

# Outlook for the Implementation of a Human-Bovine (UK) Rotavirus Reassortant Vaccine

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Presented by Harry Greenberg

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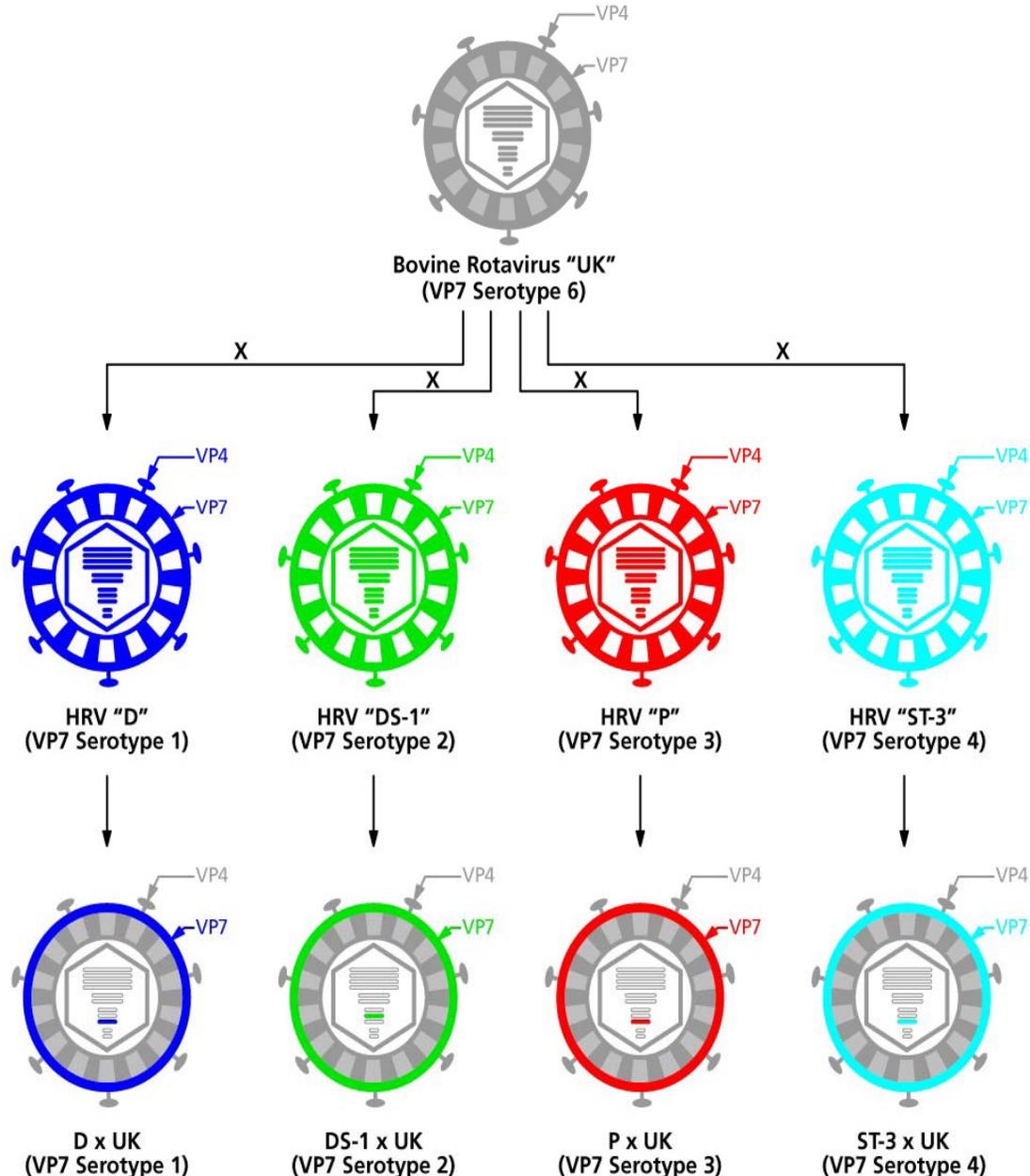
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# **Pursuit of a 2nd Generation Bovine Rotavirus-based Vaccine Began Prior to the Withdrawal of RotaShield**

- **RRV-TV associated with transient and generally low grade fever in up to one-third of vaccinees**
- **Bovine RV-based vaccines characteristically non-reactogenic**
- **Human-bovine RV reassortants available for each of the four important VP7 serotypes**

# Human Rotavirus (HRV) x Bovine RV Reassortant Quadrivalent Vaccine with VP7 Serotype 1, 2, 3 and 4 Specificities



# **Studies with Human-Bovine (UK) Rotavirus Reassortants with G1, 2, 3 or 4 Specificity**

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- In 1991 in parallel with RRV-TV vaccine studies, initiated safety and immunogenicity trials with individual human-bovine rotavirus (UK) reassortants in adults, children and infants**
  - Reassortants with G1,2,3, or 4 specificity were safe and immunogenic (Clements-Mann et al., 1999)**
  - In 1995, in parallel with RRV-TV studies initiated sequential studies with the 4 reassortants combined and showed it was safe and immunogenic (Clements-Mann et al., 2001)**
-

# **A Phase II Double-Blind Trial of Tetravalent Human-Bovine (UK) Rotavirus Reassortant (BV-TV) and RRV-TV Vaccines in Finland**

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- Study began in 1997 (Vesikari et al.)**
  - 2 month old infants enrolled at 2 centers (Tampere and Lahti) to receive 2 doses of RRV-TV or BV-TV vaccine (at 2 and 4 months of age)**
    - Enrollment of ~510 infants (170 vaccinees and 85 controls for each vaccine)**
  - Evaluate the reactogenicity, immunogenicity, and protective efficacy of each vaccine**
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## A Comparison of the Safety of Quadrivalent Rhesus Rotavirus-Based Vaccine (RotaShield) and Quadrivalent Bovine Rotavirus-Based Vaccine (BV-TV) in Finland\*

Cumulative Febrile Responses During the 7 Days Following the First Dose of Vaccine or Placebo Given at 2 Months of Age			
Temperature (Rectal)	Study Group	No. in Group	No. with Fever
$\geq 38.0^{\circ}\text{C}$ [ $\geq 100.4^{\circ}\text{F}$ ]	RotaShield	158	73 (46%) <sup>a</sup>
	Placebo	79	9 (11%) <sup>a</sup>
	BV-TV	165	25 (15%)
	Placebo	82	9 (11%)
$> 38.4^{\circ}\text{C}$ [ $> 101.1^{\circ}\text{F}$ ]	Rotashield	158	32 (20%) <sup>b</sup>
	Placebo	79	1 (1.3%) <sup>b</sup>
	BV-TV	165	3 (1.8%)
	Placebo	82	0
$> 39.1^{\circ}\text{C}$ [ $> 102.4^{\circ}\text{F}$ ]	Rotashield	158	3 (1.9%)
	Placebo	79	0
	BV-TV	165	0
	Placebo	82	0

\*A double-blind study in 2 centers in 510 infants (170 per each vaccine group and 85 per each placebo group) receiving vaccine or placebo at 2 and 4 months of age.

<sup>a</sup>p <0.0001; <sup>b</sup>p <0.0001 (Fisher Exact Test [2-tailed])

## Serum Neutralizing and IgA Responses in Infants Given 2 Doses of RRV-TV or BRV-TV at ~2 and ~4 Months of Age in Finland

Vaccine Group	No. of Infants	% with IgA Response	% with $\geq$ 4-fold Neutralizing Antibody Response vs. Indicated Strain (serotype)						Response by Any Test
			RRV (G3)	UK (G6)	Wa (G1)	DS-1 (G2)	P (G3)	VA70 (G4)	
RRV-TV	140-144	81.9% <sup>a</sup>	89.5%	—	23.6% <sup>b</sup>	35.0% <sup>c</sup>	23.9% <sup>d</sup>	7.0%	93.7%
BRV-TV	147-152	65.1% <sup>a</sup>	—	93.2%	48.7% <sup>b</sup>	12.0% <sup>c</sup>	12.8% <sup>d</sup>	8.1%	96.7%

<sup>a</sup> P=0.001

<sup>b,c</sup> P<0.0001

<sup>d</sup> P=0.015

Note:  $\leq$  2% of the combined placebo groups (N=144-148) developed a seroresponse by any of the categories above

# Protective Efficacy of Two Doses of Quadrivalent Rhesus Rotavirus (RV)-Based Vaccine (RotaShield™) on the Occurrence of RV Gastroenteritis of Varying Severity over Two RV Seasons in Finland

Parameter	Number Who Received		Protective Efficacy
	Quadrivalent Vaccine (N = 139)	Placebo (N = 70)	
All RV* Gastroenteritis	16 (12%)	17 (24%)	53% <sup>a</sup>
Severity Score of RV Gastroenteritis			
> 7 (Mod-Severe)	4 (2.9%)	12 (17%)	83% <sup>b</sup>
> 11 (Severe)	0 (0%)	3 (4.3%)	100% <sup>c</sup>

\*by EIA

<sup>a</sup>P = 0.026 (F.E.T.); 95% CI, 12, 74

<sup>b</sup>P <0.001; CI, 52, 94

<sup>c</sup>P = 0.037; CI, 34, 100

# Protective Efficacy of Two Doses of Quadrivalent Bovine Rotavirus (RV)- Based Vaccine on the Occurrence of RV Gastroenteritis of Varying Severity Over Two RV Seasons in Finland

Parameter	Number Who Received		Protective Efficacy
	Quadrivalent Vaccine (N =161)	Placebo (N = 80)	
All RV* Gastroenteritis	12 (7.5%)	15 (19%)	60% <sup>a</sup>
Severity Score of RV Gastroenteritis			
≥ 7 (Mod-Severe)	5 (3.1%)	9 (11%)	72% <sup>b</sup>
≥ 11 (Severe)	1 (0.6%)	5 (6.3%)	90% <sup>c</sup>

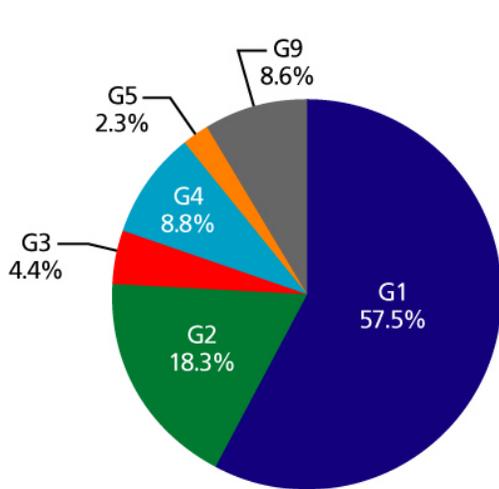
\*by EIA

<sup>a</sup>P = 0.015 (F.E.T.), 95% CI, 20, 80;      <sup>b</sup>P = 0.017; CI, 23, 93;

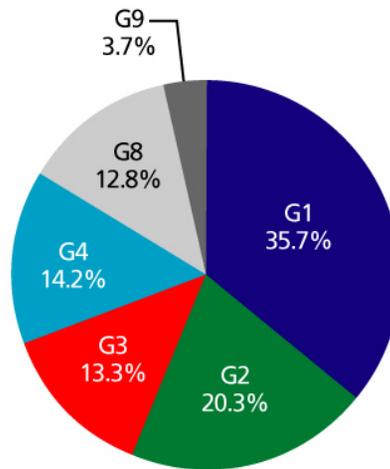
<sup>c</sup>P = 0.016; CI, 36, 99

**Will a 4 Serotype  
(Quadrivalent) Rotavirus  
Vaccine Provide Adequate  
Protection for the  
Epidemiologically Important  
Serotypes in Developing  
Countries?**

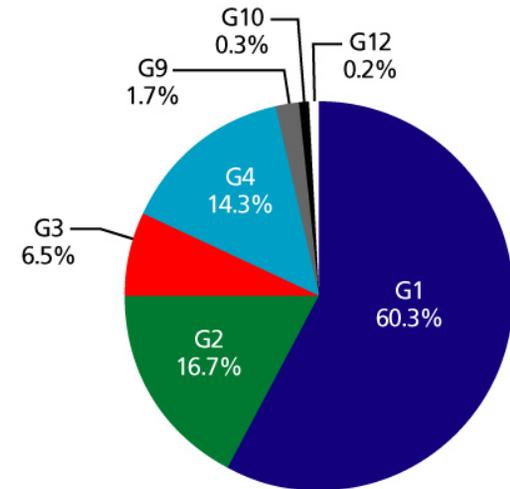
# Distribution of Human Group A Rotavirus G Serotypes by Review of Strains (N=45,571) Collected 1973-2003



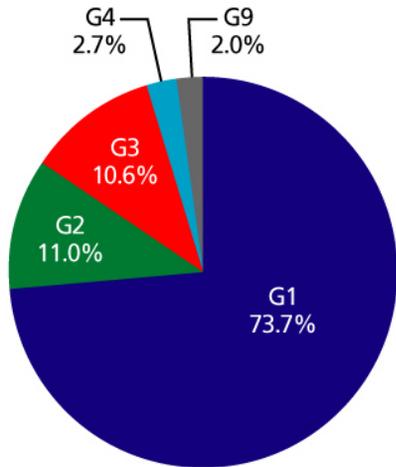
**South America & Nicaragua**  
(n = 2950)



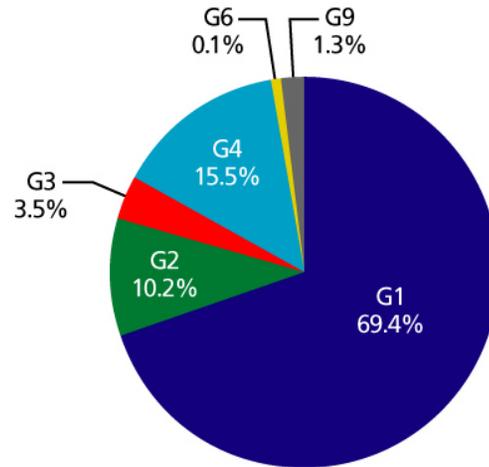
**Africa**  
(n = 2133)



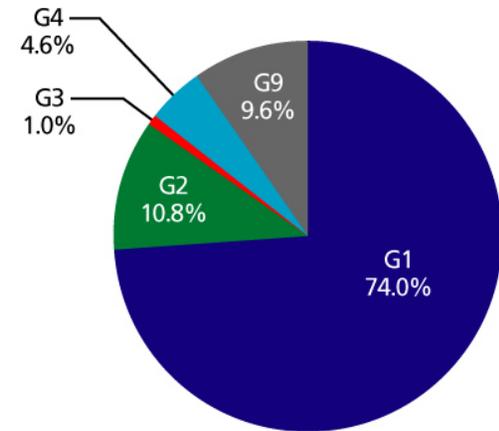
**Asia**  
(n = 13126)



**North America**  
(n = 2892)



**Europe**  
(n = 17475)



**Australia/Oceania**  
(n = 6995)

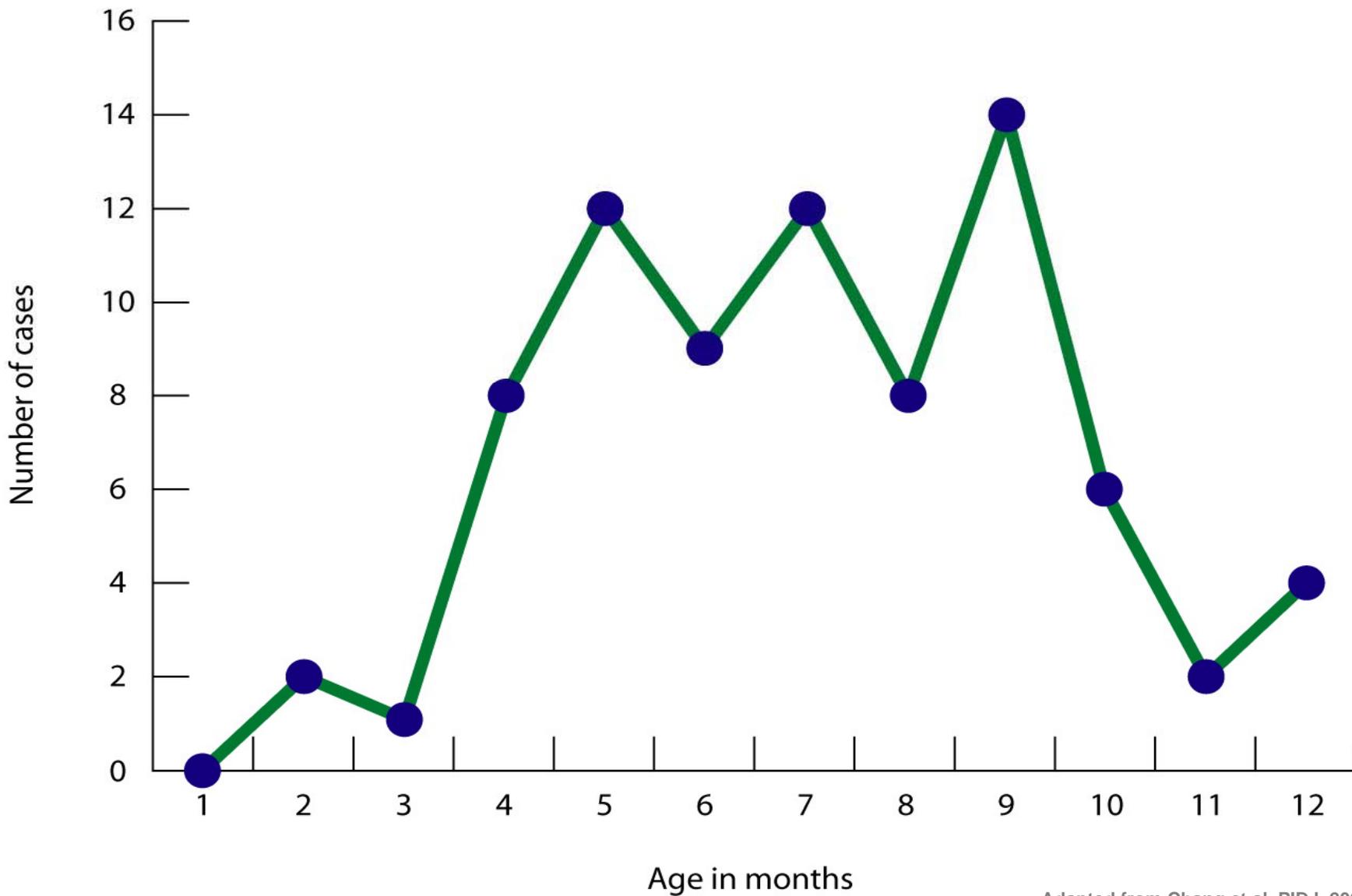
# **The Need for a “Designer” RV Vaccine for the Developing Countries**

- **Serotype G9 has emerged as an important serotype in various parts of the world (e.g. India, Brazil), whereas serotype G8 appears important in Africa**
- **One or both of these two serotypes could be added to the quadrivalent RV vaccine, thus formulating a pentavalent or hexavalent vaccine**
- **Coverage of the VP7 serotypes will eliminate the need to protect against the various VP4 specificities recognized for various VP7 serotypes;**
- **Reassortants for these emerging serotypes are available.**

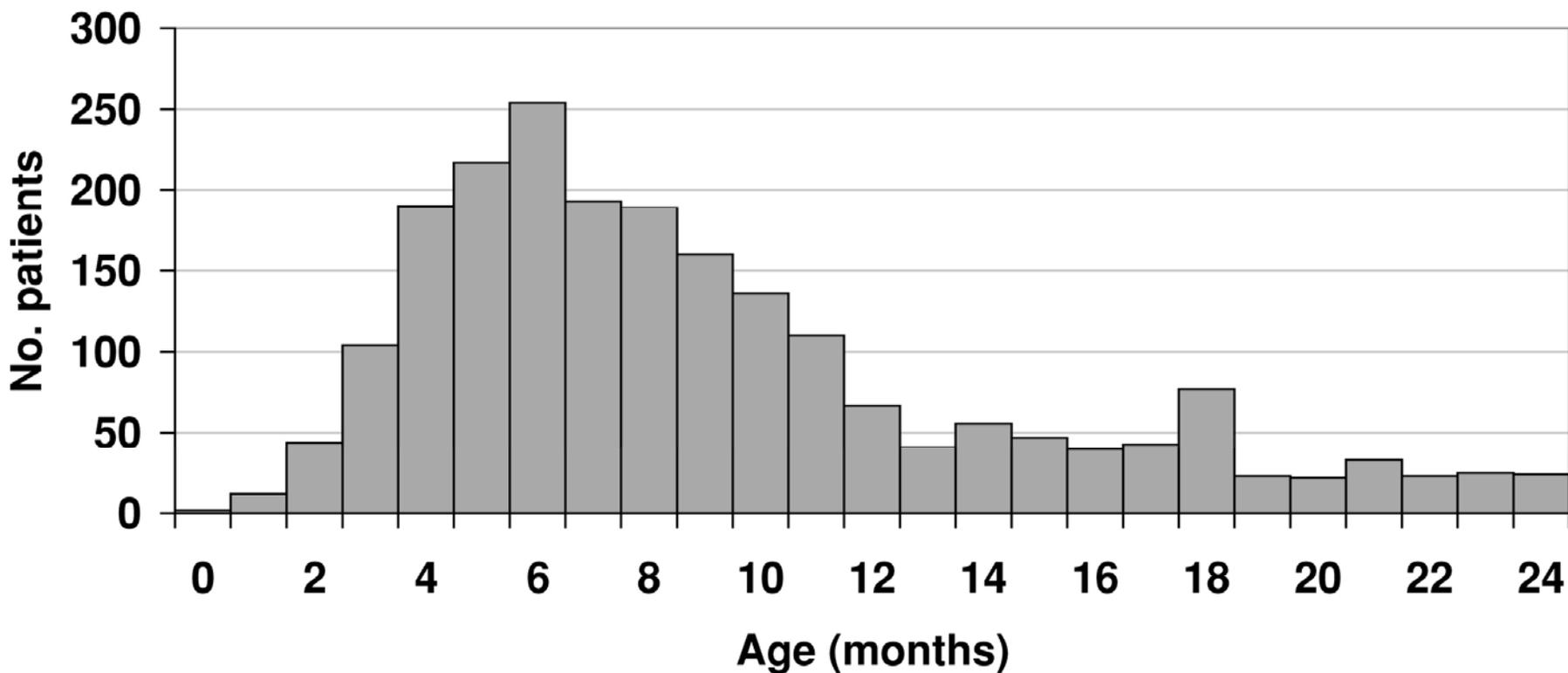
# **The Risk of Intussusception Clouds the Future of All Live Rotavirus Vaccines**

**A Strategy of Vaccine Delivery  
Derived from Lessons Learned  
from RotaShield™ that has the  
Potential to Eliminate the Risk  
of Intussusception**

# Age Distribution of Intussusception in Children ≤ 12 months old in a Southern California H.M.O. (Oct.1992-July 1999)

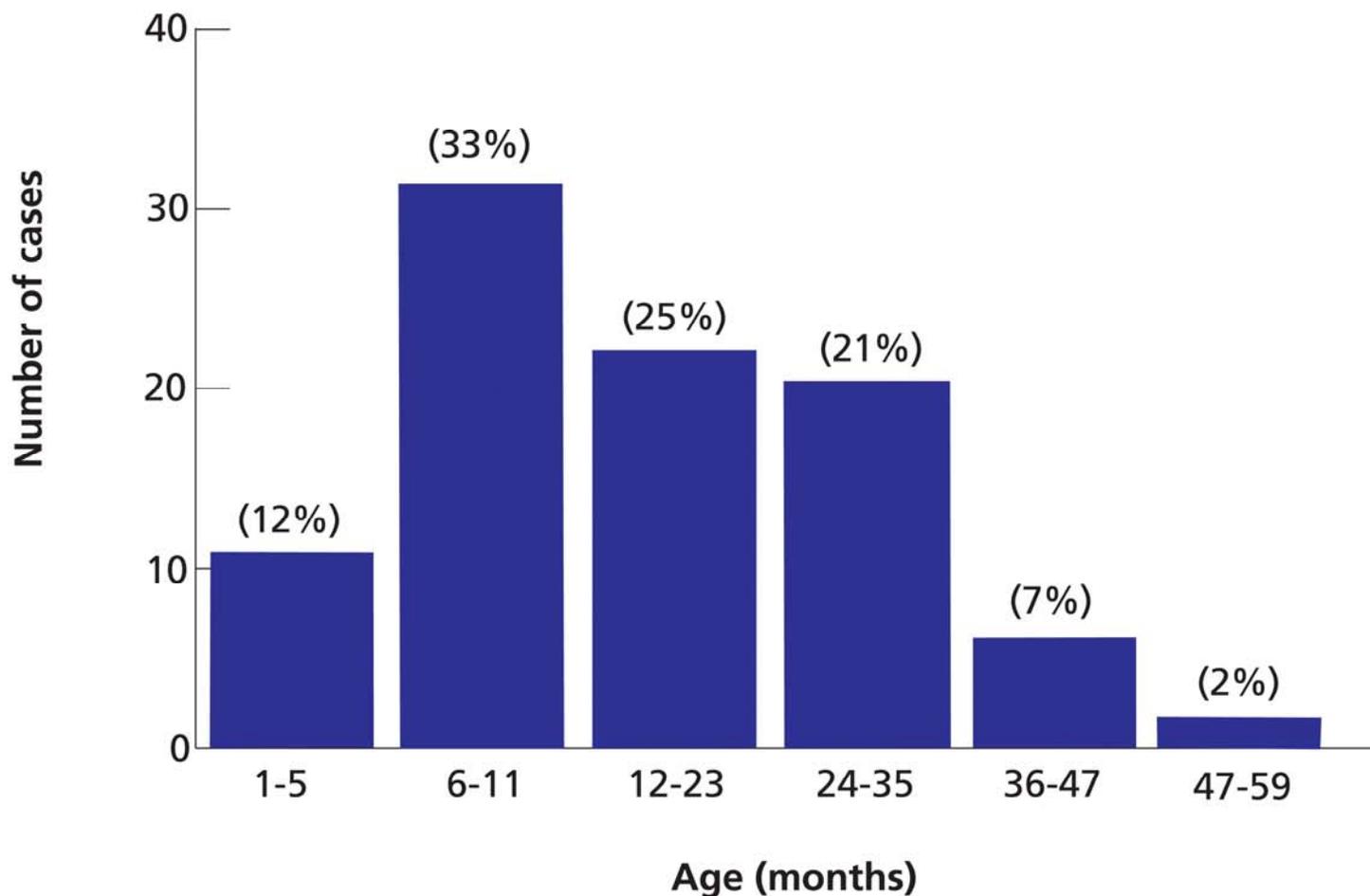


# Age of Children . 2 years of age hospitalized with intussusception over a 7 year period (1994-2000) in Australia

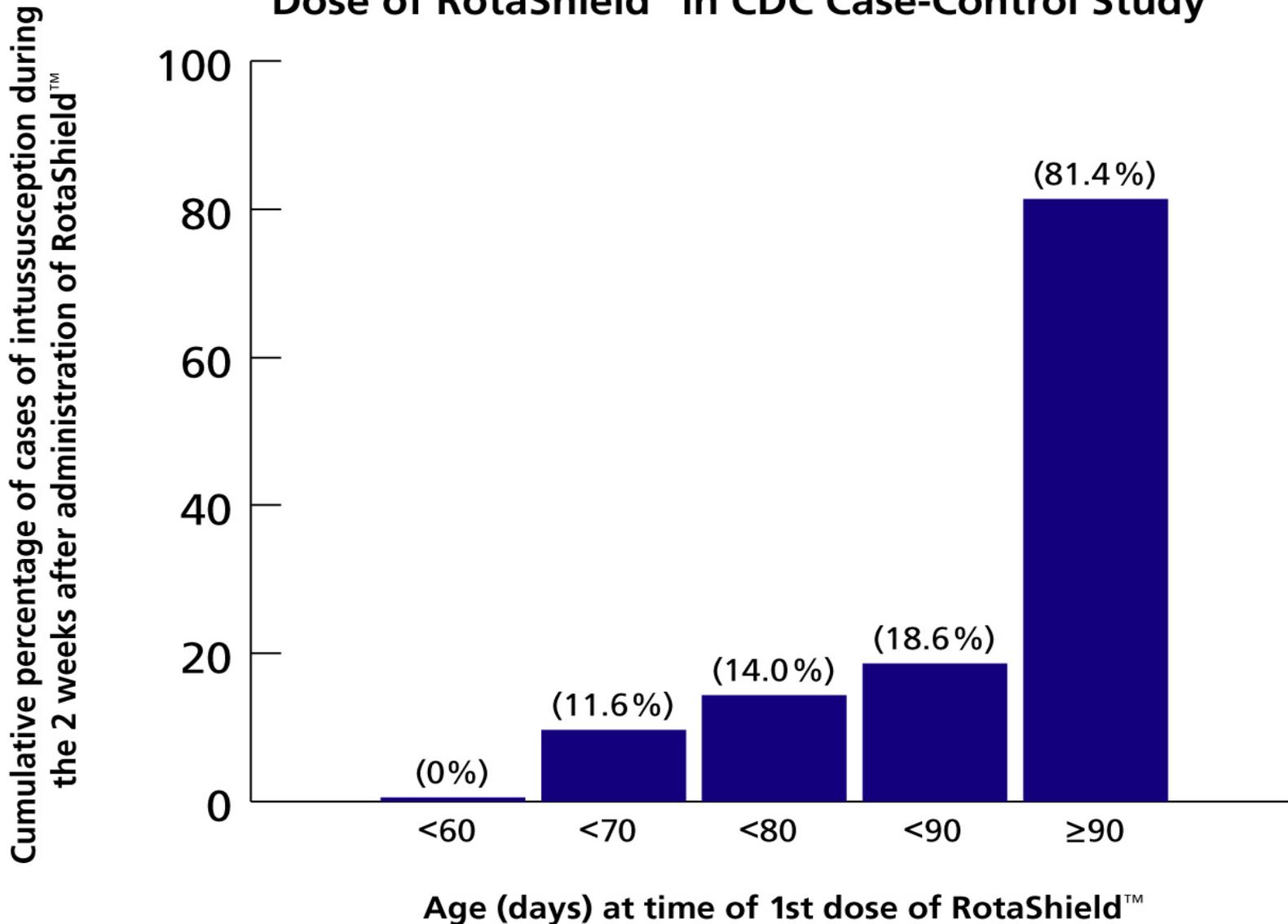


Note: Included 3274 cases < 1 month to 91 years of age; over one-half were <1yr of age with peak at 6 months (where month was recorded [n=1611]). Excludes 93/94, 94/95, 95/96 for Queensland and 93/94, 95/96 for South Australia

## Age Distribution of 91 Hospitalized Cases of Intussusception in <5 Year Old Children Over a 25 Year Period (1978-2002) in Akita, Japan



# Age Distribution of 43 Cases of Intussusception With Onset During the 2 Weeks After the 1st Dose of RotaShield™ in CDC Case-Control Study



Note: 62% of vaccinees in the 19 states included in CDC database received 1st dose at <90 days of age [16% or ~70,000 infants (weighted estimate) were <60 days of age] according to CDC database for N.I.S.

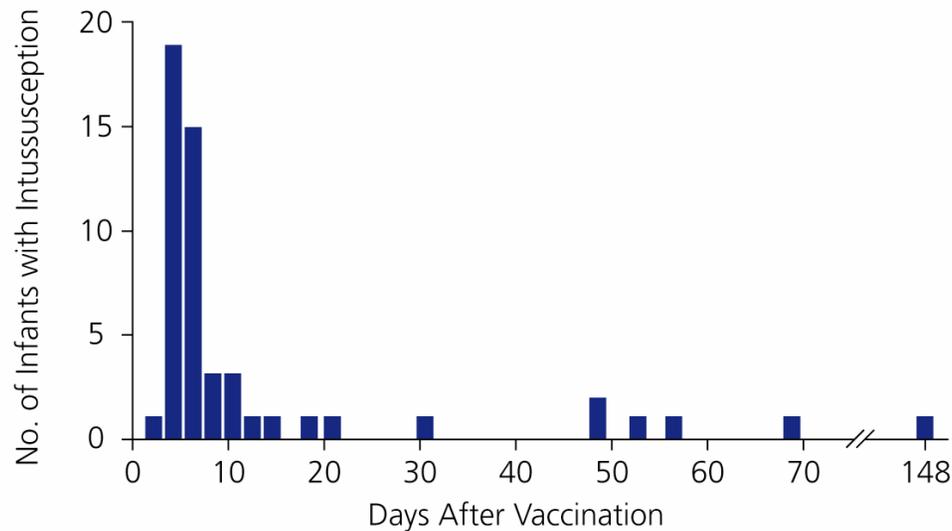
Adapted from: Kapikian et al, JID (Suppl) 2005  
Source of data: Simonsen et al JID (Suppl) 2005 and personal communication

# Effect of Age of Vaccination on Occurrence of Intussusception

- Vaccinees .90 days of age at 1<sup>st</sup> dose developed 81% (35/43) of all cases occurring within 2 weeks after vaccination in CDC case-control study
- Vaccinees .90 days of age received only 38% of all 1<sup>st</sup> doses according to CDC National Immunization Survey
- No cases detected in <60 day old vaccinees (received 16% [ $\sim$ 70,000] of  $\sim$ 433,000 1<sup>st</sup> doses)
- **Conclusion: “Catch-up” vaccination of older infants (1<sup>st</sup> dose given after the ideally recommended age of 2 months) contributed disproportionately to the number of cases. Therefore, the vaccination age had a striking effect on the absolute risk of intussusception (Simonsen et al).**

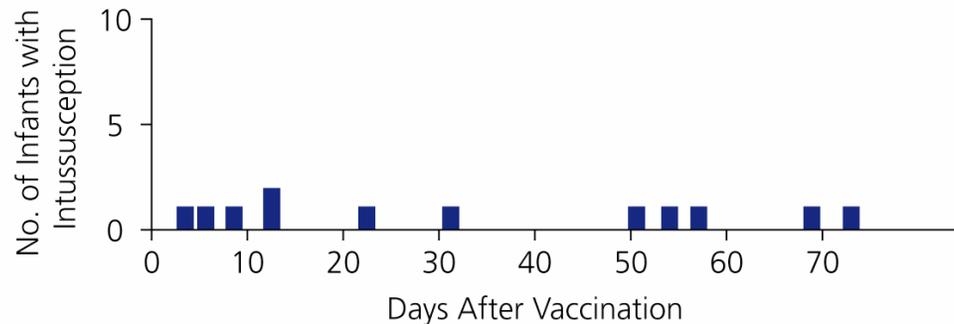
## Occurrence of Intussusception in Infants Who Received the First Dose of RotaShield at 60-209 days (2-6 months) of Age

A



## Occurrence of Intussusception in Infants Who Received the First Dose of RotaShield at <70 days of Age

B



A. Adapted from Murphy et al, NEJM, 2001; NIS. (B). From: Simonsen, personal communication

Note (A) The mean age at 1st dose was 123 days (NIS) ; 435,000 infants vaccinated in the 19 states (NIS)

(B)The mean age at 1st dose was ~8 weeks (similar to GSK trial); ~135,000 vaccinated in the 19 states (NIS)

ORIGINAL ARTICLE

# Safety and Efficacy of a Pentavalent Human–Bovine (WC3) Reassortant Rotavirus Vaccine

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for the Rotavirus Efficacy and Safety Trial (REST) Study Team

# Age of Infants at Entry into Pentavalent RV Vaccine (Rotateq) Trial

**Table 1.** Baseline Demographic Characteristics of the Subjects.\*

Variable	Large-Scale Study	
	Vaccine Group	Placebo Group
Randomly assigned to study group — no.	34,644	34,630
Sex — no. (%)		
Male	17,586 (50.8)	17,529 (50.6)
Female	17,058 (49.2)	17,101 (49.4)
Age at entry — wk		
Mean	9.8±1.4	9.8±1.4
Median	10	10
Range	3–13	1–16

Extracted from: Vesikari et al, NEJM 2006

**Note: Mean and median ages of 34,644 vaccinees and 34,630 controls at “dose”1 were 2 months (68.6 and 70 days, respectively)**

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## Safety and Efficacy of an Attenuated Vaccine against Severe Rotavirus Gastroenteritis

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for the Human Rotavirus Vaccine Study Group\*

# Age of Infants at Time of Administration of Monovalent RV Vaccine (Rotarix) in Safety Trial

Table 1. Characteristics of the Study Populations, According to Study Group.\*

Characteristic	Safety Study	
	HRV Vaccine	Placebo
Infants — no.	31,673	31,552
Male sex — no. (%)	16,105 (50.8)	16,150 (51.2)
Age — wk		
At dose 1	8.2±2.39	8.2±2.39
At dose 2	15.8±3.75	15.8±3.79

Extracted from Ruiz-Palacios et al, NEJM 2006

Note: Mean age of 31,673 vaccinees and 31,552 controls at “dose 1” was 2 months (57.4 days)

# **Proposed Revised Schedule for Pentavalent or Hexavalent Human-Bovine (UK) Reassortant Rotavirus Vaccine**

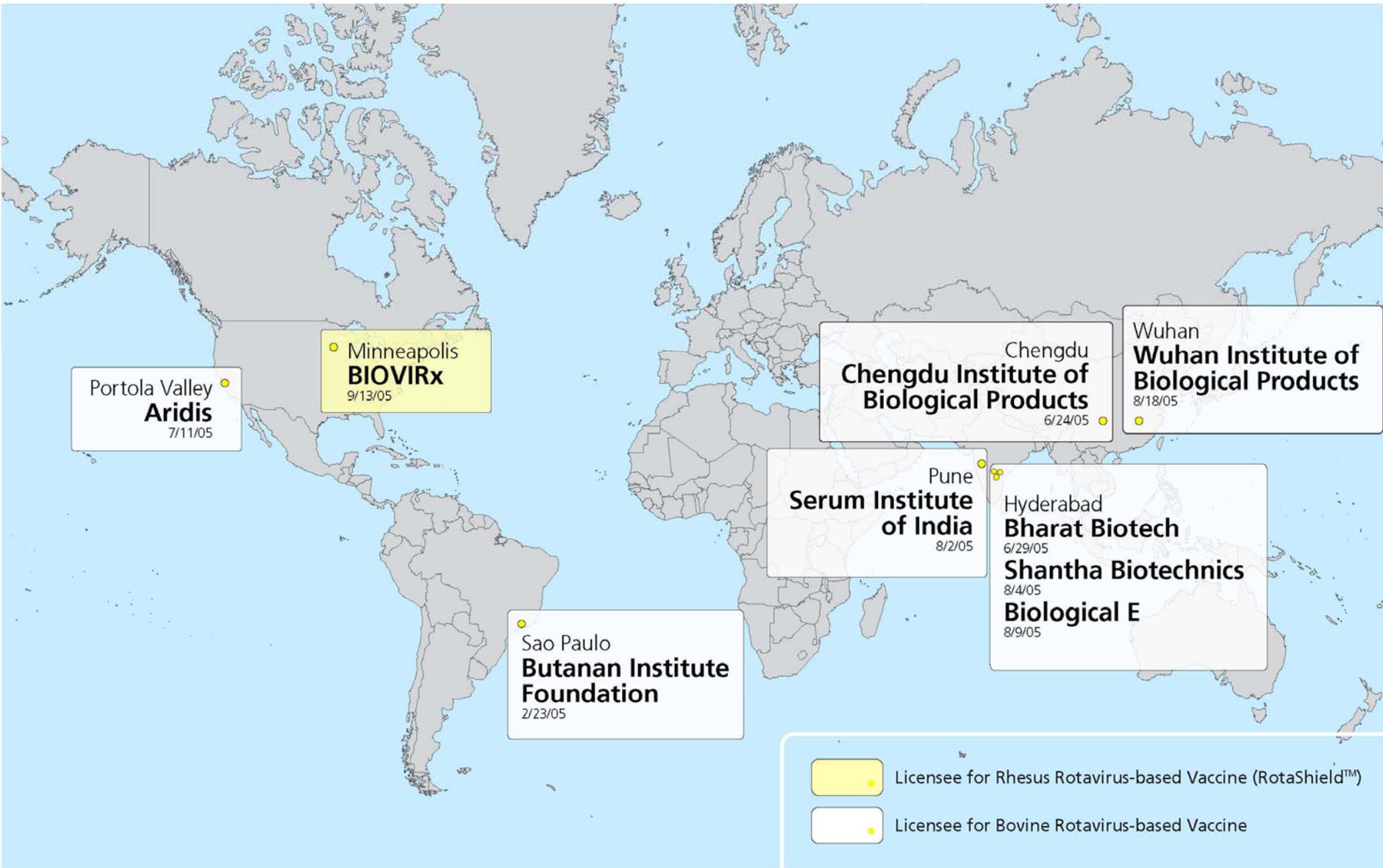
- **1st oral dose given at 0-4 weeks of age;**
- **2nd oral dose given at 4-8 weeks of age with a minimum of 3 weeks between the 1st and 2nd doses**
- **No “catch up” vaccination beyond 8 weeks of age**

**Rationale: Avoid vaccination in period of maximum vulnerability for intussusception (4-9 mo)**

# **Will a 2-Dose Schedule Beginning in the 1<sup>st</sup> Month of Life Induce Protection?**

- **Natural subclinical neonatal RV infection induced protection against severe RV diarrhea in Australia (Bishop et al, Bhan et al)**
- **Neonatal bovine RV (NCDV) vaccination modified severity of RV GE in Finland (Vesikari et al)**
- **Neonatal dose of RRV-TV protected against fever associated with 2nd dose at 2 months of age in Finland (Vesikari et al)**

# The NIH Office of Technology Transfer Has Granted licenses to Develop and Commercialize the Rhesus Rotavirus-based Vaccine (Rotashield™) to One Group and the Bovine Rotavirus-based Vaccine to Eight Groups



# Progress in the Shipment of Human-Bovine (UK) Reassortant Rotavirus Vaccine Strains to Licensees for Vaccine Production

Institution	Location	Date Sent
Butantan Inst Foundation	Brazil	Nov 2005*
Shantha Biotechnics	India	Feb 2006*
Chengdu Inst of Biological Products	China	March 2006
Wutan Inst of Biological Products	China	March 2006
Bharat Biotech	India	April 2006
Serum Inst of India	India	Pending
Biological E	India	Pending
Aridis	USA	Pending

\*In production

# Summary of Procedures to Develop Human-Bovine Rotavirus Vaccine

Pre-seed reassortants with VP7 (G) 1,2,3,4 specificity with final passages in FRhL<sub>2</sub> cells (NIH and Flow)  
Also, pre-seed reassortants with VP7 (G) 8 or 9 specificity grown in primary AGMK cells (NIH)



Pre-seeds (except G8) adapted to vero cells (13 passages including 3 for cloning) [Wyeth]



Master Virus Seed (MVS) made in vero cells (Wyeth; ~3 liters each of G1-4,9)  
Tested for adventitious agents (Wyeth)  
MVS provided to licensees (NIH)



Manufacturer's Working Virus Seed (MWVS) for each serotype to be made by licensee (~10 liters)



A single passage of aliquot of MWVS of each serotype used to make vaccine for clinical study and commercial product



Vaccine preparations tested in human clinical studies

# Potential Advantages of Bovine (UK) RV-based Vaccine

- Will be made in developing countries where it is needed
- Will be produced at an affordable price in developing countries and thus should be readily available
- Can be given to infants at an age when they are relatively refractory to the development of intussusception
- 
- Can be a pentavalent or hexavalent formulation designed for developing countries with inclusion of important G8/ 9 types

# Cost Matters in Developed Countries, Too



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**Last Update:** Thursday, July 13, 2006. 7:28pm (AEST) [Print](#) [Email](#)

## Cost behind rotavirus vaccine rejection

The Federal Government says a decision not to vaccinate babies against rotavirus is because of cost, not safety.

The Pharmaceutical Benefits Advisory Committee today announced it is rejected applications from two drug companies to have rotavirus vaccines given all infants.

The Federal Government says the decision was made because of uncertainty over the vaccine's cost-effectiveness.

That has outraged the Australian Medical Association's NT president, Paul Bauert, who says Darwin is already suffering a rotavirus epidemic.

"We can at times have most of our infectious wards taken up with kids with rotaviral disease," he said.

The disease causes fever, vomiting and diarrhoea.

Dr Bauert says if governments at both levels do not act quickly, the epidemic will spread to remote communities which are already hard-hit by the virus.