Phase III Clinical Results of Rotavirus Vaccine Trials and Efforts to Accelerate Introduction to the Developing World

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PATH

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PATH
A catalyst for global health

Outline

I. Background

II. RotaTeq® (Merck)

III. Rotarix® (GSK)

IV. Accelerated Development and Introduction Plan (ADIP)

V. Summary

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2006 An incredible year for Rotavirus Vaccines

1. US FDA licenses RotaTeq®.
2. ACIP recommends RotaTeq® for routine immunization of all American children.
3. EMEA licenses Rotarix®.
4. Brazil and Panama begin national programs of childhood immunization.
5. >30 countries have licensed a RV vaccine.

The Saga of Rotashield®

- Live, human-rhesus rotavirus reassortant vaccine
- Licensed in 1998, but withdrawn from market in 1999 due to unexpected, increased risk of intussusception
- Abrupt demise of first vaccine licensed after 20 years of research
- Vaccine licensed by NIH to BioVirix, Inc, in 2004
- Seeking commercialization, but no success to date

Challenges of Rotavirus Vaccine Development in Face of Intussusception

- Design a study that is large enough to provide a meaningful evaluation of an uncommon event, yet feasible to implement prelicensure.
- Develop a safety monitoring system to detect a potential increased risk of intussusception early and minimize risk to trial participants.
- Decide on safety criteria for demonstrating that the vaccine is clinically acceptable for licensure.

RotaTeq® and Rotarix®

Characteristic	RotaTeq®	Rotarix®
Manufacturer	Merck	GSK
Parent strain	Bovine Rotavirus strain WC3	Human Rotavirus strain 89-12
Method of Attenuation	Animal strain naturally attenuated; further passaged 7-69 times	Passaged 43 times
Final Vaccine	Live, human-bovine rotavirus reassortants (G1, G2, G3, G4, P1A[8])	Live, attenuated human rotavirus (G1, P1A[8])
Presentation	Oral suspension in liquid buffer (2 mL)	Lyophilized, reconstituted with liquid diluent prior to administration (1 mL)
Buffer	Citrate phosphate sucrose	Calcium carbonate

RotaTeq® and Rotarix® continued

Characteristic	RotaTeq®	Rotarix®
Route of administration	Oral, administered directly from tube; no restriction on food or liquid	Oral, administered by syringe, no restriction on food or liquid
Dose (end of shelf-life)	~ 2-3 x 10^6/virus; ~ total 1-1.5 x 10^7 infectious units	~ 1 x 10^6 infectious units
Cell substrate	Vero cells	Vero cells
Storage	2°-8° C	2°-8° C
Shelf life	24 months	36 months
Regimen	3 doses, 1st at 6-12 wks, subsequent dose at 4-10 wk intervals	2 doses, 1st at 6-14 wks, 2nd at 1-2 mo interval
Post-dose shedding	~10%	>50%

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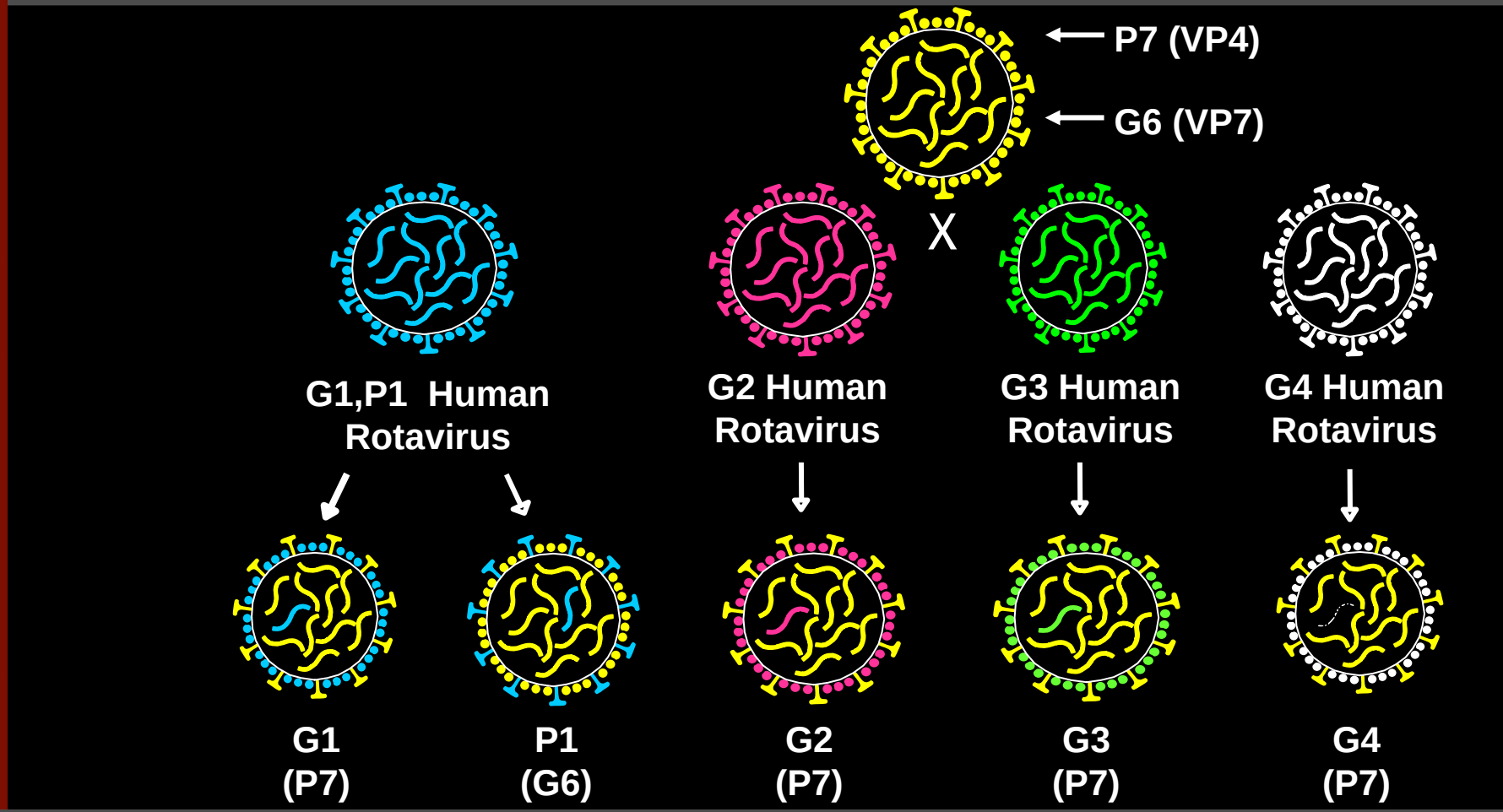
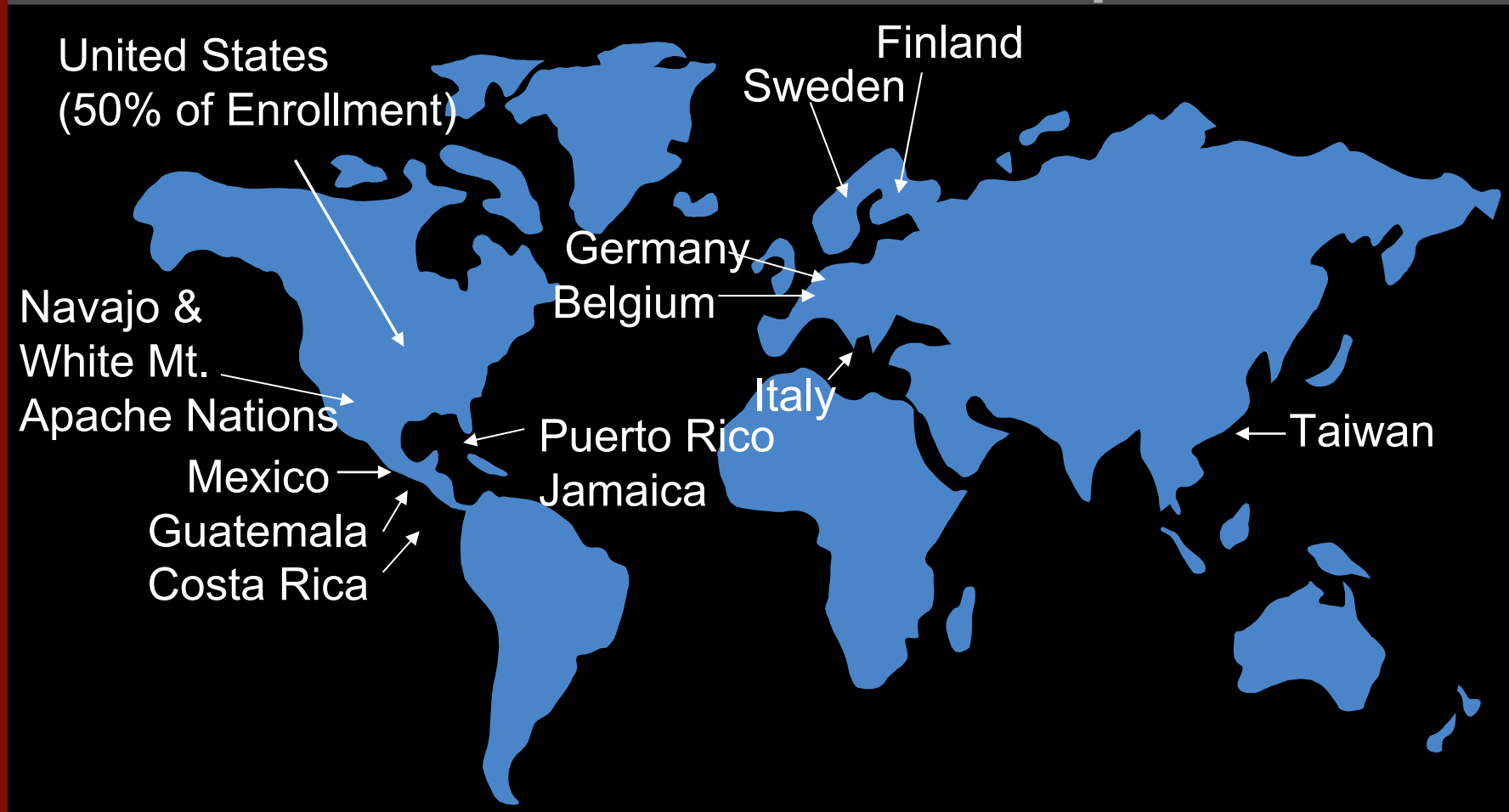
Bovine (WC3) Rotavirus



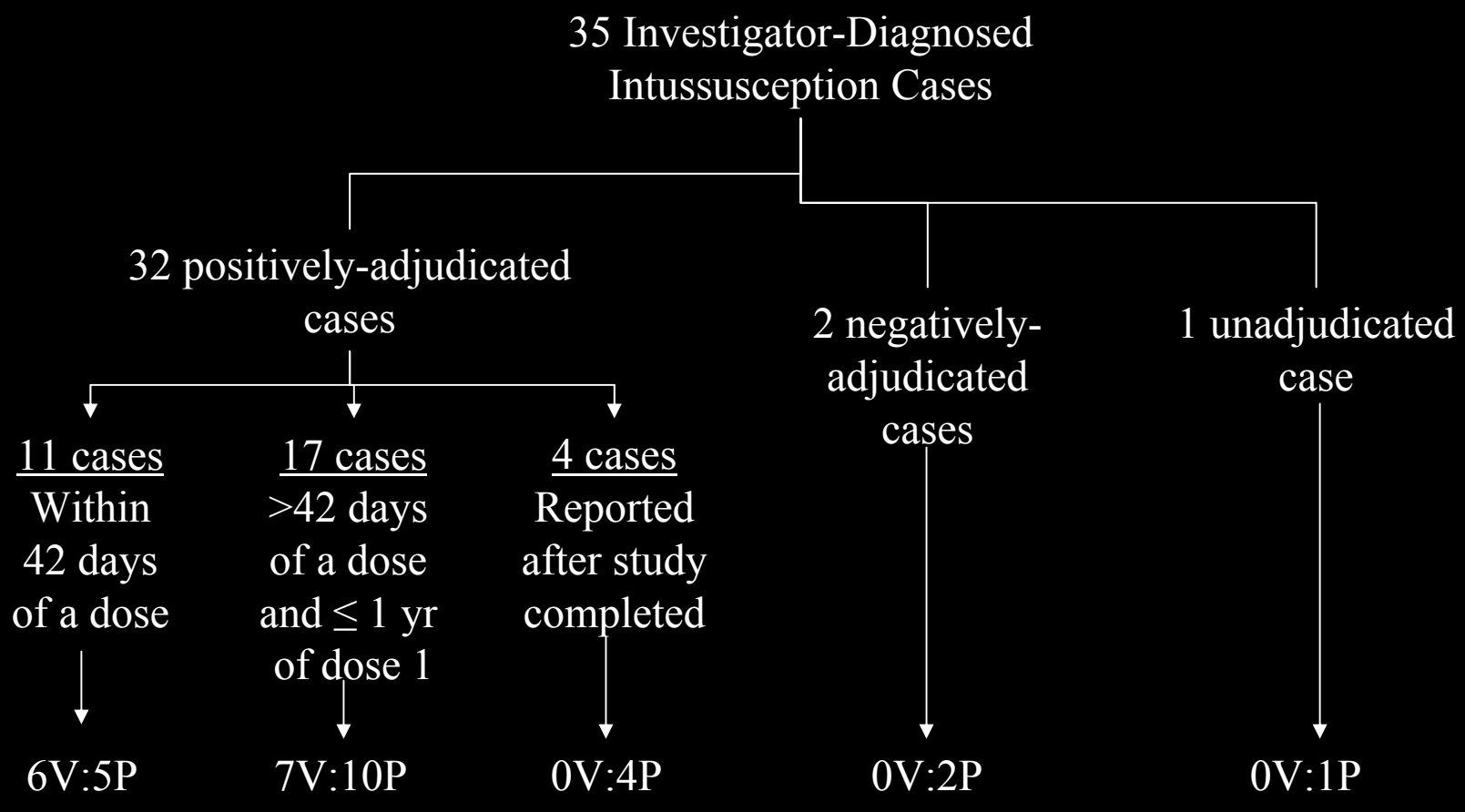
Rotavirus Efficacy and Safety Trial (REST) Study Design

- Sample size: ≥ 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

71,799 Subjects in 11 Countries Vaccinated
36,203 in RotaTeq® Group
35,596 in Placebo Group



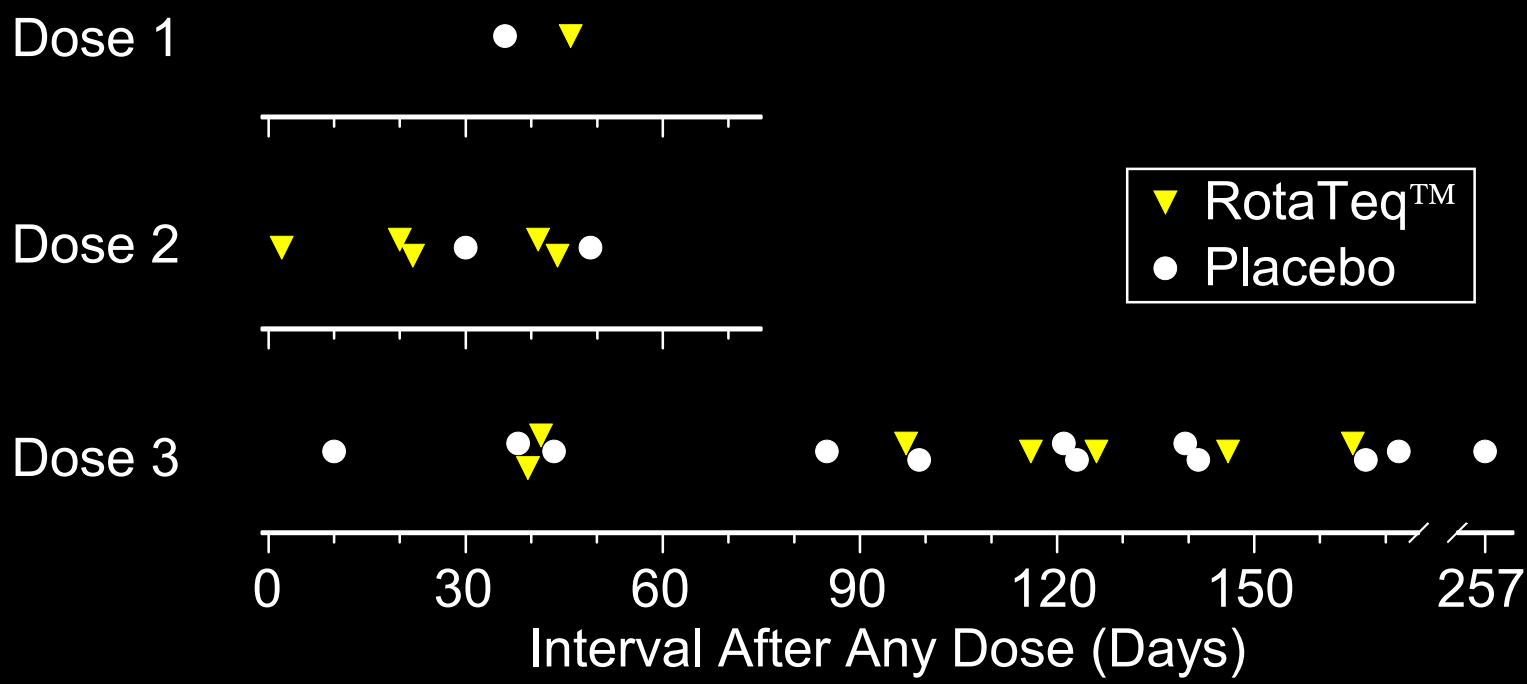
REST Intussusception Results



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



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

Efficacy Cohort

Disease Severity	Vaccine (N=3484)	Placebo (N=3499)	% Efficacy	95% CI
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

Type of Health Care Encounter	Number of Cases		% Rate Reduction	95% CI
	Vaccine	Placebo		
Hospitalizations†	6	144	95.8	90.5, 98.2
Emerg. Dept. Visits†	14	225	93.7	88.8, 96.5
Office Visits‡	13	98	86.0	73.9, 92.5

† 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.

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Rotarix®

- G1, P1A[8] human virus attenuated by passage through cell culture
  - Shares neutralizing epitopes with G1, G3, G4, and G9 RV types

Rotarix® Pivotal Phase 3 Trial: Latin America and Finland

Primary immunization phase:
Analysis of intussusception and safety
(N>63,000 infants)

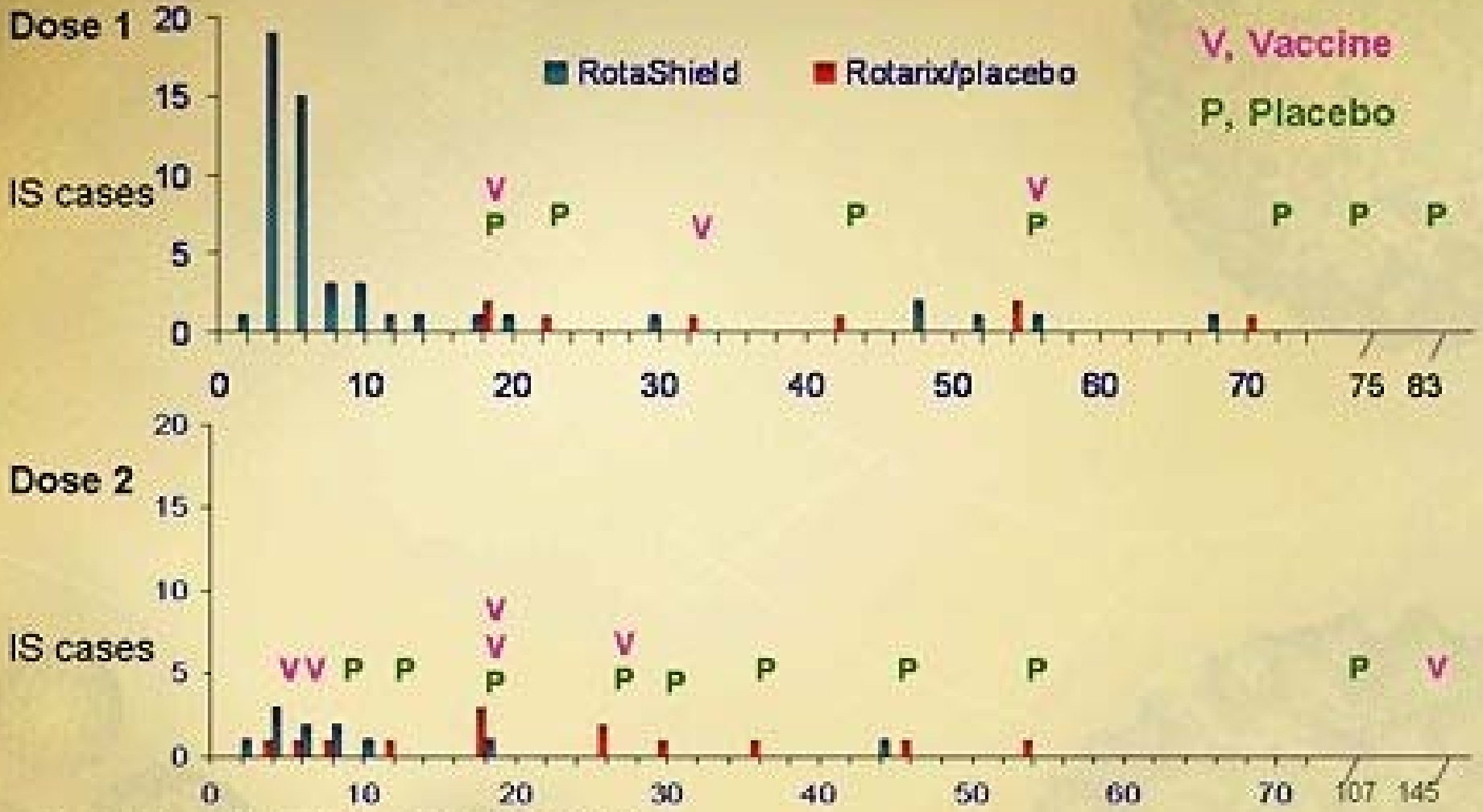
1-year follow-up:
Nested analysis of efficacy and safety
(N>20,000 infants)

Rotarix® intussusception (IS) data

	Number of IS Cases	
	Vaccine group N=31,673	Placebo group N=31,552
Total 0 → 31 days	**6**	**7**
Risk Difference = -0.32/10.000 vaccines (95% CI: -2.91 to 2.18)		
Relative Risk = 0.85 (95% CI: 0.30 to 2.42)		
0 → 31 days post dose 1	**1**	**2**
0 → 31 days post dose 2	**5**	**5**

Ruiz-Palacios G. et al N. Engl. J. Med. 2006; 354: 11-22

Intussusception: *Rotarix*® Compared With *RotaShield*®



Murphy TV, et al. *N Engl J Med*. 2001;187:1309-1313.
Ruiz-Palacios et al. *NEJM* 2006;354:11-22

Efficacy of Rotarix® against RVGE

	Number of Cases			
Disease Severity	HRV (N=9009)	Placebo (N=8858)	% Efficacy	95% CI
Severe	12	77	**84.7**	71.7, 92.4
Hospitalized	9	59	**85.0**	69.6, 93.5

Ruiz-Palacios G. et al N. Engl. J. Med. 2006; 354: 11-22

Efficacy of Rotarix®: Serotype Specific Against Rotavirus Disease of Any Severity

	Cases, N			
Serotype	Vaccine (n=9009)	Placebo (n=8858)	% Efficacy	95% CI
G1	3	36	91.8	74.1, 98.4
G2	1	6	41.0	<0.0, 82.4
G3, G4 or G9	4	31	87.3	64.1, 96.7

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PATH's Rotavirus Vaccine Program (RVP) Goals

- **Goal 1:** Provide information that enables national decision-makers, and the GAVI Board and its partners, to make evidence-based decisions regarding the use of rotavirus vaccines.
- **Goal 2:** Accelerate the availability of new rotavirus vaccines appropriate for use in developing countries.

Building the Evidence Base

Disease burden
(global/country)

- Disease surveillance
- Serotype distribution
- Intussusception surveillance

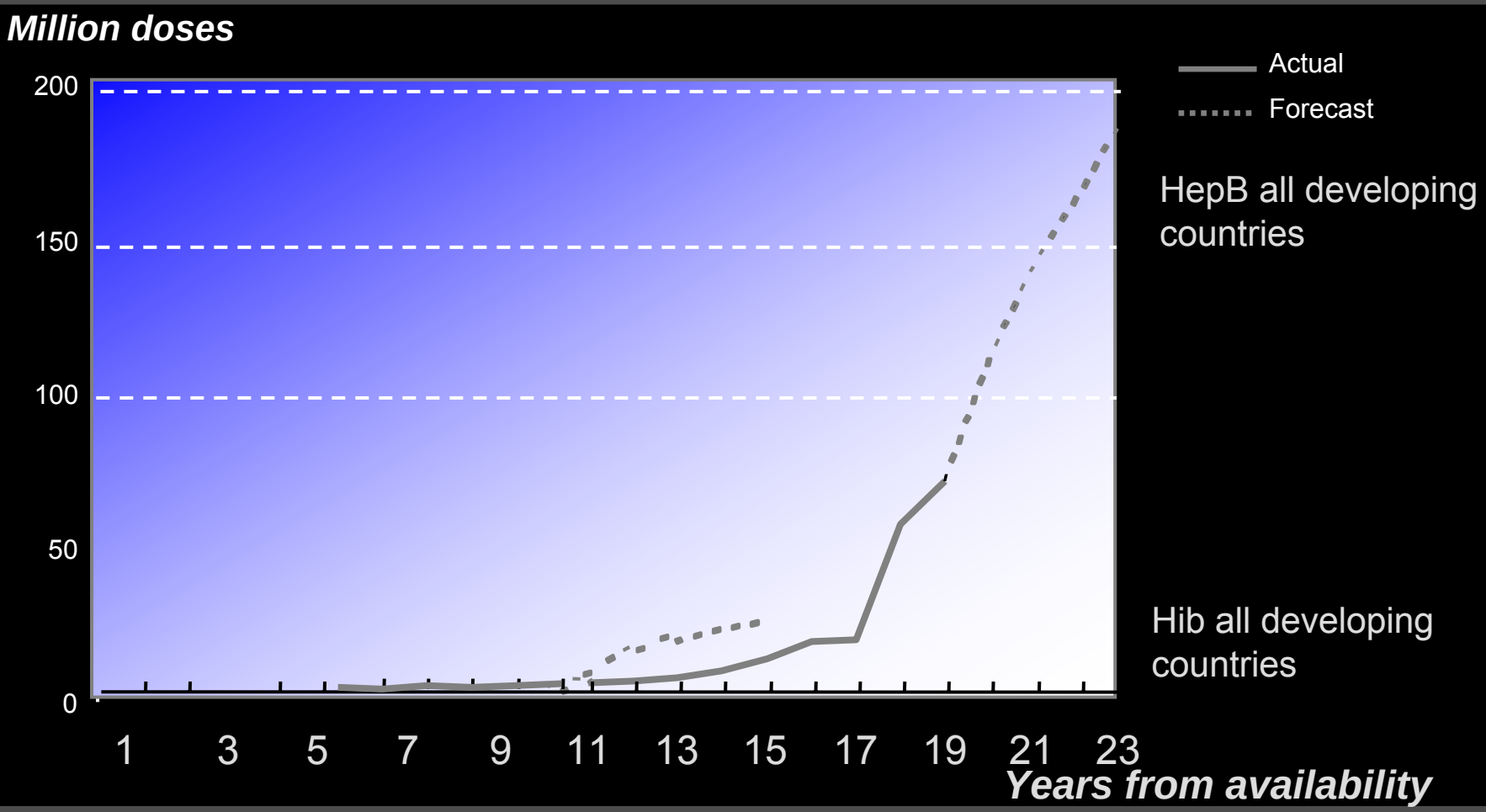
Vaccine safety and efficacy
(regional)

- Clinical trials in developing countries (Asia, Africa)

Economics
(global/country)

- Economic burden of preventable illness/death
- Cost-effectiveness of vaccination

Vaccine Introduction Scenario Perspective



Source: McKinsey & Co.;
PATH's Rotavirus Vaccine Program

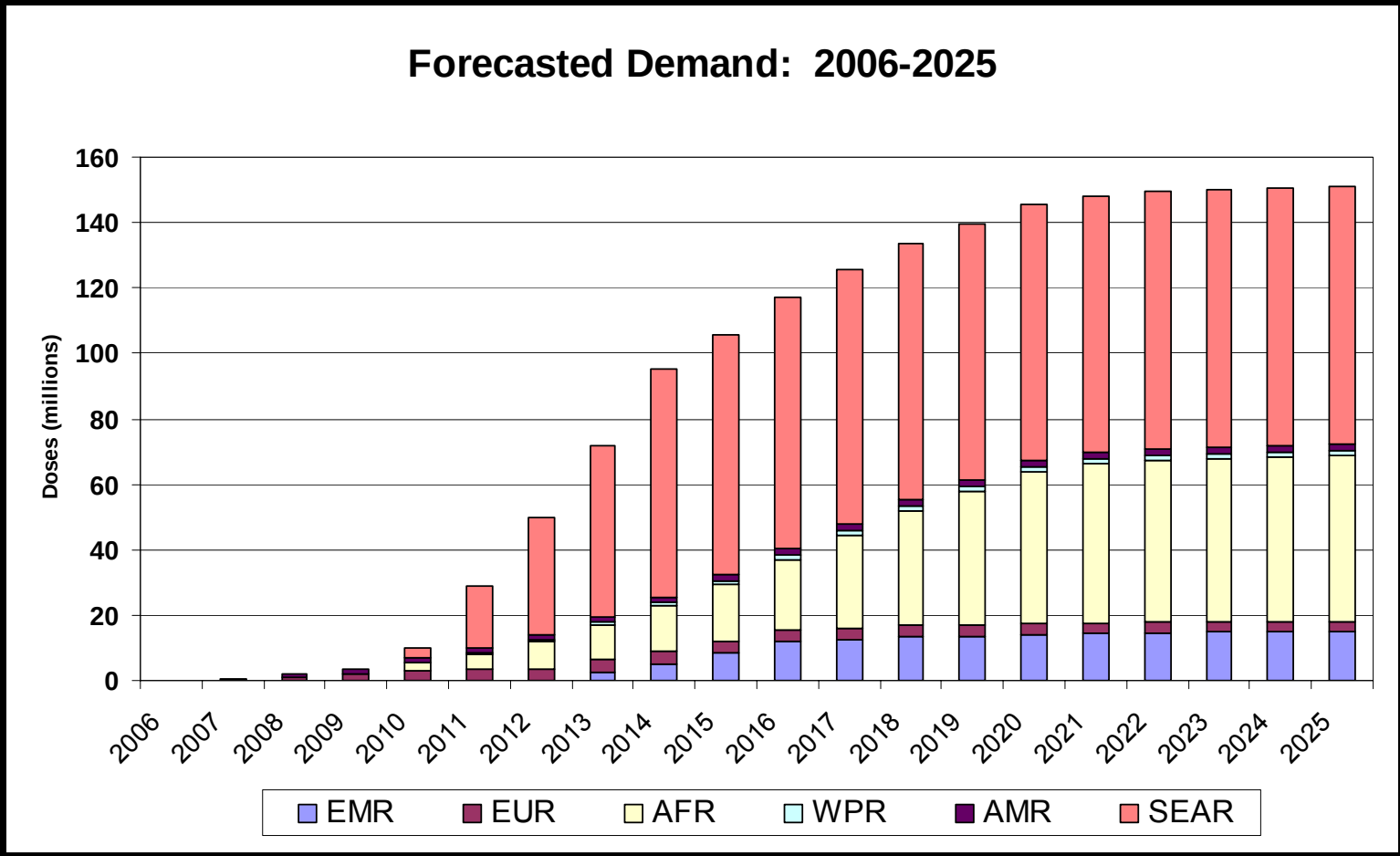
Will live oral rotavirus vaccines work well for children in Africa and Asia?

- Live oral vaccines less efficacious in developing world
- Differences in nutritional status, breastfeeding patterns, bacterial and parasitic infections, HIV prevalence
- Different rotavirus serotypes

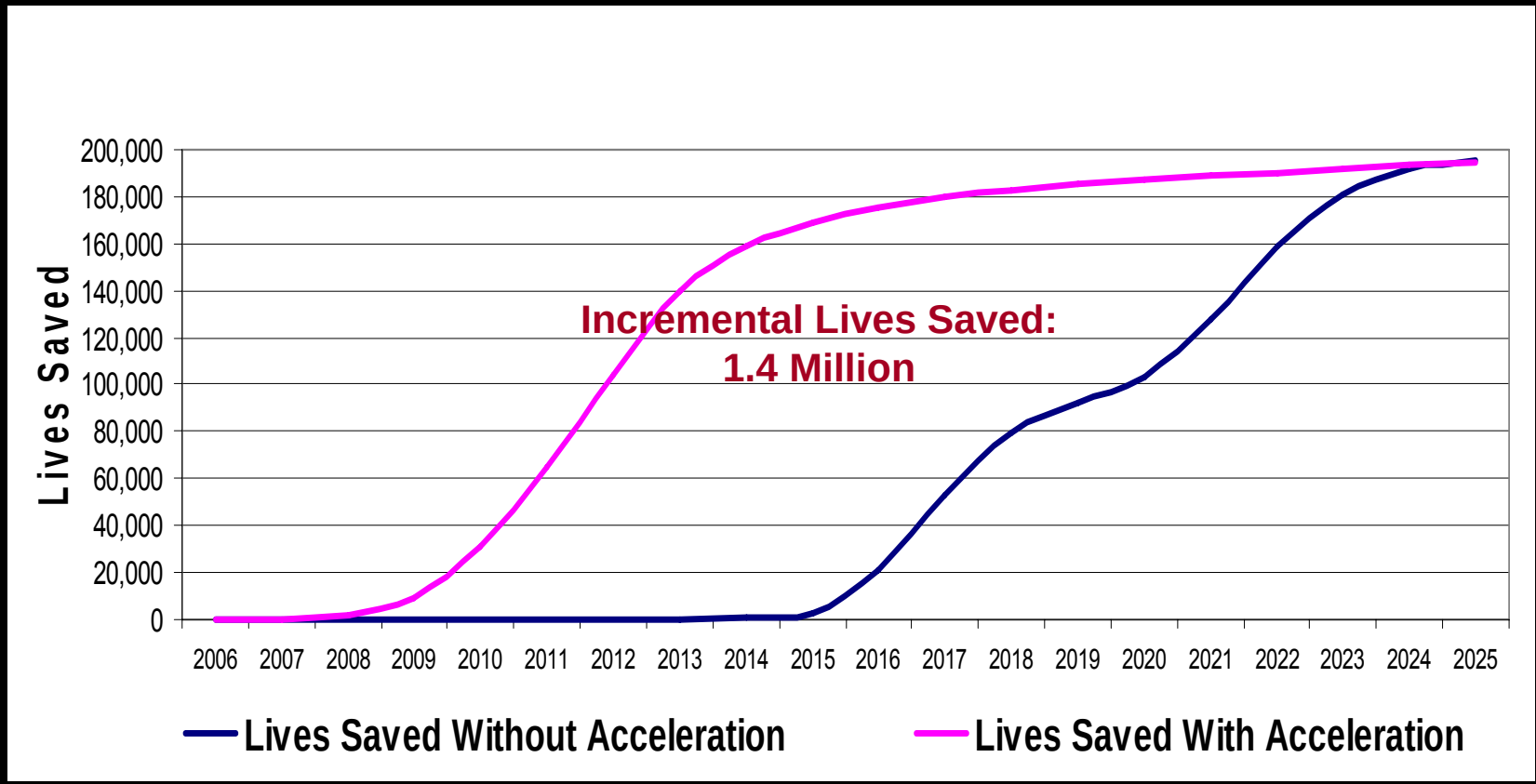
Will live oral rotavirus vaccines work well for children in Africa and Asia – how many efficacy trials are needed?

	GSK: Human, monovalent	Merck: Bovine reassortment, multivalent
Africa	Phase III Underway	Phase III target start date: late 2006
Asia	GSK Phase II: Bangladesh, India, Vietnam	Phase III target start date: early 2007

How Many Doses are Required for GAVI-eligible Countries?



How Many Lives Can Be Saved with Accelerated Rotavirus Vaccine Introduction?



Hospital and Outpatient Visits Avoided[2]: 60 Million
Health System Costs Avoided[3]: $300 Million

1 Adapted from Rheingans et.al 2005 (unpublished) and Parashar 2003; Range: 0.9 to 2.3 Million Lives Saved
2Adapted from Rheingans et.al. 2005 (unpublished) and Parashar 2003: 130 hospitalizations and outpatient visits avoided per 1000 infants vaccinated
3 Based on avg. cost per visit = $5.00

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Summary

- Rotavirus prevention efforts were set back by the withdrawal of *RotaShield*®
- New safe and effective rotavirus vaccines offer the best hope of reducing the toll of acute rotavirus gastroenteritis in developed and developing countries
- *RotaTeq*® and *Rotarix*® have demonstrated safety and efficacy in controlled clinical trials and licensure efforts are underway around the globe.
- Accelerated implementation programs are striving to deliver these vaccines to areas where they are needed most.

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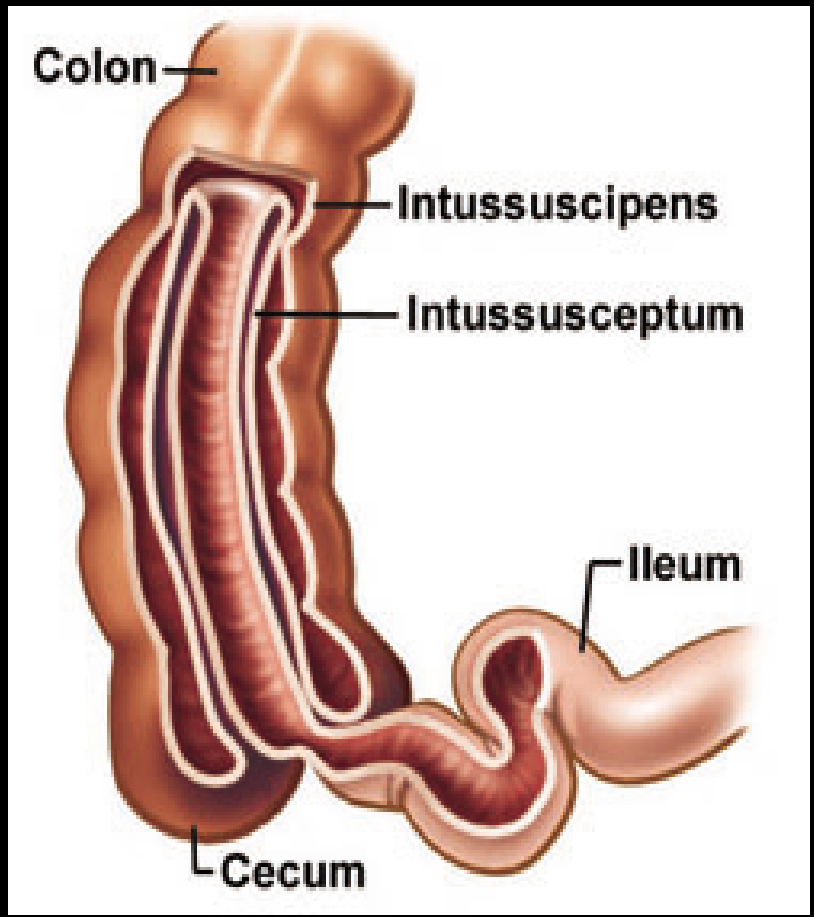
Backup Slides

Rhesus Rotavirus Vaccine -- Rotashield®

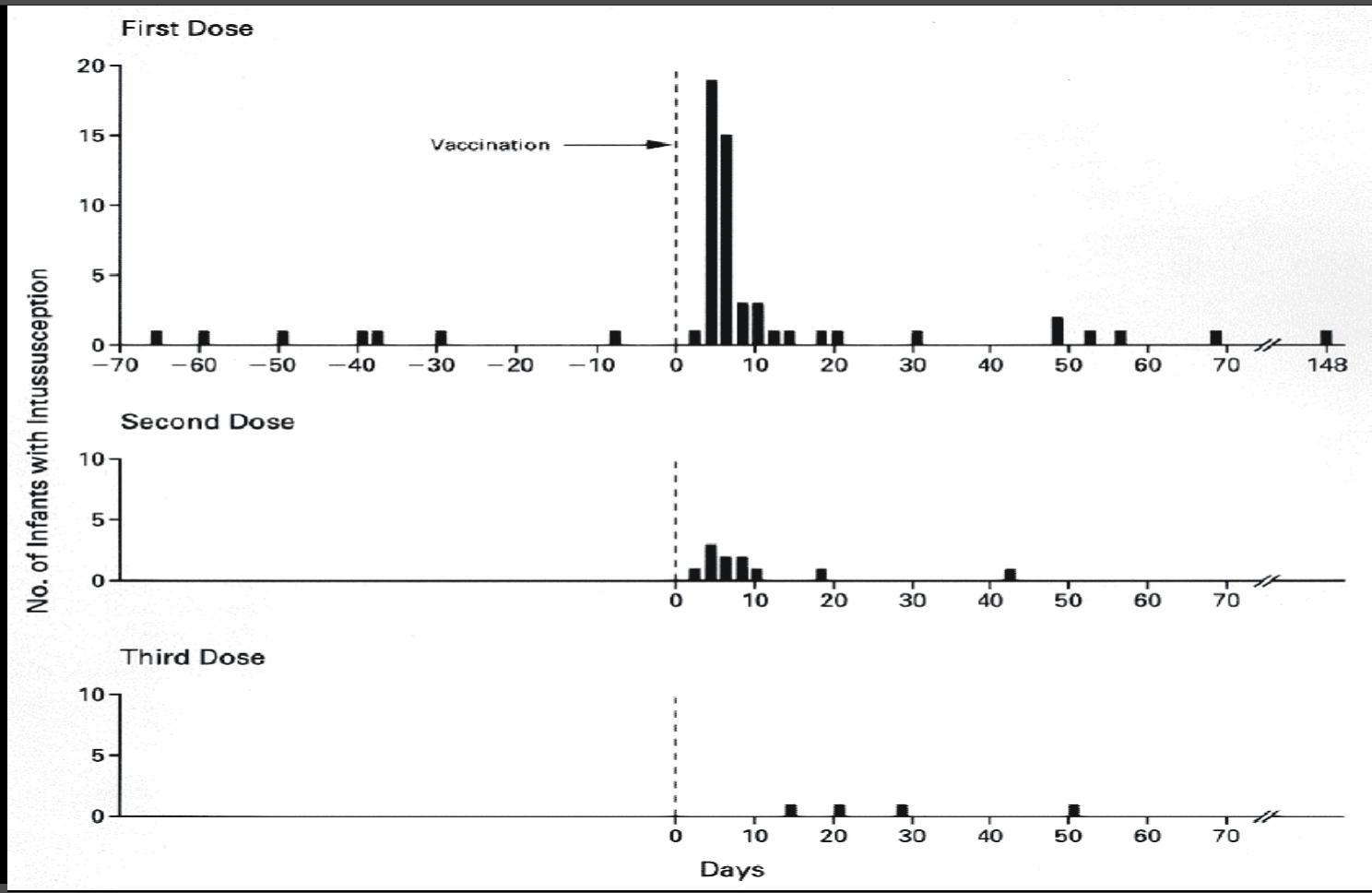
- Live oral vaccine
- 3 doses given at 2, 4, 6 months
- Safety – mild fevers on day 3-5 <10%
- Efficacy – 70% against mild RV diarrhea, >85% against severe RV diarrhea

Characteristics of Naturally-Occurring Intussusception



- Etiology not well defined
- Uncommon: Incidence ~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

Interval between Rotashield vaccine and Intussusception



Murphy TV, et al, 2001

PATH

PATH creates sustainable, culturally relevant solutions that enable communities worldwide to break longstanding cycles of poor health by:

- Advancing technologies, e.g. vaccines – malaria, meningococcal, rotavirus, HPV, JE, pneumococcal
- Strengthening health systems
- Encouraging healthy behaviors

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