

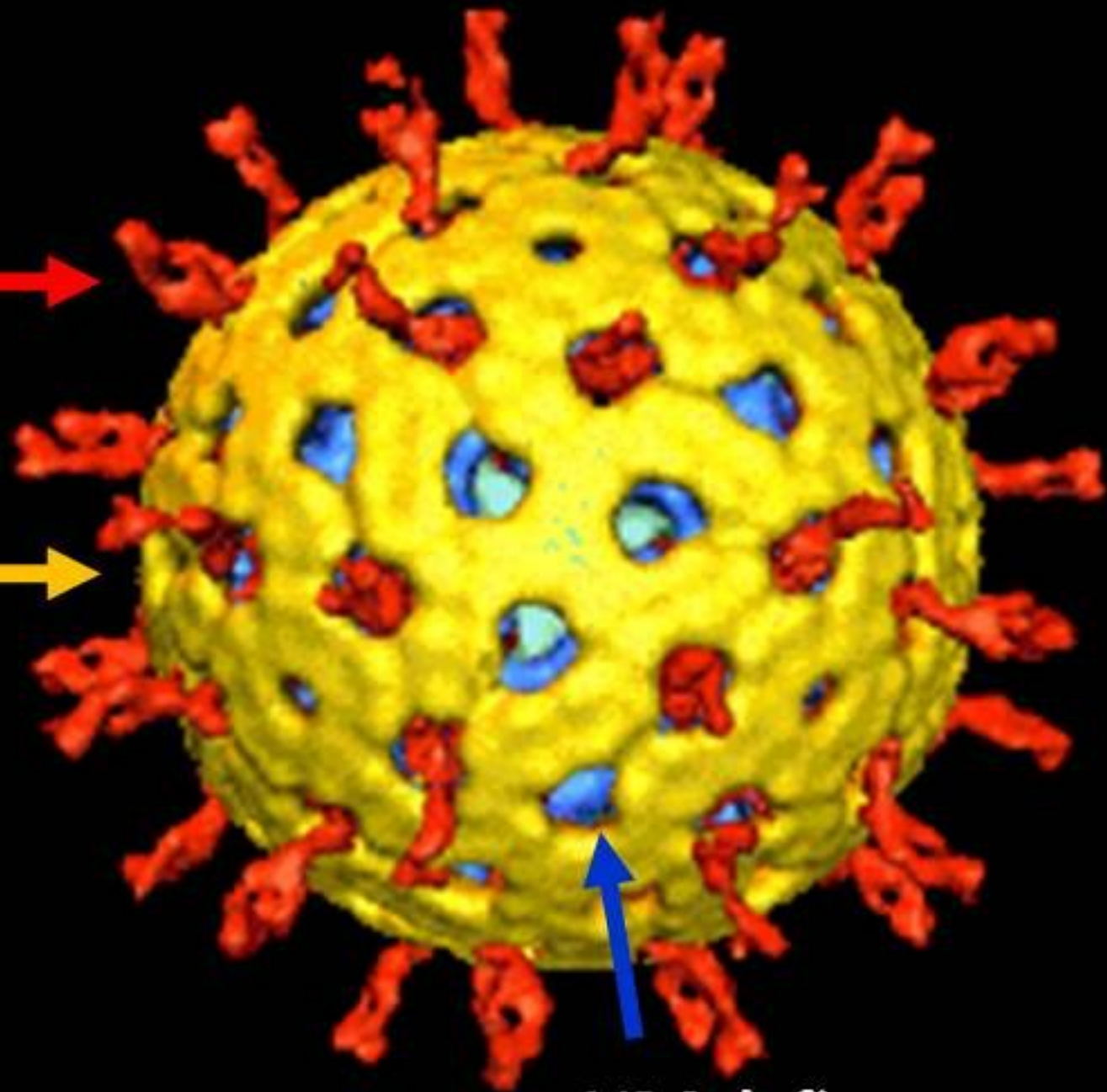
Rotavirus Immunization: What We Know and What Is Still Unanswered

K.TELM

VP4 defines P serotypes



VP7 defines G serotypes



VP6 defines groups and subgroups



Rotavirus

Amount of virus shed in stool:

- 10-100 billion virions/gram of stool!

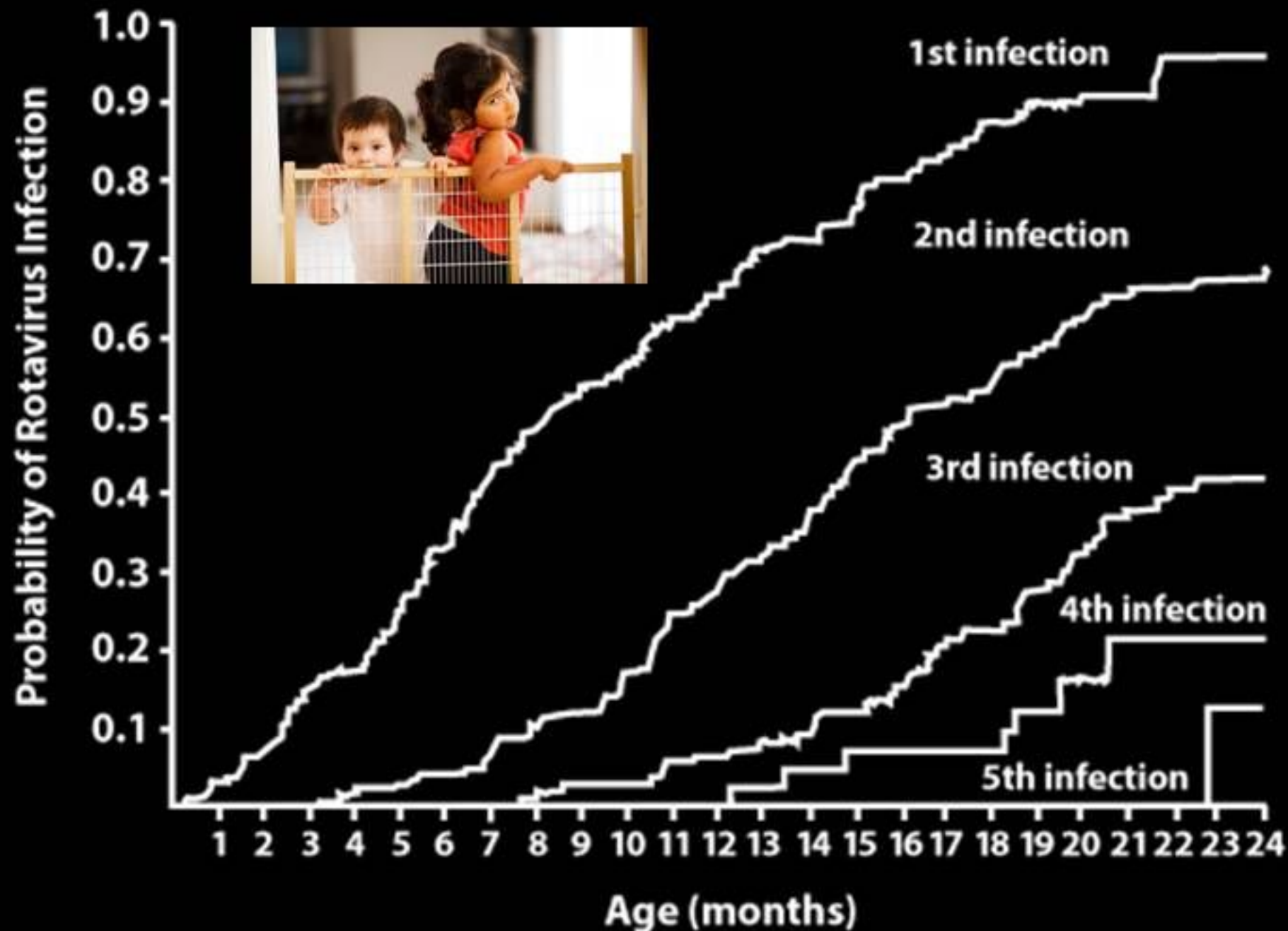
Amount of ingested virus required to cause infection:

- As few as 10 infectious virions!

Amount of stool that needs to be ingested to potentially result in infection:

- ~ 0.000001 mg!

**“My children don’t need a rotavirus vaccination.
I constantly wash their hands.”**



Velazquez F, et al. *N Engl J Med*. 1996;335:1022-1028. © 1996. Massachusetts Medical Society. All rights reserved.

“You can be infected with rotavirus only once, right?”

Clinical Outcome	First Infection	Second Infection	Third Infection
Asymptomatic	38	62	74
Mild Diarrhea	73	75	99
Moderate-to-Severe Diarrhea	87	100	-

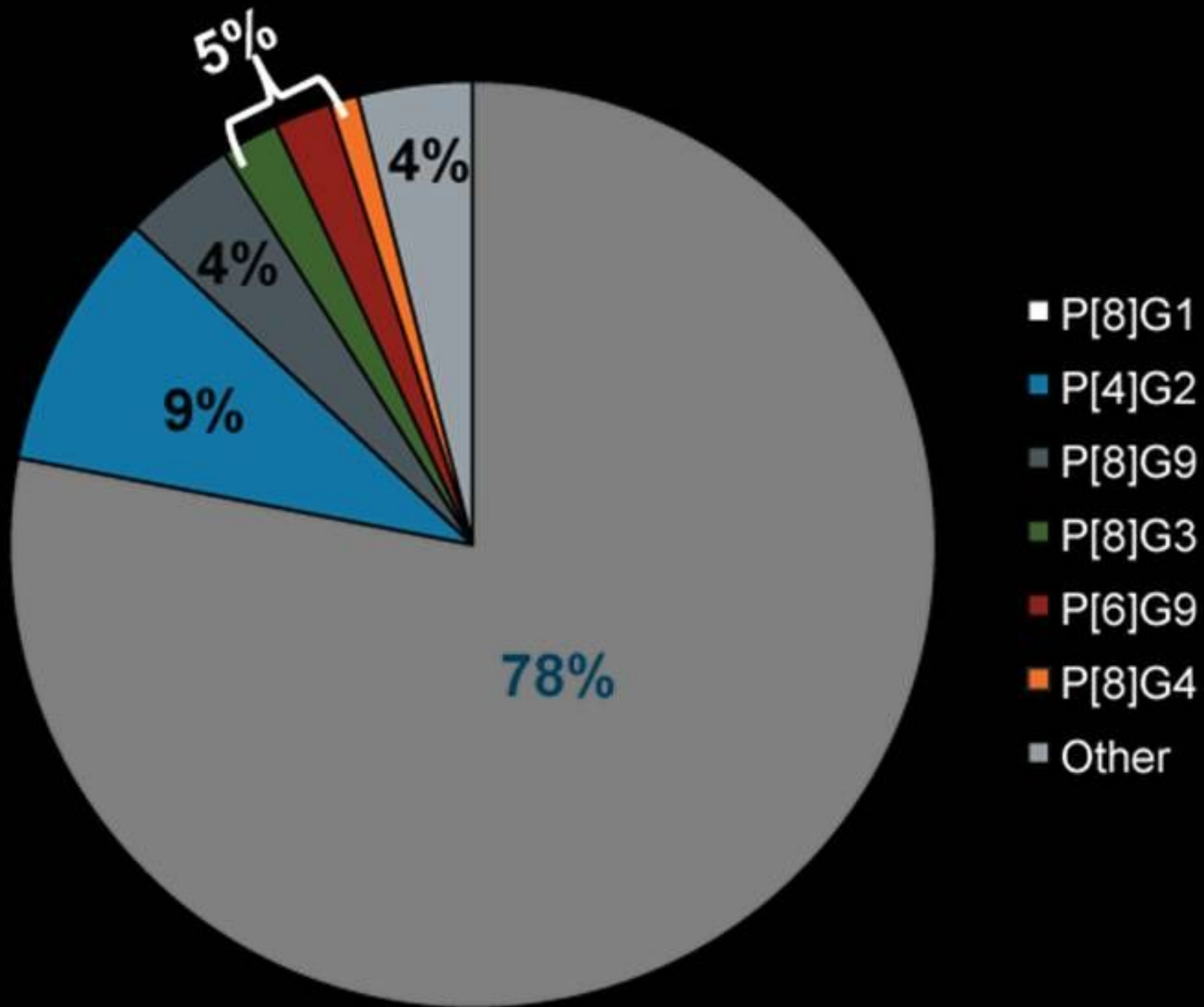
Velasquez F, et al. *N Engl J Med*. 1996;335:1022-1028.

Adjusted Efficacy After Each Infection

		Second Infection			
		G1	G2	G3	G4
First Infection	G1	1	4	4	0
	G2	0	0	1	1
	G3	2	7	1	1
	G4	0	0	0	0

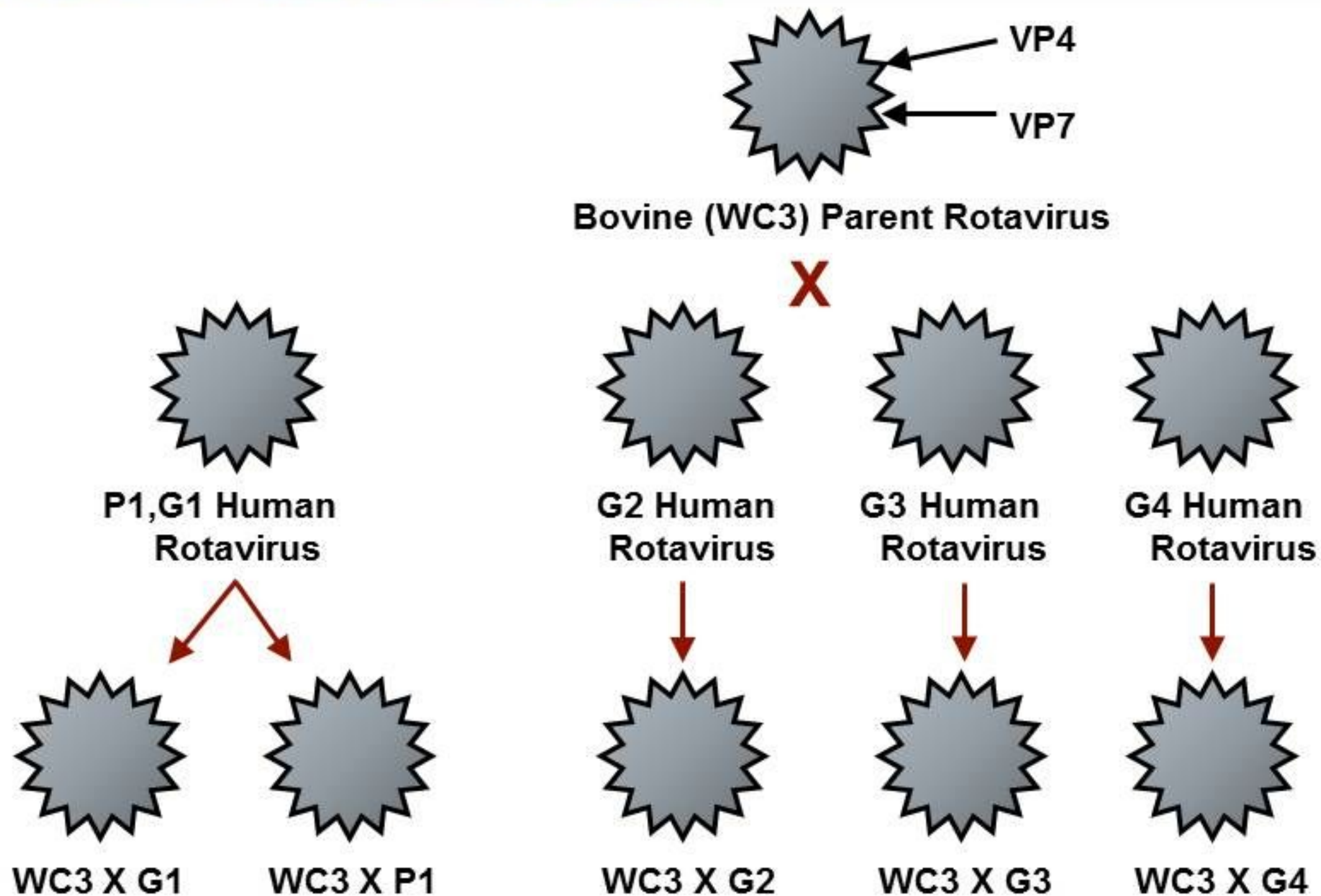
Gladstone BP, et al. *N Engl J Med.* 2011;365:337-346.

**Distribution of Rotavirus G Types Identified in Focal Specimens
Obtained During First and Second Infections (N = 22)**



Frequency of Rotavirus Isolates

RotaTeq[®] (RV5)*: Human Bovine Reassortant Vaccine



Rotarix[®] (RV1)*: Live Attenuated Human Vaccine

Human rotavirus: G1P1A[8]



G1P1A[8]



The virus is attenuated by serial passage in cell culture.

One strain of human rotavirus (G1P[8]) shares neutralizing epitopes with G1, G3, G4, and G9 serotypes.

Clinical Trials Demonstrated Efficacy of Rotavirus Vaccines

- RV5^[a] (RotaTeq)
- RV1^[b] (Rotarix)
- Cumulative results
 - 60,000-70,000 infants entered into each trial
 - Efficacy against severe disease 85%-98%

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

b. Ruiz-Palacios GM, et al. *N Engl J Med*. 2006;354:11-22.

RotaTeq^[a]**Rotarix^[b]**

Manufacturer	Merck & Co., Inc.	GlaxoSmithKline
Genetic framework	Bovine rotavirus-WC3	Human rotavirus-89-12
Composition	5 human, bovine reassortant	Single human rotavirus
Genotypes	G1, 2, 3, 4, and [P8]	G1[P8]
Dosage schedule	3 doses at 2, 4, and 6 months	2 doses at 2 and 4 months
Route of administration	Oral	Oral
Presentation	Liquid	Lyophilized-reconstituted
Efficacy against severe disease*	85%	95%
Virus shedding	Up to 13%	17%-27%

*Different scoring systems were used so results are not directly comparable.

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

b. Ruiz-Palacios GM, et al. *N Engl J Med*. 2006;354:11-22.

**“The vaccine doesn’t provide
100% protection, so why bother?”**

Vaccine Efficacy Against Severe Rotavirus Gastroenteritis in the First Year of Life in Developing Countries

Region	Vaccine	Countries	Efficacy (%) [*]	95% CI (%)
Africa ^[a]	Rotarix	Malawi, South Africa	61.7	44.0, 73.2
Africa ^[b]	RotaTeq	Ghana, Kenya, Mali	64.2	40.2, 79.4
Asia ^[c]	RotaTeq	Bangladesh, Vietnam	51.0	12.8, 73.3

^{*}Because the disease burden is so high despite relatively low efficacy rates, use of vaccine in these countries has the potential to save many lives.

a. Madhi SA, et al. *N Engl J Med*. 2010;362:346-357.

b. Zaman K, et al. *Lancet*. 2010;376:614-625.

c. Armah GE, et al. *Lancet*. 2010;376:606-613.

Normal intestine



**Intussusception
(intestinal folding)**



Cut section of small intestine

“Intussusception is a major risk, right?”

	Admissions Per Year	Deaths Per Year
Mexico		
Rotavirus events averted by vaccination	-11,551	-663
Intussusception events caused by vaccination	+63	+2
Brazil		
Rotavirus events averted by vaccination	-69,572	-640
Intussusception events caused by vaccination	+55	+3

The risk for severe illness and death in unvaccinated children is much greater than the risk for side effects or serious illness in vaccinated children.

Monitoring of intussusception after RV-US, VAERS 2006-2012

- Intussusception 3-6 days after both vaccines
- RV5 dose 1 (RR=3.75; 95% CI=1.90-7.39)
- RV5 dose 2 (RR= 1.43; 95% CI=0.85-2.40)
- RV5 dose 3 (RR= 0.75; 95% CI=0.40-1.42)
- 3 dose (RR= 0.79; 95% CI=-0.04-1.62)

Rotavirus Vaccine: Precautions

Precautions^[a]

- Altered immunocompetence: HIV, SCID
 - SCID: contraindicated
 - HIV: safe and effective^[b]
- Preexisting chronic gastrointestinal disease
 - Short gut
- Infants with spina bifida or bladder extrophy are at high risk for latex allergy
 - Use Rotarix with caution^[c,d] (administration system contains latex)
 - Use of RotaTeq is preferable to minimize latex exposure
 - If RotaTeq is unavailable, Rotarix should be administered because the benefit of vaccination is considered greater than the risk for sensitization

SCID = severe combined immunodeficiency disease

a. Cortese MM, et al. *MMWR*. 2009;58(RR-02):1-35.

b. Steele AD, et al. *Pediatr Infect Dis*. 2011;30:125-130.

c. Cortese MM, Parashar UD. *MMWR Recomm Rep*. 2009;58:1-25.

d. American Academy of Pediatrics. Recommended immunization schedule for persons aged 0-6 years. Available at: <http://aapredbook.aappublications.org/resources/IZSchedule0-6yrs.pdf>

What Should I Do About Late Starters?

Dosage and Timing	FDA Licensing Recommendations		ACIP/AAP Recommendations	
	RotaTeq	Rotarix	RotaTeq	Rotarix
Formulation/ route of administration	Liquid/oral	Lyophilized/oral	Liquid/oral	Lyophilized/oral
Ideal timing of doses	2, 4, and 6 months	2 and 4 months	2, 4, and 6 months	2 and 4 months
Timing of first dose	6-12 weeks	Beginning at 6 weeks	6-14 weeks and 6 days	
Minimum dose interval	4 weeks	4 weeks	4 weeks	
Maximum dose interval	10 weeks	Not stated	None	
Maximum age last dose	≤ 32 weeks	< 24 weeks	8 months, 0 days	

There is no catch-up schedule.

Ongoing Challenges: International Settings

- Vaccine effectiveness in resource-poor settings
 - Year-round disease, less seasonality
 - Emergence of different serotypes, question of cross-protection
- Nutritional issues affect vaccine uptake in gut: malnutrition, micronutrient deficiencies
- Other competing enteric pathogens
- Breastfeeding
 - Effect of competing maternal antibodies

Impact of withholding breastfeeding around the time of Rotarix on the immunogenicity of Rotarix vaccine- Study in Pakistan

- Method : this open-label, randomized, control trial. 400 infants in 2 Arms
- Analysis plan: seroconversion when anti Rota IgA ≥ 20 UI/ml
- Conclusion: withholding breastfeeding around the time of Rotarix administration may increase the immunogenicity of this vaccine

Influence of oral polio vaccines on performance of RV1 and RV5 vaccines

		↓seroconversion	↓GMC	↓Shedding
South Africa	6-10 W Dose1 dose2	61% 16%	40% 14%	
	10-14W Dose1 Dose2	25% -11%	40% 14%	
Banglades		38%	15%	43%
Six Latin American countries	Domi, Per, Arg, Bra, Hon, Col	18%	32%	

Influence of oral polio vaccines on performance of RV1 and RV5 vaccines

	↓seroconversion	↓GMC
Four Latin American countries	5%	47%
Mex, Cos, Gua, Bra		

Comparision the immunogenicity of RV1 vaccine when administered 6-10w, 10-14w, 6-10-14w of age in Pakistan

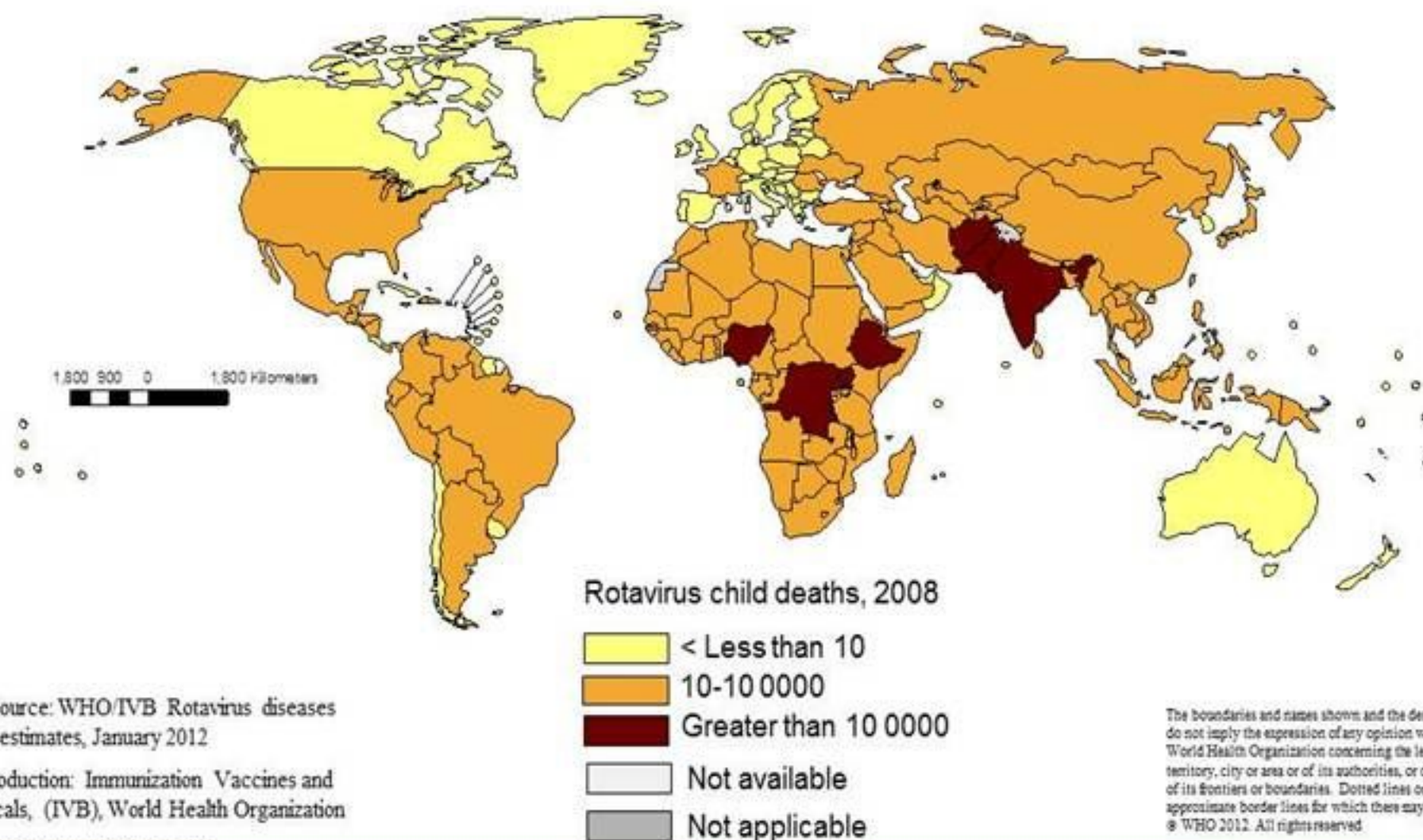
Method:

- > Open-label, randomized, controlled trial
- > Urban slum outside of Karachi
- > 600 infants in EPI vaccines in 3 arms
- > Arm1: 6-10w, arm2: 10-14w, arm3: 6-10-14w

Analysis plan: seroconversion when anti Rota IgA ≥ 20 UI/ml

Conclusion: arm2=3 > arm1

453,000 Global Child Rotavirus Deaths, 2008



Data Source: WHO/IVB Rotavirus diseases burden estimates, January 2012

Map production: Immunization Vaccines and Biologicals, (IVB), World Health Organization

Date of slide: 02 February 2012

2 | TITLE from VIEW and SLIDE MASTER | February 21, 2012



World Health Organization

Estimated rotavirus deaths for children under 5 years of age: 2008, 453 000.
http://www.who.int/immunization_monitoring/burden/rotavirus_estimates/en/.

Cost and Productivity Burden of Rotavirus in Hospitalized Children < 5 Years of Age in the US in the Prevaccine Era

Hospitalization cost

- Median = \$2999^a - \$4565^b

Length of hospital stay

- 1.9 days

Parent lost work days

- 3.4 days



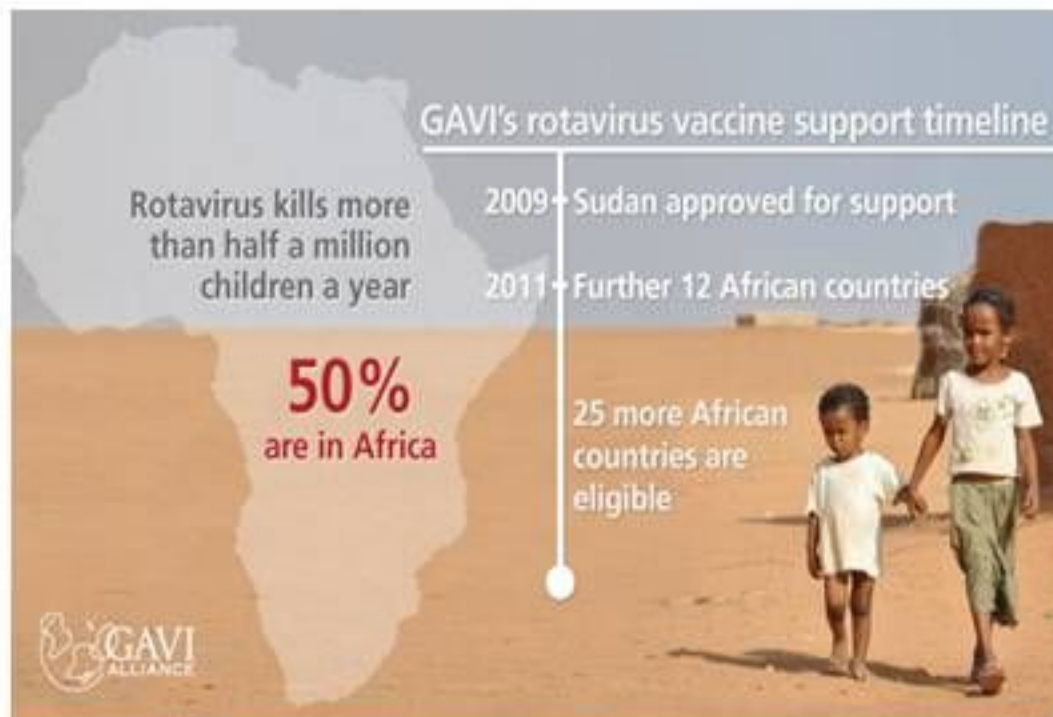
a. Malek MA, et al. *Pediatrics*. 2006;117:1887-1892.

b. Mast TC, et al. *Pediatr Infect Dis J*. 2010;29:e19-e25.



Enteric and Diarrheal Diseases

“Guided by the belief that all lives have equal value, the Bill & Melinda Gates Foundation works to help all people lead healthy, productive lives. Our Global Health Program supports this mission by harnessing advances in science and technology to save lives in poor countries.”



Images used courtesy of the Bill and Melinda Gates Foundation.

<http://www.gatesfoundation.org/diarrhea/pages/default.aspx>. Accessed August 10, 2012.

Conclusions

- Clinical trials and postlicensure studies have shown that rotavirus vaccines are effective and safe.
- The impact of rotavirus immunization programs in the United States and other countries is dramatic.
- The burden of rotavirus disease worldwide is largely preventable.
- Additional studies are needed to optimize the effectiveness of rotavirus vaccines in resource-poor countries.

XIN CHÂN THÀNH CÁM ƠN

