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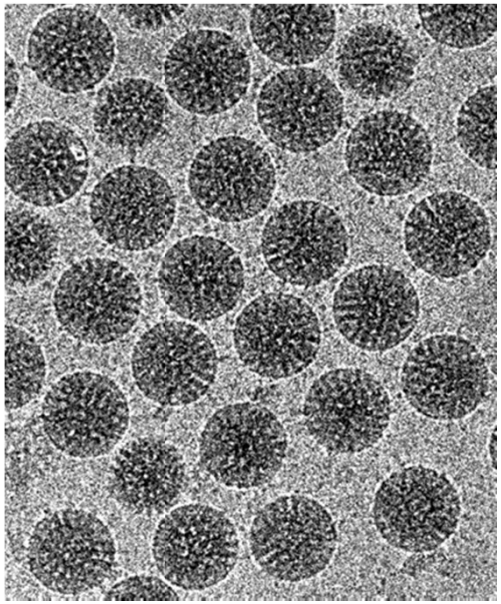
Developing Next Generation Rotavirus Vaccines: Prospects from the Pipeline to Address Remaining Public Health Needs



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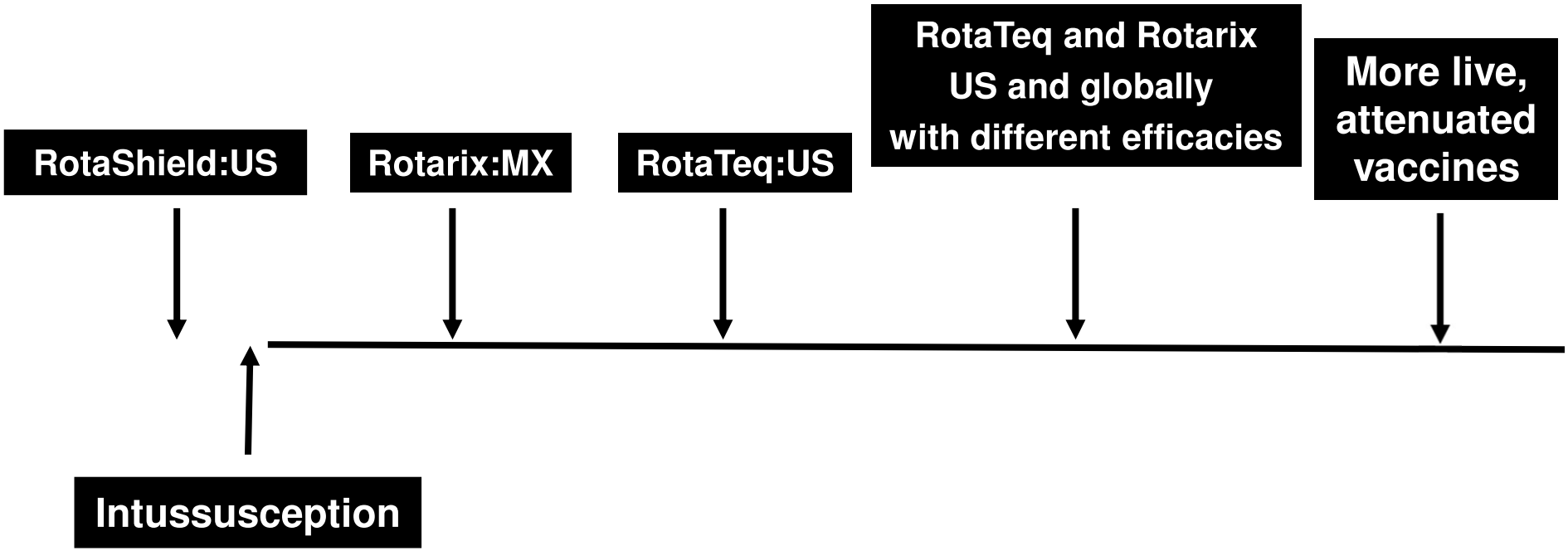
Rotavirus Vaccine Development

- Based on clear need from global disease burden
- Lack of disease in children > 5 yrs of age indicated immunity develops
- What type of vaccine will best induce protective immunity?
  - Live, attenuated, oral vaccines
    - Less expensive to produce
    - Induce IgA, IgG and herd immunity
  - Non-replicating vaccines
    - May improve efficacy in children
      - in children in some settings
    - Less safety risks

Live Attenuated Rotavirus Vaccine Development



Rationale for More Live-Attenuated Rotavirus Vaccines

- Currently licensed oral live, attenuated rotavirus vaccines offer great benefit to populations in resource-limited countries but are costly and have reduced efficacy in those populations
- Vaccines must provide protection early, be safe and effective in the presence of maternal antibody
- Production of initial vaccines not sufficient to cover all children

New Rotavirus Vaccines in the Pipeline

- ROTAVAC – Bharat 116E G9P[11]
  - Licensed in India, 2014
- RV3-BB G3P[6] (from Australia) with Biofarma in Indonesia
  - Phase 1 and phase 2 immunogenicity trials completed and phase 2b immuno/safety trial ongoing with evaluation of neonatal dose
- Lanzhou monovalent G10P[12] licensed and in use in China
- Rotavin-IM G1P[8] licensed in Vietnam
- Live, attenuated reassortant rotaviruses
  - BRV-Hu reassortant (pentavalent G1-4 with G9)
  - Multivalent reassortant lamb rotavirus

Rationale: Next Generation Rotavirus Vaccines

- Subunit protein NRRV candidates:
  - May provide superior efficacy in target populations
  - Projected to be less expensive (<$1 per dose)
  - May be added to EPI vaccines, facilitating delivery
- Parenteral vaccines can protect against enteric diseases (e.g., polio, cholera, typhoid, hepatitis A)
- Focus on vaccines capable of eliciting a rotavirus neutralizing antibody response as passive transfer of such antibodies can provide protection

Non-replicating RV Vaccine Candidates

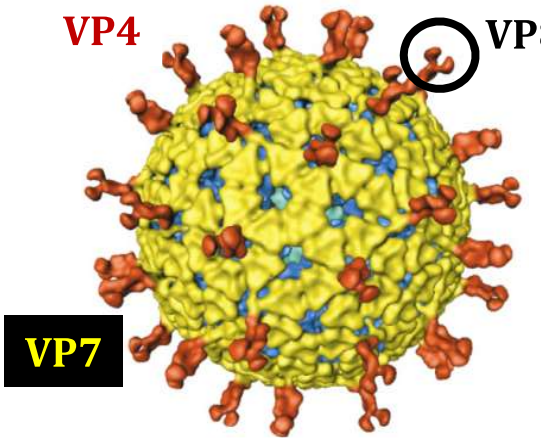
- Protein subunit vaccines
  - two VP8 formulations
- Inactivated virus
- Virus-like particle (VLP) vaccines

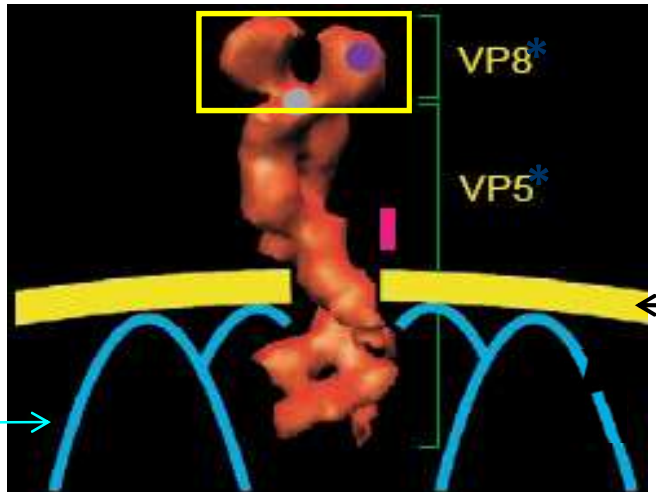
Characteristics of P2-VP8 Vaccine

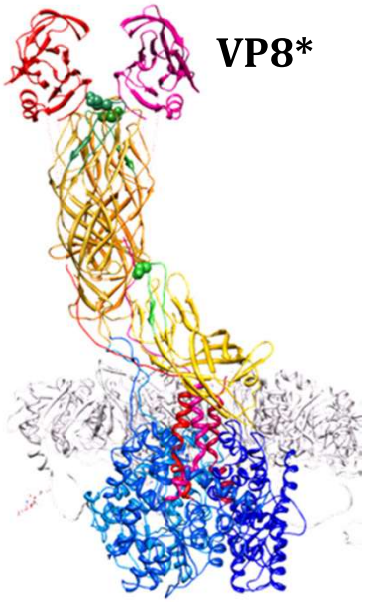
- Developed at US NIH, led by Dr. Yasutaka Hoshino
- Truncated VP8 subunit from human Wa strain (G1P[8]) fused to the tetanus toxin P2 CD4 epitope
  - Expressed in *E. coli*
  - Purified using hydrophobic interaction and anion exchange liquid chromatography
  - Liquid formulation, adsorbed to aluminum hydroxide
- Preclinical toxicity testing in rabbits at doses up to 60 µg
- Non-pyrogenic
- Elicits homotypic and heterotypic antibodies that neutralize P[8] and P[4] rotavirus strains in preclinical studies

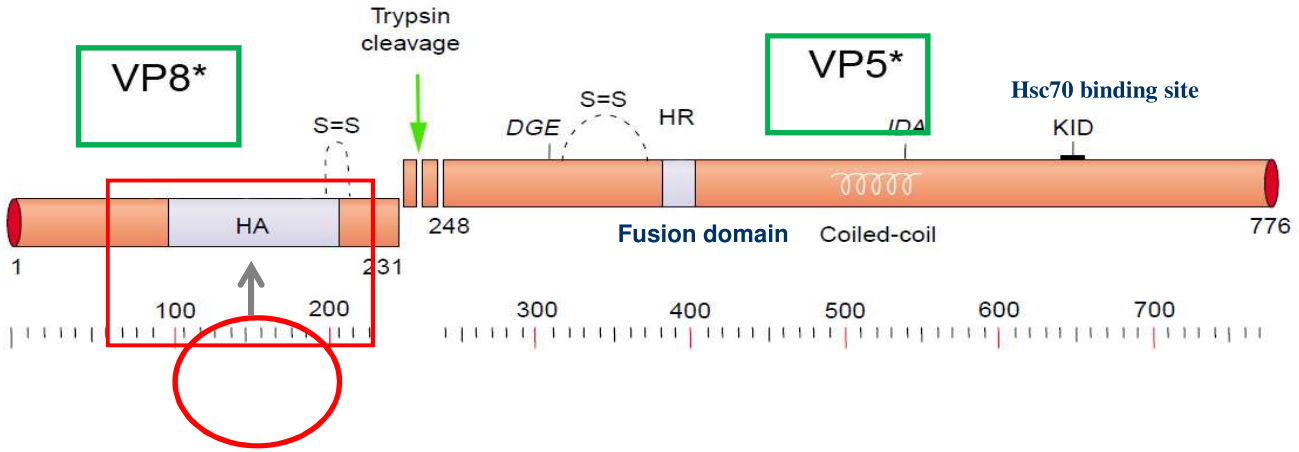
Wen 2012 Vaccine

Rotavirus VP8*









Rationale for Vaccine Construct and Formulation: Preclinical Studies

- Inclusion of P2 T-cell epitope engendered more rapid rise in neutralizing antibody
- Addition of aluminum adjuvant increased overall titer and promoted earlier neutralizing antibody titer
- P2-VP8 subunit vaccine elicited good heterotypic neutralizing antibody response to P4 strains (but not P6)
- Protection from disease in neonatal piglets (delayed onset and shorter duration; trend to decreased shedding)

VAC 009

"A Phase 1 Double-blinded, Randomized, Placebo-controlled Dose Escalation Study to Examine the Safety, Reactogenicity, Tolerability and Immunogenicity of the P2-VP8 Subunit Rotavirus Vaccine in Healthy Adult Volunteers"

- First-in-human testing of the P2-VP8 subunit rotavirus vaccine
- Enrollment: Dec 2012 – Feb 2013

VAC 009 Study Schema

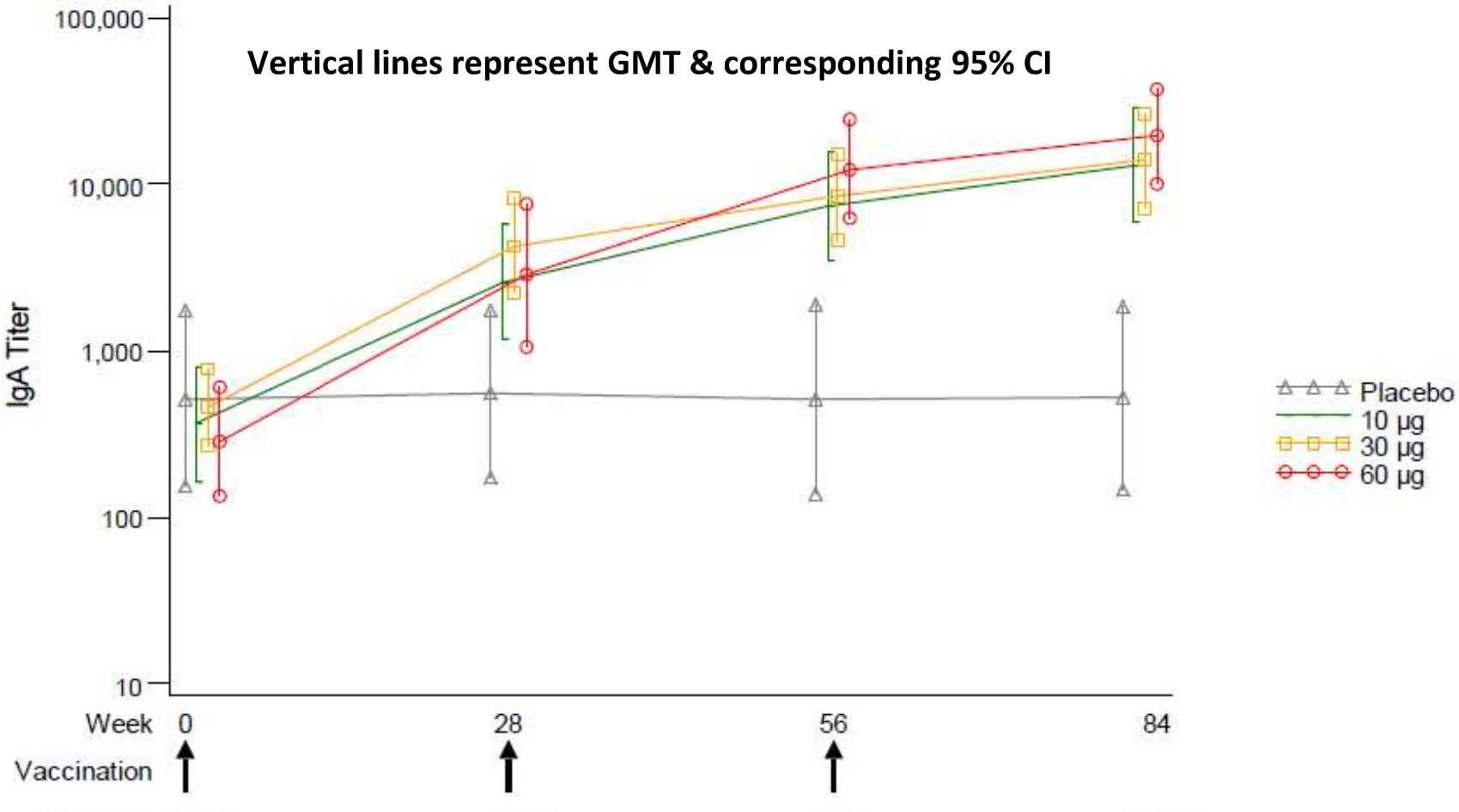
Cohort	Dosing Groups	N
1	10 µg vaccine with $Al(OH)_3$	12
	Placebo	4
2	30 µg vaccine with $Al(OH)_3$	12
	Placebo	4
3	60 µg vaccine with $Al(OH)_3$	12
	Placebo	4
	Total	36 vaccine 12 placebo

Vaccine Schedule: Days 0, 28 and 56

Good Safety Profile

- No SAEs during the active vaccination phase
- One SAE identified in long-term follow-up
  - Pneumonia 4 months after final vaccination

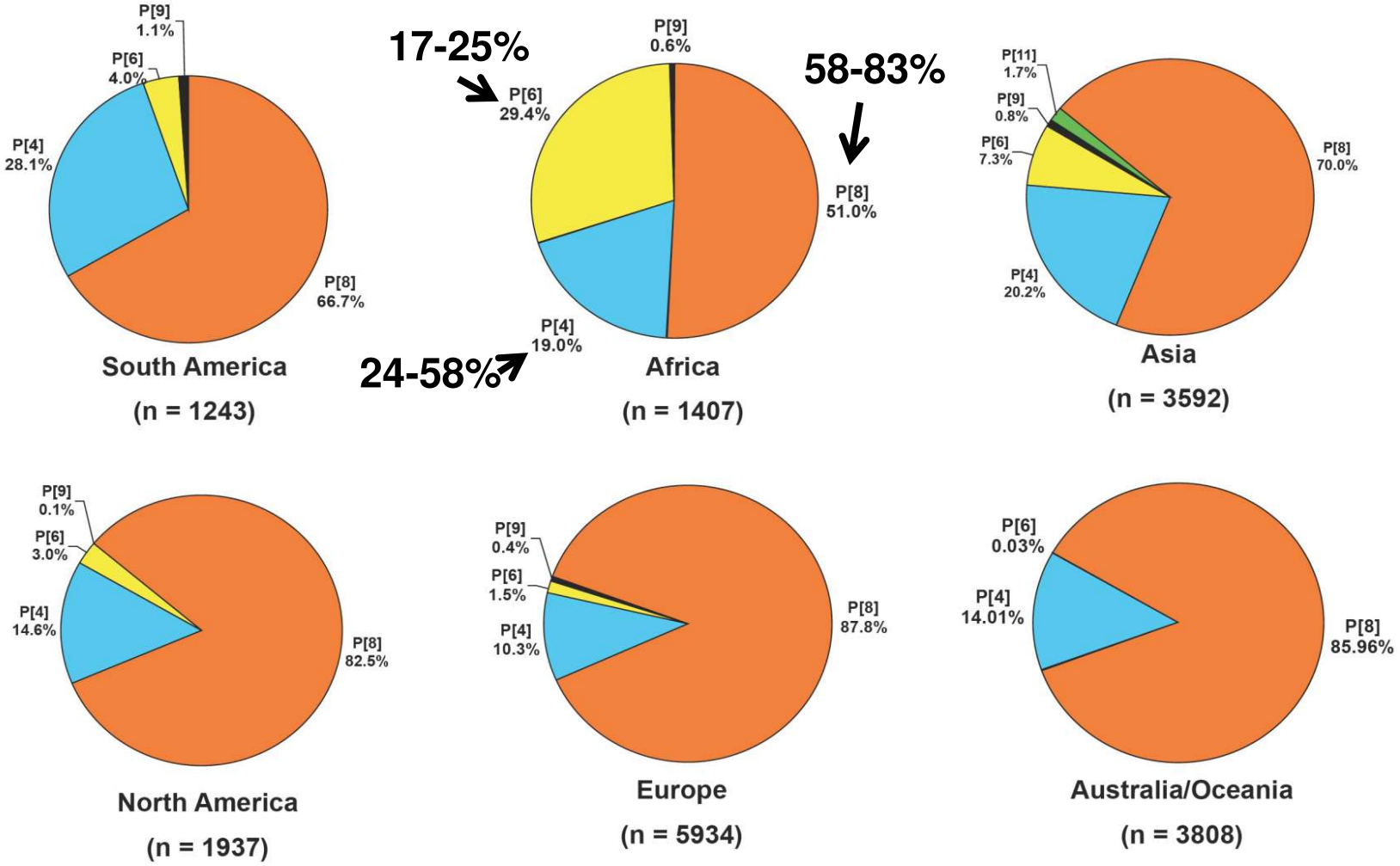
Anti-P2-VP8 IgA EIA Titers (IgG also)



	0	28	56	84
Placebo	0.0%	0.0%	0.0%	0.0%
10 µg	0.0%	66.7%	90.9%	100.0%
30 µg	0.0%	75.0%	91.7%	100.0%
60 µg	0.0%	66.7%	91.7%	100.0%

Proportion of responses ≥4-fold

Neutralization Antibody Responses to Human Rotavirus VP4 (P) Types at 60 μg (≥ 4-fold increase 28 days after 3d dose)



Santos and Hoshino, 2004

Conclusions from Phase 1 Trial

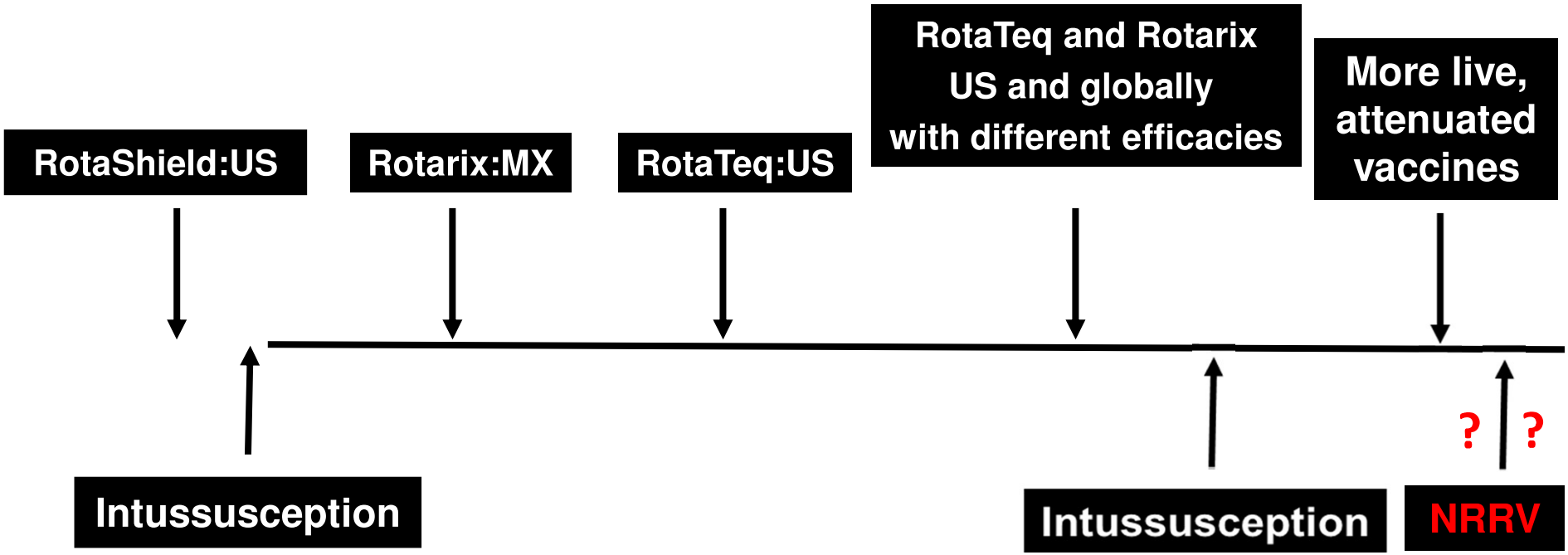
- Vaccine safe and well tolerated
- Vaccine elicits a robust antibody response to several homologous P[8] strains of rotavirus
  - Modest response to a P[4] strain
  - Meager response to a P[6] strain
- Response rates lower in those with high levels of pre-existing antibody
- May need to add P[6] & P[4] component to assure optimally broad protective responses
- Performance of the vaccine in immunologically naïve subjects remains to be determined

Next Steps

- Descending-age, dose-escalation trial in toddlers and infants in South Africa
  - Safety/tolerability
  - Immunogenicity
  - “Efficacy” against shedding with Rotarix challenge

- Preclinical assessment of additional P genotypes to broaden neutralizing responses

Live Attenuated Rotavirus Vaccine Development



NRRV Vaccine Development: Discussion

- What level of efficacy will be expected/needed in developing country populations?
- Safety – will NRRVs reduce the small risk of intussusception observed?
- Pricing – will NRRVs be much less expensive?
- Programatic issues: will another injectable vaccine be acceptable in the EPI system?
  - Will the potential for combination vaccines with other enteric pathogens (ST-ETEC, EPEC, Shigella, Norovirus) help address this question?
- Manufacturers: in developing countries?

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