Approval

- Recommendations are developed in Working Groups
  - Have a mixture of ACIP members, liaisons from AAP, AAFP, FDA, NIH, CDC and other interested parties
  - Present proposed recommendations to the full ACIP
- ACIP members comment on proposed recommendations
- Working group revises recommendations as needed based on feedback from full ACIP
- Final recommendations require approval of the full ACIP

American Academy of Pediatrics Recommendations

- Vaccine recommendations authored by the Committee on Infectious Diseases
  - Appointed committee of experts with 13 members
  - Nonvoting liaisons from CDC, FDA, NIH, CPS, AAFP, NVPO
- AAP issues policy statements on use of vaccines
  - Reviewed by the whole Board of Directors of AAP
  - Published in *Pediatrics*
  - Published on the *Pediatrics* website (www.pediatrics.org)

Childhood Vaccine Financing in the US

Table 1. The role of programs in vaccination

Program	Target Population(s)	Principal Benefit(s)	Population Covered[14]
Vaccine for Children Program (VFC)	Medicaid-eligible children Uninsured children American Indians Alaska Natives Underinsured, ie, children with insurance that does not cover vaccines	Vaccines	40%
Section 317	Low-income children not eligible for VFC Underinsured children Children of working poor/with insurance deductibles or other costs that parents cannot cover	Vaccines and administration	8%
State programs	Varies by state: may include all or some children, all or some vaccines, regardless of insurance status	Vaccines and administration	7%
Medicaid	Low-income and disabled children (criteria vary by state)	Administration	
State Child Health Insurance Program	Low-income children up to 200% of federal poverty level (sometimes more, depending on state)	Vaccines and administration	
Private insurance		Vaccines and administration; may require copays, deductibles, or other cost sharing	45%

BROWN
Alpert Medical School

Barriers to Vaccine Implementation

- Limitations in both federal and state vaccine financing the dominant barriers
- Vaccine supply or allocation

Rotavirus Vaccine as a Model

BROWN
Alpert Medical School

Rotavirus Structure

- Outer layer made of VP7 and VP4 proteins
  - –VP7 determines G-serotype
  - –VP4 determines P-serotype
- VP7 and VP4 are important for immunity
  - –Induce serotype-specific neutralizing antibodies in vivo

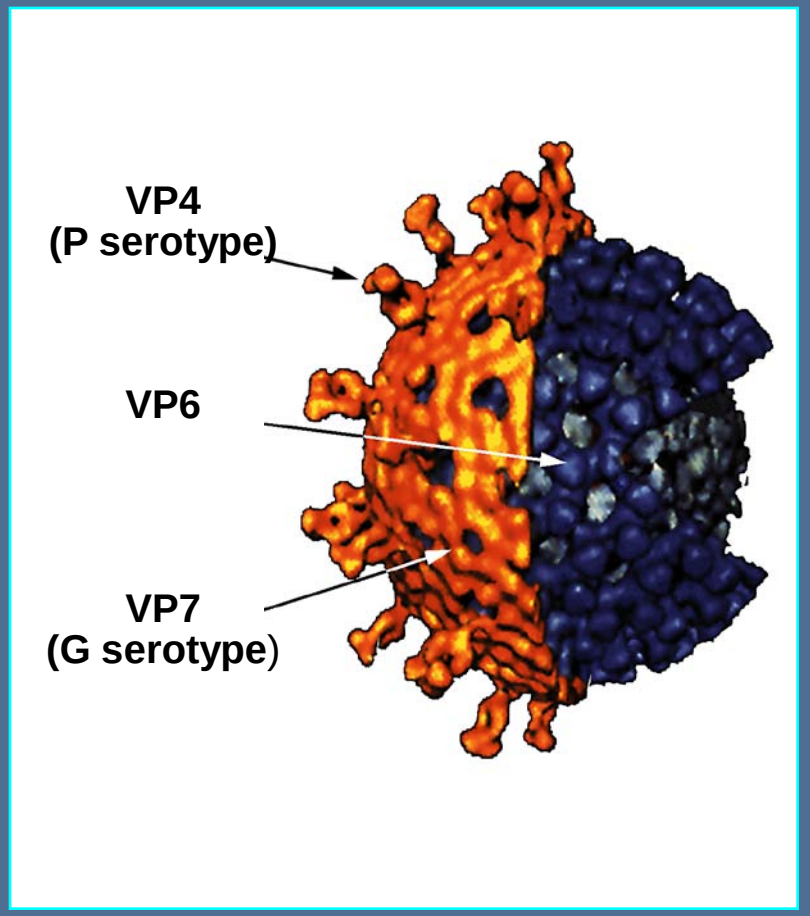


Figure adapted from Estes MK. *J Infect Dis.* 1996;174(Suppl 1):S37-S46.

Natural Immunity and Rotavirus Gastroenteritis

- Many children infected more than once
  - First infections more likely to result in severe gastroenteritis than subsequent infections
- Protective immunity develops after natural infection,
  - Strongest against moderate-to-severe disease
  - Serotype specific
  - Serologic correlates of immunity have not been established
- As a result field studies have been necessary to demonstrate the efficacy of rotavirus vaccines

BROWN
Alpert Medical School

Goals for a Rotavirus Vaccine

- To duplicate the degree of protection that follows natural infection
- To prevent moderate to severe disease but not mild disease from rotavirus
- To reduce the disease burden
- Vaccine most needed in developing countries where mortality with rotavirus is high

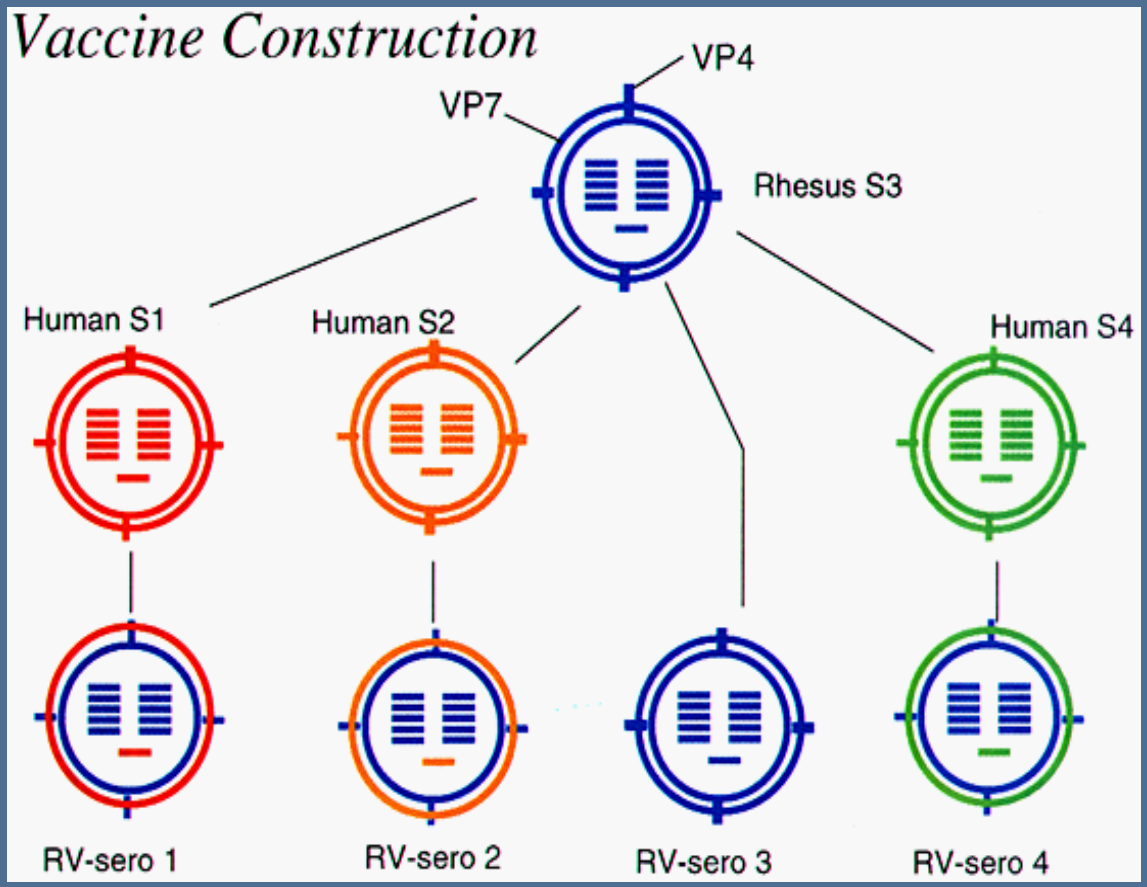
Vaccine -Development Approaches

- Monovalent animal rotavirus vaccines
- Multivalent human-animal reassortant vaccines
- Attenuated human strains

Multivalent Human-Animal Reassortant Vaccines

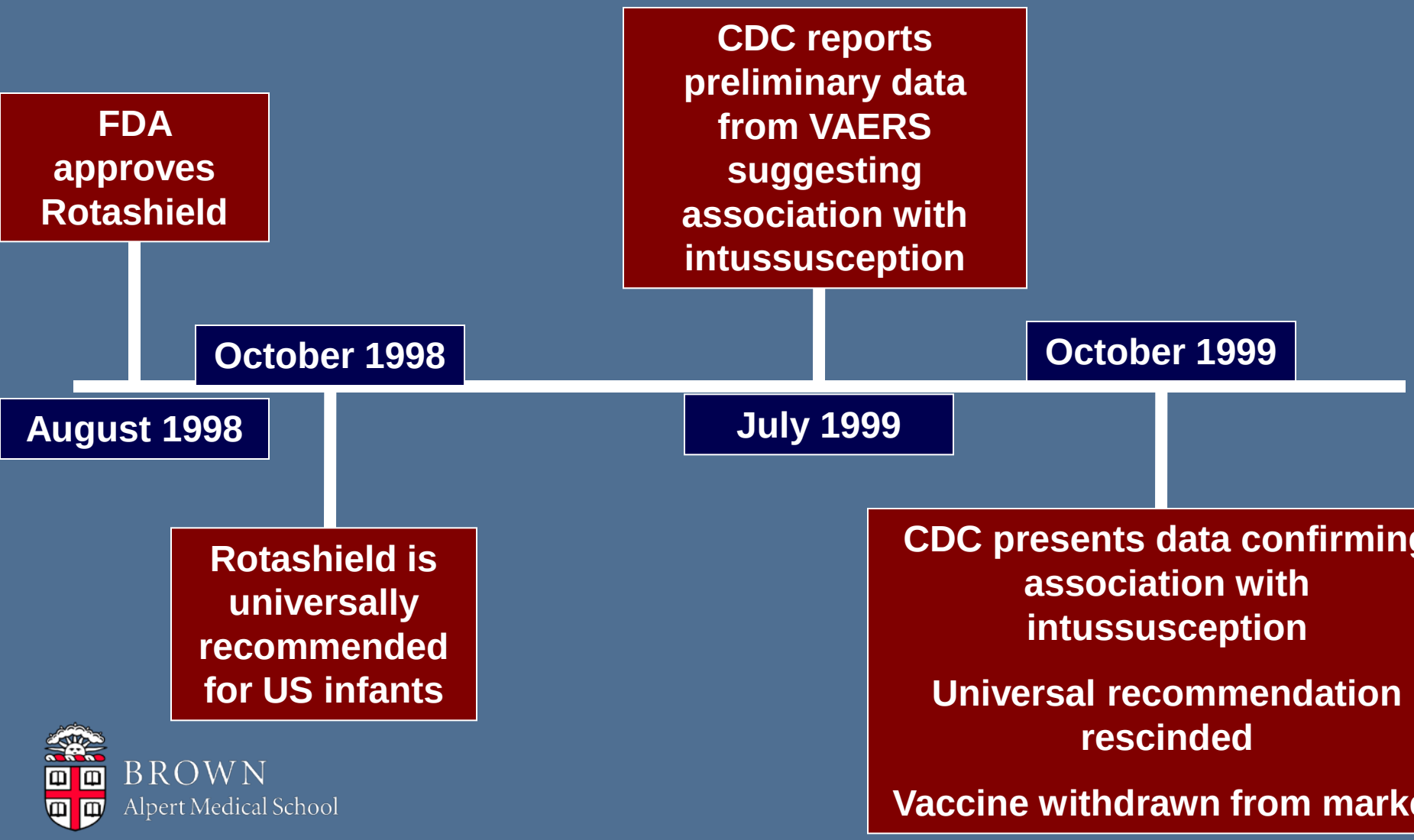
- Vaccines contain genes from an animal parent virus and VP4 and/or VP7 gene from human strain
- Simian-based vaccines
  - Rotashield®
- Bovine-based vaccines
  - RotaTeq™

Reassortant Human-Rhesus Rotavirus Vaccine (Rotashield)



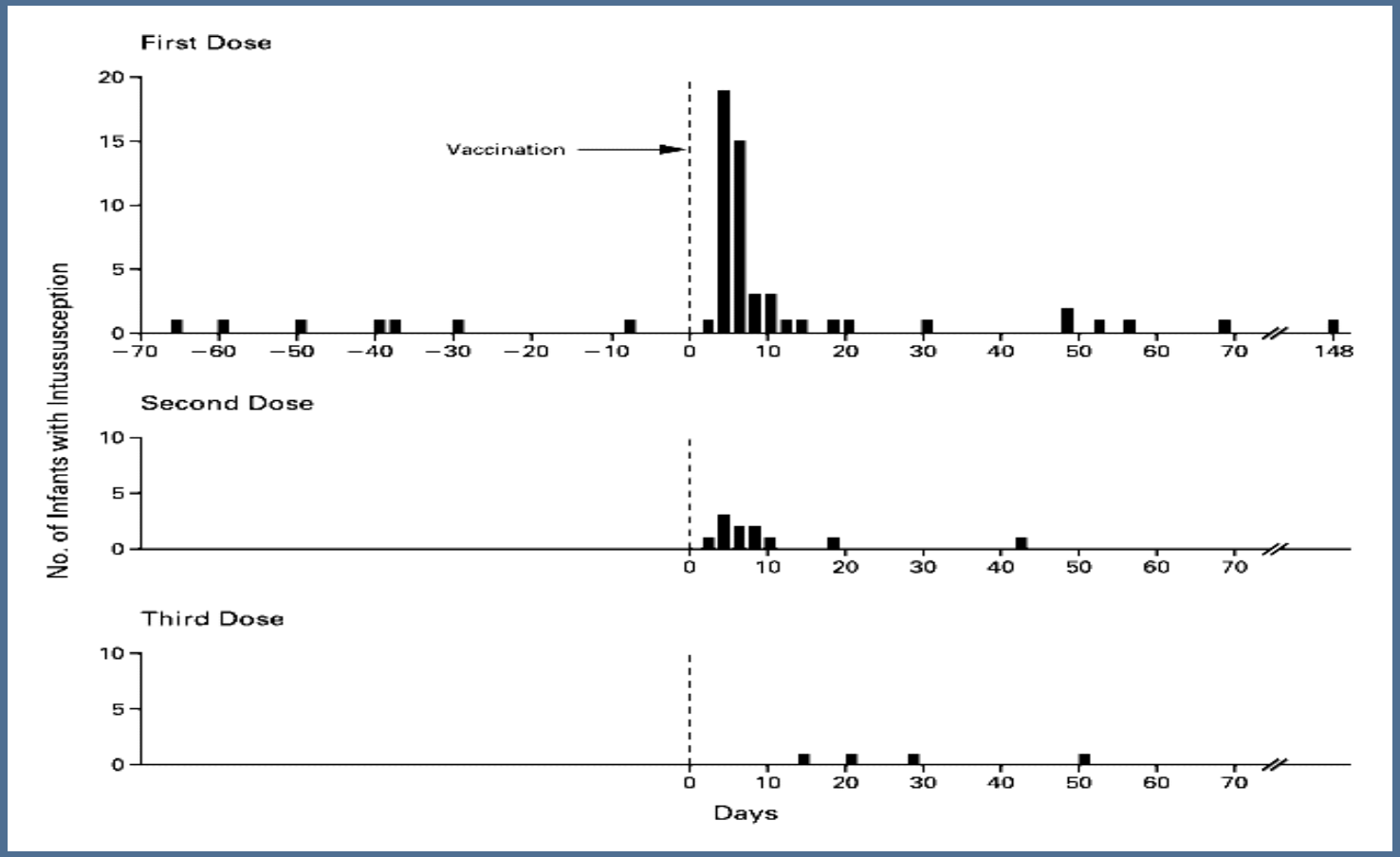
BROWN
Alpert Medical School

Rotashield Story



BROWN
Alpert Medical School

Rotavirus Vaccine and Intussusception - CDC Case Control Study



BROWN
Alpert Medical School

Murphy, et al. NEJM 20:410, 2001

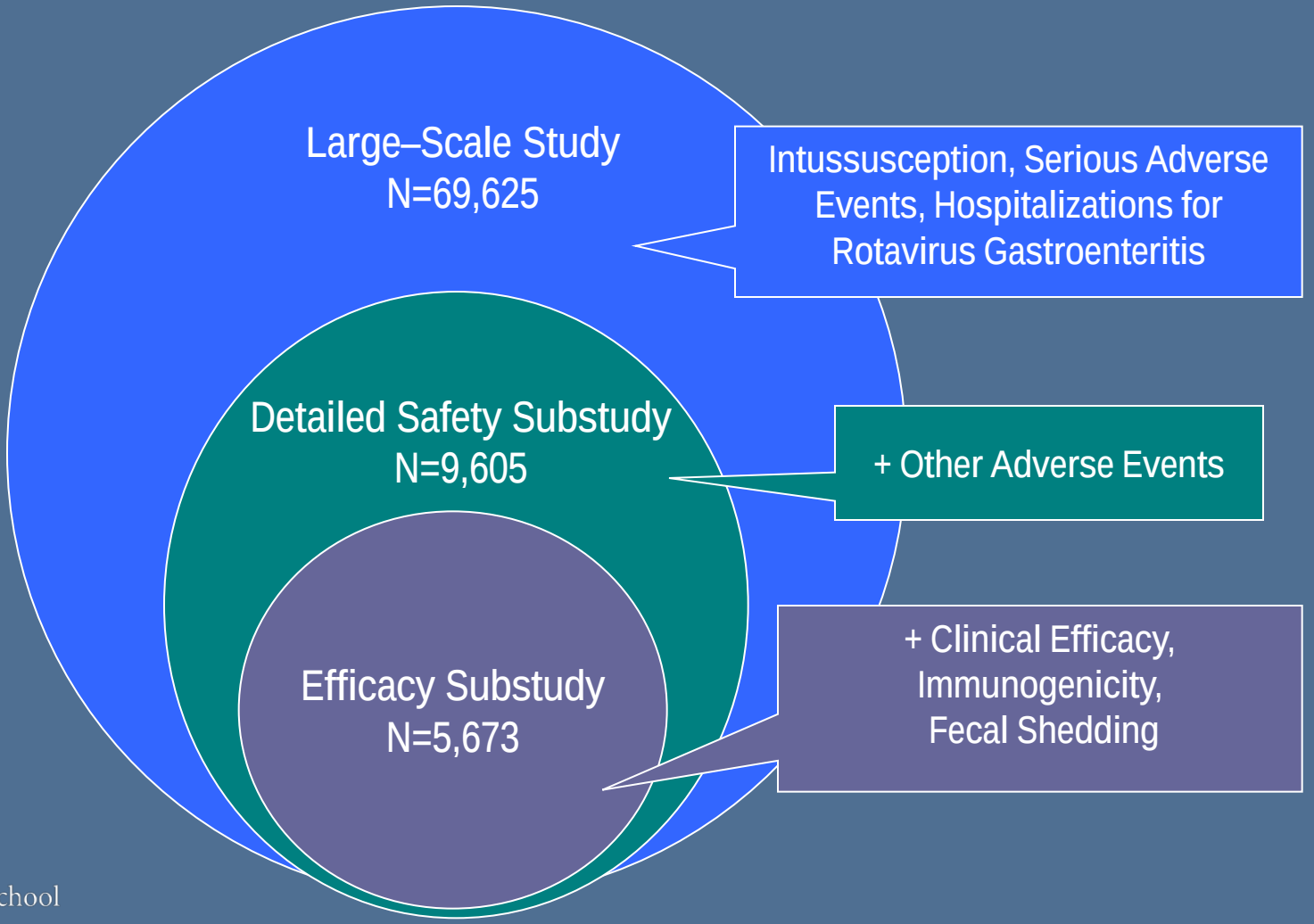
Implications of Rotashield Withdrawal on Development of New Rotavirus Vaccines

- Estimated rate of intussusception with Rotashield
  - 1 case per 10,000 doses
- Studies of new vaccines need to be quite large to exclude the possibility of intussusception (>60,000 subjects)

Bovine Rotavirus Vaccine – RV5 [RotaTeq™]

- 5 human-bovine reassortants
  - G serotypes - Human G1, G2, G3, G4
  - P serotype - Human P[8]
- Phase II studies - efficacious and generally well tolerated

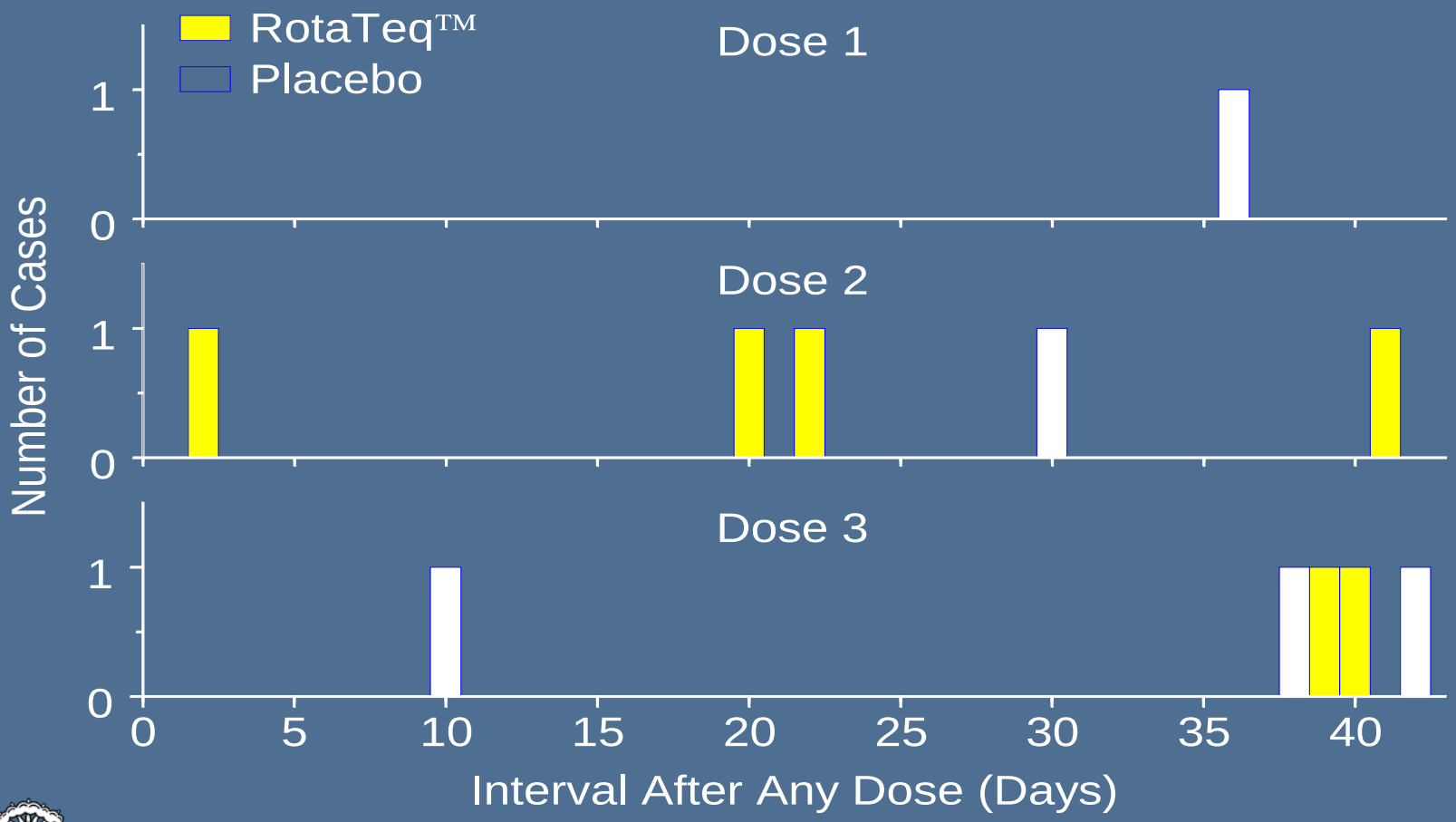
REST Organization and Objectives



BROWN
Alpert Medical School

REST: Intussusception Cases

6 Vaccine : 5 Placebo



BROWN
Alpert Medical School

Vesikari T, et al. N Engl J Med. 2006;354:23-33.

Efficacy of RV5 Against G1–G4 Rotavirus AGE

Disease Severity	Number of Cases: Vaccine	Number of Cases: Placebo	% Efficacy	95% CI
Any	82	315	74	67, 80
Severe*	1	51	98	88, 100

*As defined by clinical scoring system.

BROWN
Alpert Medical School

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

Efficacy of PRV to Reduce Health Care Visits

Type of Health Care Contact	Number of Cases		% Rate Reduction	95% CI
	Vaccine	Placebo		
Hospitalizations	6	144	96	91, 98
Emerg. Dept. Visits	14	213	93	88, 96
Non-urgent Visits	13	99	86	74, 93

BROWN
Alpert Medical School

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

Live Attenuated Human Rotavirus Vaccine RV1 [Rotarix®]

- Contains one strain of human rotavirus (G1P[8])
  - Shares neutralizing epitopes with G1, G3, G4 and G9 serotypes
- Several small efficacy studies showed that RV1 was efficacious and generally well tolerated

Phase III Study of RV1 in Latin America & Finland

Primary Immunization Phase:
Analysis of Intussusception & Safety
>63,000 infants

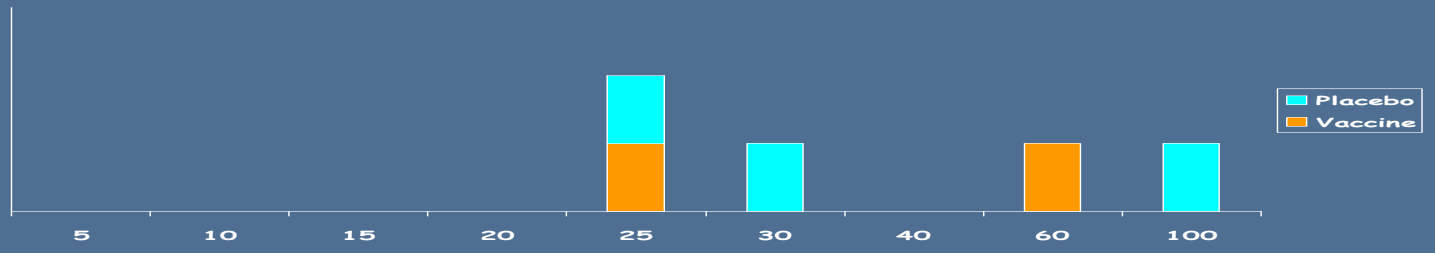
1-Year follow-up :
Nested Analysis of Efficacy & Safety
>20,000 infants

BROWN
Alpert Medical School

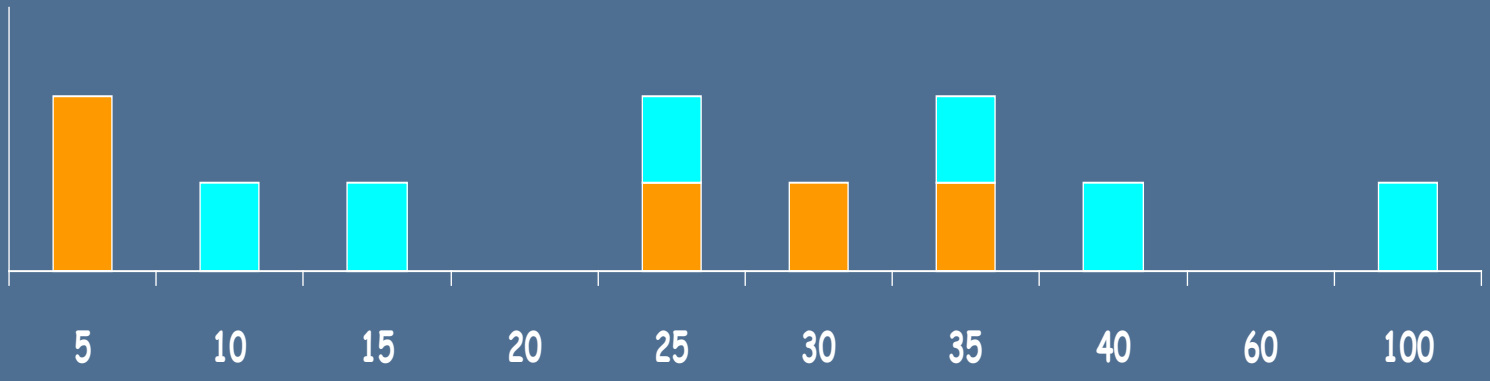
Ruiz-Palacios et al. NEJM 2006;354:11-22

Occurrence of IS Cases with RV1

Dose 1



Dose 2



Days after Vaccination

BROWN
Alpert Medical School

RV1 Vaccine Efficacy

- Phase III trials included more than 67,000 infants
- Efficacy in Latin America
  - Severe rotavirus disease - 85%
  - Rotavirus-related hospitalization - 85%
- Efficacy in Europe
  - Severe rotavirus disease - 96%
  - Rotavirus-related hospitalization - 100%
  - Medical attention for RV AGE - 92%
  - For any rotavirus disease after one dose - 87%

BROWN
Alpert Medical School

N Eng J Med 2006;354:23-33
Lancet 2007;370:1757-1763

Rotavirus Vaccine Licensing and Recommendations in the US

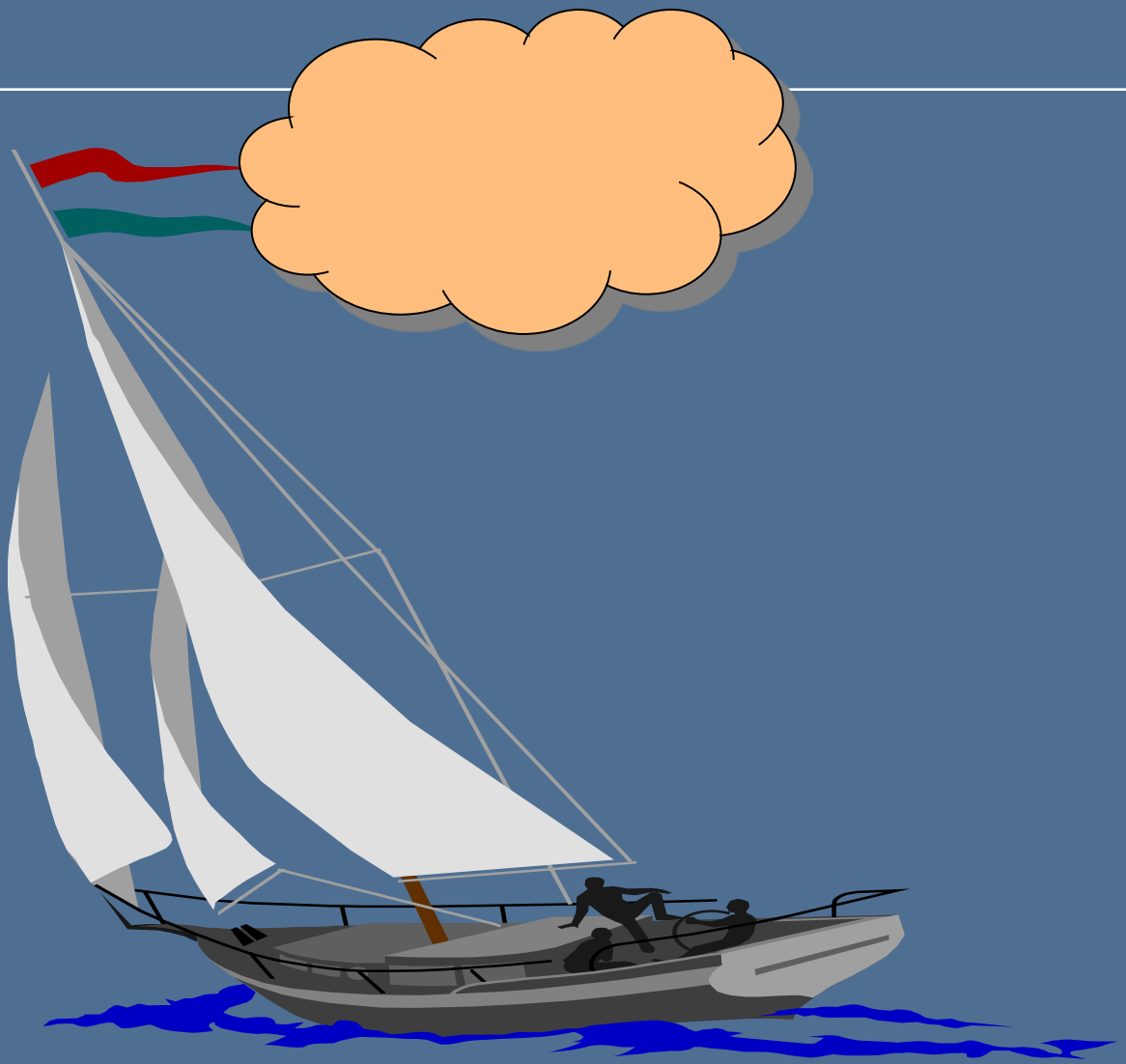
	RV5	RV1
Licensed	2/3/06	4/3/08
ACIP added to recommended vaccine schedule	2/21/06	6/28/08
MMWR statement published	8/11/06	2/6/09
AAP recommendations published in Pediatrics	January 2007	April 2009

BROWN
Alpert Medical School

Rotavirus Vaccine Implementation

- Factors Associated With Adoption
  - Perception of a high burden of rotavirus disease
  - A high level of confidence in pre-licensure studies of vaccine safety
- Barriers
  - Concerns about uniform coverage of vaccine by insurers
  - Lack of adequate reimbursement
  - Concern about parental reluctance because of withdrawal of previous rotavirus vaccine

Questions



BROWN
Alpert Medical School