Rotavirus vaccine update - next generation products

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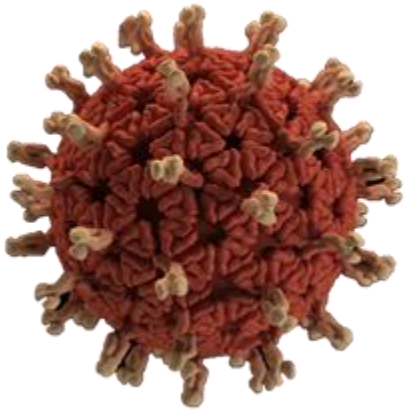
Bill & Melinda Gates Foundation

WHO PDVAC Meeting, Geneva

11 December 2024.



WHO Pre-qualified oral rotavirus vaccines

Rotarix (GSK)	RotaVac (Bharat)	RotaSIIL (Serum Institute)	RotaTeq (Merck)
Monovalent, attenuated human rotavirus strain	Monovalent, attenuated human strain	Pentavalent, bovine-human reassortant vaccine	Pentavalent, bovine-human reassortant vaccine
G1P[8]	G9P[11]	G1-4, G9 human rotavirus proteins with VP4 P[5] of the bovine backbone	G1-4, P[8] human rotavirus proteins in WC3 backbone
2 dose regimen	3 dose regimen	3 dose regimen	3 dose regimen
liquid presentation 1.0ml, single dose Plastic/BFS	'frozen' & 'liquid', 0.5ml, 1 & 5 dose presentation vials	lyophilized & liquid 2ml, 1 & 2 dose presentation	Do not supply GAVI

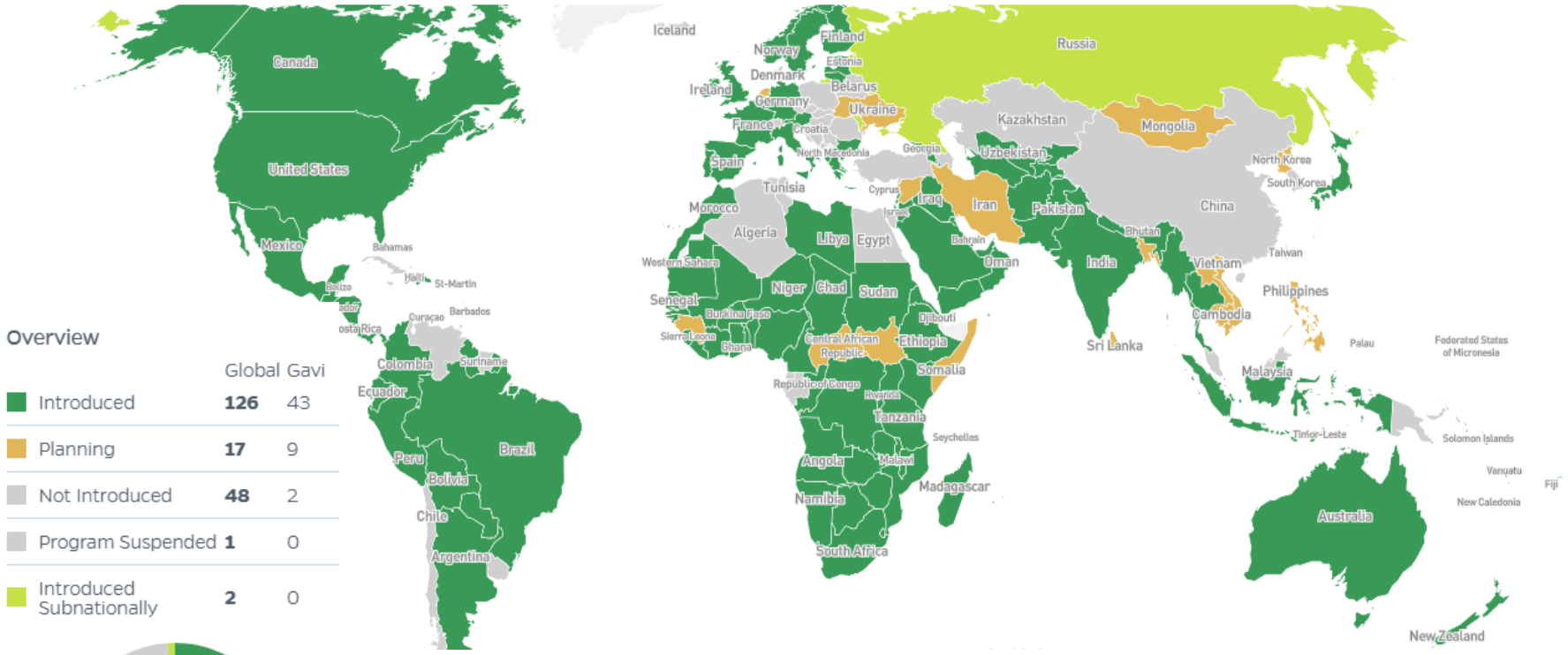
WHO Strategic Advisory Group of Experts (SAGE) Oct 2020 – reaffirmed RV vaccines should be included in all NIP and should be a priority:

- First dose from 6 weeks of age.
- Support catch up campaigns in high burden settings.
- Not recommended for children >24 months of age.
- All four WHO PQ live-attenuated, oral, rotavirus vaccines are recommended for use.

Nationally available oral rotavirus vaccines and upcoming products

VACCINE	COMPANY	STATUS	STRAIN(S)
Rotavin M1 (human strain)	POLYVAC (Viet Nam)	Licensed in Vietnam. Effectiveness study completed. Partial introduction in country	G1P[8]
LLR/LLR+ Lamb rotavirus (lamb-human reassortant)	Lanzhou Biologicals / Xinkexian Biological Technology (China)	LLR - Licensed in China (2000) LLR+ - Licensed in China (2023). Effectiveness studies completed.	Lamb (G10P[12]) + G1, G2, G3, G4
RV3-BB (human strain)	Biofarma (Indonesia)	Ph3 clinical trial completed in Indonesia, Ph2 completed in Malawi & New Zealand Planned use in Indonesian NIP in 2025	G3P[6]
UK-BRV (bovine-human reassortant)	NIH (bovine-human reassortant) Licensed to various manufacturers: Wuhan (China); Butantan (Brazil)	Wuhan completed Ph 3 clinical trials Butantan restarting developing program in partnership	Bovine (G6P[7]) + G1, G2, G3, G4 reassortants

Rotavirus vaccine introductions globally



Today, four attenuated live, oral rotavirus vaccines are available on the global market in various formulations: Rotarix, RotaTeq, Rotasiil, and Rotavac.

Despite widespread use of these vaccines, rotavirus remains the leading cause of severe diarrheal disease in young children.

https://view-hub.org/vaccine/rota

Rotavirus is still the major cause of severe diarrheal disease in young children, despite the advent of these vaccines

Rotavirus vaccines introduced in 126 countries (43 Gavi-eligible countries) (October 2024)

Table 3. Estimated all-cause and pathogen-attributable diarrhoeal deaths in 2017-2018 with 95% confidence intervals both globally and by WHO region in children less than 5 years of age.

	Global	African Region	Region of the Americas	Eastern Mediterranean Region*	European Region	South-East Asian Region	Western Pacific Region
All-cause	582295 (493241, 683788)	396459 (321310, 482064)	10483 (7385, 14682)	79661 (56853, 108689)	1623 (1069, 2597)	84565 (70943, 101038)	8175 (6057, 10868)
Rotavirus	208009 (169561, 259216)	148931 (115068, 191171)	1857 (1221, 2898)	28343 (20445, 39430)	342 (207, 560)	25829 (20780, 31466)	2283 (1590, 3307)
Shigella	62853 (48656, 78805)	43947 (30852, 57086)	1570 (995, 2376)	7837 (5221, 11774)	193 (116, 319)	9164 (6608, 11997)	106 (54, 211)
Adenovirus 40/41	36922 (28469, 46672)	15117 (9339, 20597)	765 (439, 1166)	8182 (5333, 12275)	54 (17, 97)	12701 (9130, 16202)	175 (100, 250)
Norovirus	35914 (27258, 46516)	19562 (13936, 26002)	1843 (1201, 2883)	5881 (3267, 9851)	156 (96, 243)	6960 (3958, 11553)	1094 (816, 1475)
Sapovirus	22704 (16452, 29354)	17060 (12249, 22275)	396 (245, 605)	2539 (1176, 4507)	108 (65, 185)	2302 (578, 4550)	143 (103, 208)
ETEC	22530 (17762, 28869)	18879 (14817, 24304)	338 (205, 559)	1988 (1224, 2971)	63 (37, 109)	1158 (726, 1700)	28 (17, 52)
Cryptosporidium	19905 (14364, 26984)	17121 (11950, 23540)	116 (62, 194)	1553 (949, 2527)	51 (22, 95)	984 (664, 1278)	22 (8, 55)
Astrovirus	17213 (12095, 22573)	13208 (8547, 18064)	289 (164, 460)	1832 (1077, 2773)	63 (32, 110)	1670 (862, 2477)	110 (80, 151)
C. jejuni/C. coli	9741 (4023, 15478)	4130 (2144, 6778)	321 (150, 503)	2263 (372, 4468)	9 (5, 16)	3032 (291, 5388)	92 (53, 153)
Salmonella	6021 (3391, 8442)	3688 (1188, 5794)	55 (29, 97)	965 (614, 1404)	1 (0, 3)	1160 (788, 1450)	104 (44, 175)

Cohen A and Platts-Mills J *et al. BMJ Global Health* 2021.

…But challenges around rotavirus vaccination remain

Large body of evidence demonstrates the impact of rotavirus vaccines (>30 studies):

- Significant reduction in diarrheal deaths, rotavirus hospitalizations, and all cause diarrhea.
- Resulted in saved lives and improved child health

However, Rotarix and RotaTeq vaccine effectiveness against rotavirus hospitalizations differs based on mortality strata:

- Low U5 childhood mortality settings (US/Finland)

  75-100% VE against severe RVGE hospitalisation

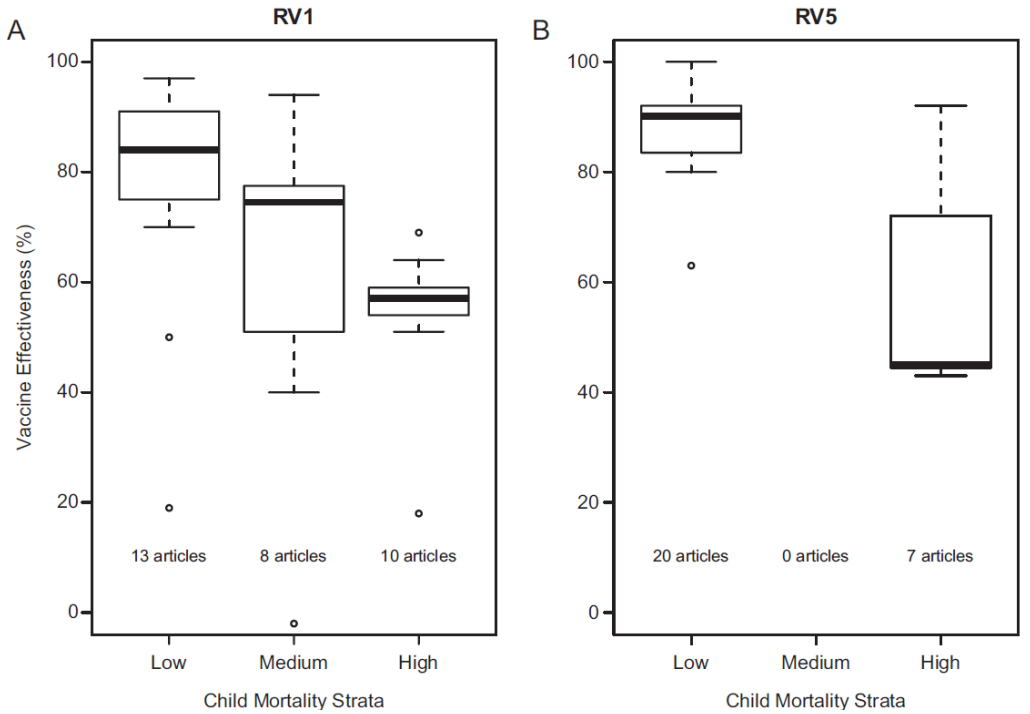
- High U5 childhood mortality settings (Africa/ SE Asia)

  50-70 % VE against severe RVGE hospitalisation

Thus, issues remain:

1. A lower protective effectiveness in the first 1-2 years of life in high mortality countries in Asia and Africa (burden of moderate-to-severe rotavirus diarrhea)

2. Rotavirus remains major cause of AGE, despite vaccine introduction.

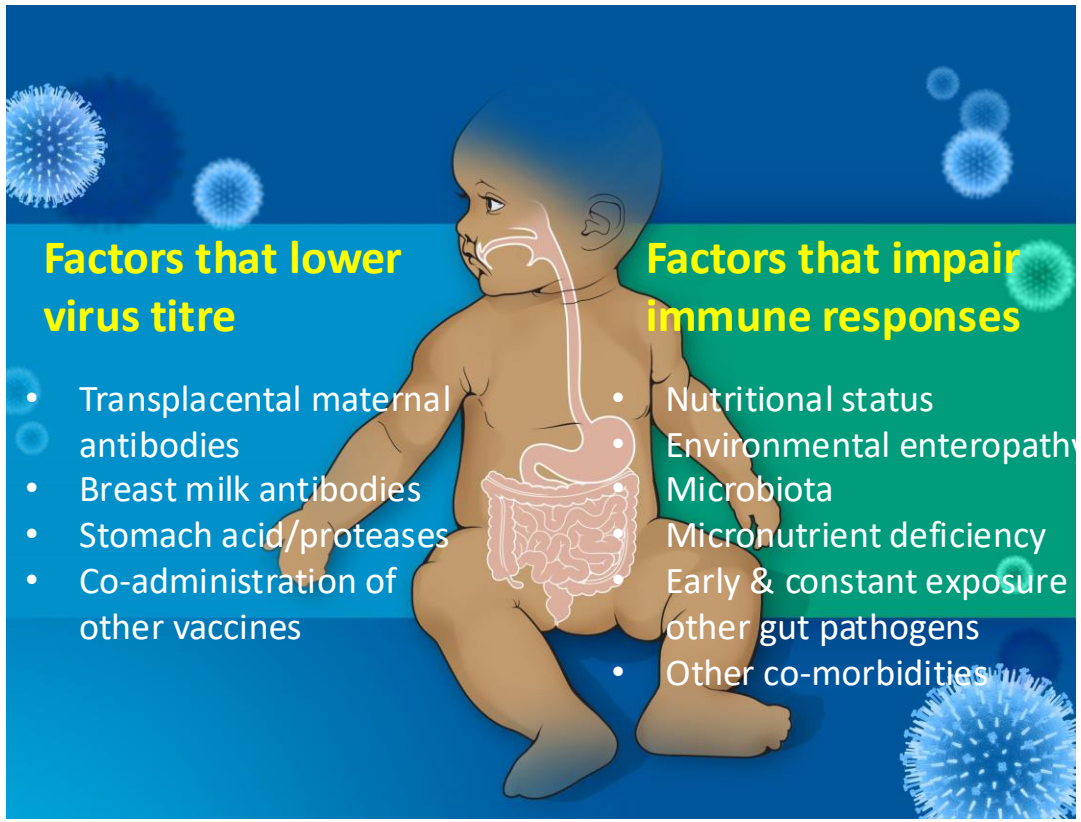


Rotarix; VE 84% low mortality countries
VE 75% in medium mortality countries
VE 57% in high mortality countries

RotaTeq: VE 90% low mortality countries
VE 45% in high mortality countries

Jonesteller et al. Clin Infect Dis. 2017; Burnett E et al. Lancet Global Health 2021

Why do oral vaccines fail? Can we do better?



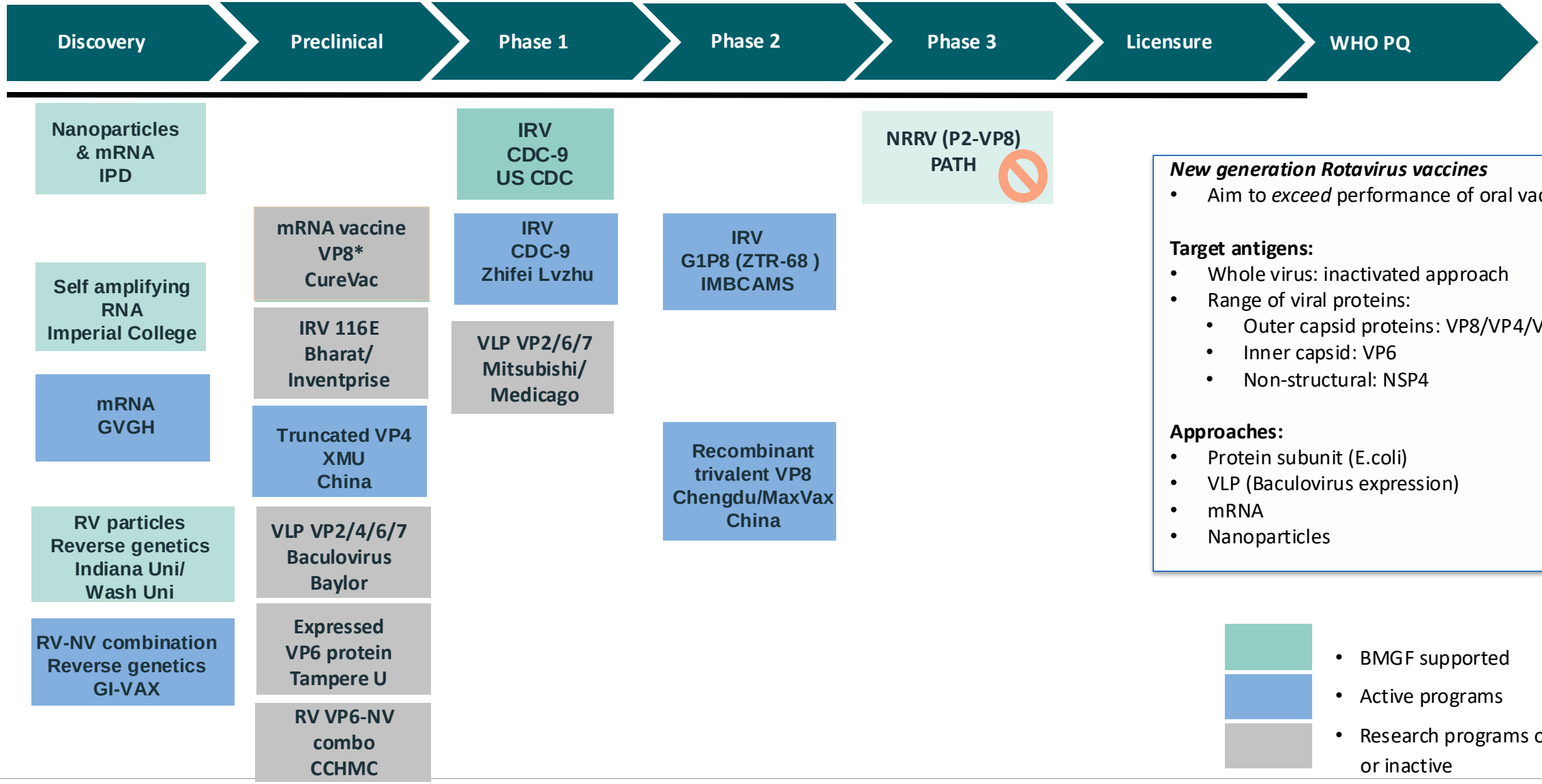
- **Gut enteropathy:** unclear solutions
- **Nutritional status:** mixed evidence
- **Interference from OPV:** strong evidence, but not logistically feasible
- **Interference from breastmilk:** withholding NOT demonstrated to improve VE
- **Interference from transplacentally acquired IgG**
  - Higher pre-vaccine maternal IgG associated with lower seroconversion
  - Higher efficacy with delayed dosing schedule
- **Genetic polymorphisms:** infants with *FUT2*-inactivating mutations (non-secretors) less likely to seroconvert

Eventual move away from oral vaccines??

Rotavirus Vaccine pipeline:

- Development of non replicating candidates

What is next in terms of rotavirus vaccines?
Next-generation non replicating rotavirus vaccine pipeline



New generation Rotavirus vaccines

- Aim to *exceed* performance of oral vaccines

Target antigens:

- Whole virus: inactivated approach
- Range of viral proteins:
  - Outer capsid proteins: VP8/VP4/VP7/
  - Inner capsid: VP6
  - Non-structural: NSP4

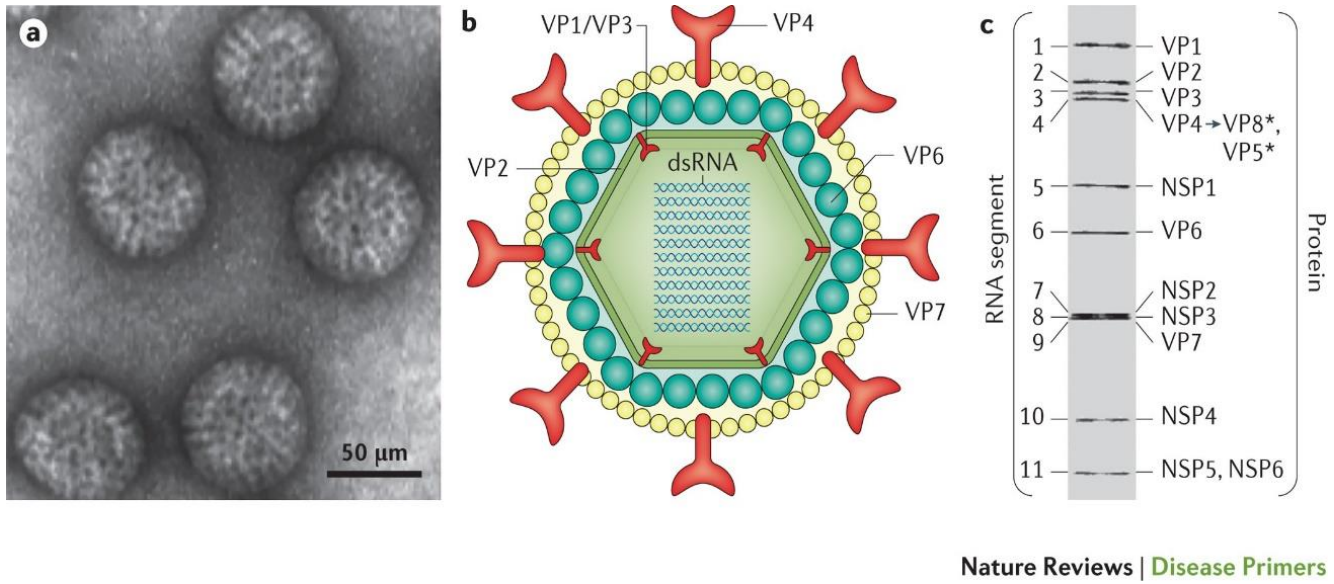
Approaches:

- Protein subunit (E.coli)
- VLP (Baculovirus expression)
- mRNA
- Nanoparticles

- BMGF supported
- Active programs
- Research programs only or inactive

Models of next generation rotavirus vaccine candidates

Most experimental approaches have targeted the neutralizing antigens – VP2 and VP6 at the core, and VP4 and VP7 as neutralizing antigens



Virus attachment involves recognition of cell receptors (VP4)

- integrins & glycans on cell surface
- Recently, histo blood group antigens identified as cell attachment factors for human rotaviruses

Family *Reoviridae*,

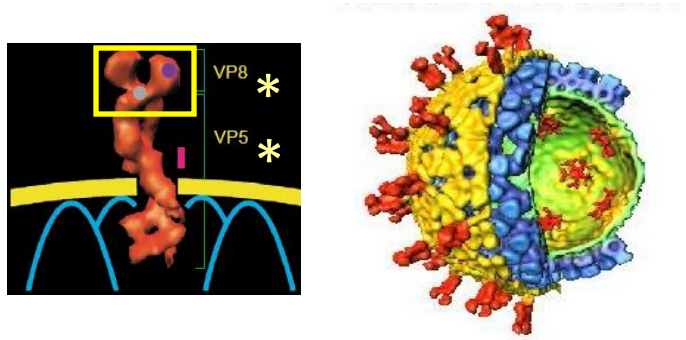
- non-enveloped, icosahedral, triple layered capsid (75nm diameter)
- outer capsid: VP4 and VP7 proteins – major neutralizing antigens
- inner core capsid: VP6 – major antigenic mass of virion
- 11 segments of dsRNA ~ 18,550bp (660bp – 3300bp), encoding 6 structural and 6 non-structural proteins

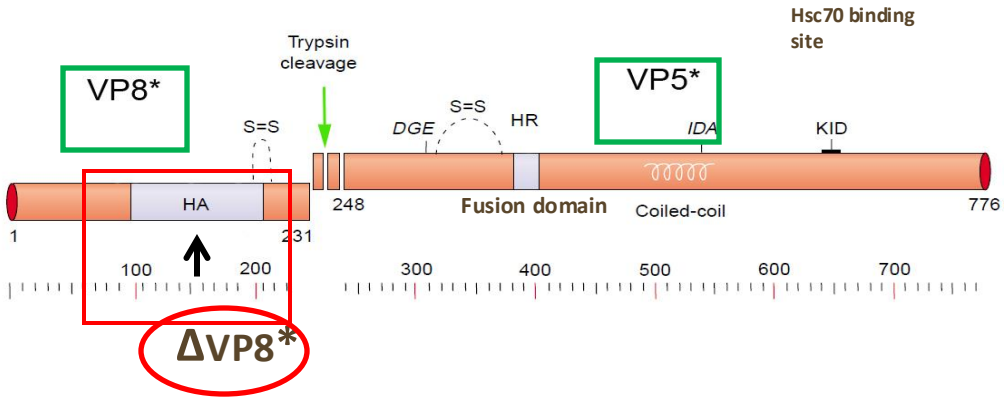
Crawford, S. E. *et al.* (2017) Rotavirus infection. *Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2017.83

Non-replicating Rotavirus Vaccine (NRRV)

- Developed by PATH, using NIH constructs.
  - SK Bioscience (S. Korea) - commercial partner

- Trivalent vaccine (P2- VP8*):
  - based on constructs of truncated VP8* subunits of VP4 outer capsid protein - P[4], P[6] and P[8] genotypes
  - fused to tetanus toxin P2 CD4 epitope
  - expressed in *E. coli* (T7 promoter)
  - Adjuvant - aluminum hydroxide
  - 3 doses delivered via parenteral administration route





Intervention Target Product Profile	
Indication	Prevention of severe rotavirus gastroenteritis in infants
Target population	3 immunizations at approximately 6, 10, and 14 weeks of age
Efficacy	≥ 75%
Safety	Clinically acceptable safety profile
Route Of Admin.	IM
Cost	<$0.75/dose

Wen X et al. Vaccine 2014; Wen X et al. HVI 2015

P2-VP8 (NRRV) – showed good immunogenicity in Ph1 and Ph2 clinical studies

Phase 1/2a immunogenicity studies:

- Safe & well tolerated, robust immunogenicity to monovalent P2-VP8 vaccine
- Reduction in Rotarix shedding (57%)

Phase 2 study: Trivalent P2-VP8 immunogenicity study

- dose-escalating, age-descending study placebo-controlled study
- doses (15/30/90 ug total) n= 588; (139 /arm)
- 3 IM doses – 6/10/14 weeks;

Immunogenicity results:

- trivalent vaccine was highly immunogenic
- Fourfold seroconversion: IgG (97.9-100%) & IgA (58.3 - 80.9%) P4, P6, P8
- Homotypic neutralizing antibody response to all 3 antigens
  - 30ug – 64.9-71% seroconversion
  - 90ug – 67.9-73.1% seroconversion

Proportion Shedding			
Placebo	**15 µg**	**30 µg**	**90 µg**
24/53 45%	22/52 41%	19/56 34%	15/56 27%
Percent Reduction in Shedding, vs Placebo			
	15 µg	**30 µg**	**90 µg**
	6.6% (-44%, 40%)	**25%** (-20%, 53%)	**41%** (0.1%, 65%)

Challenge study:

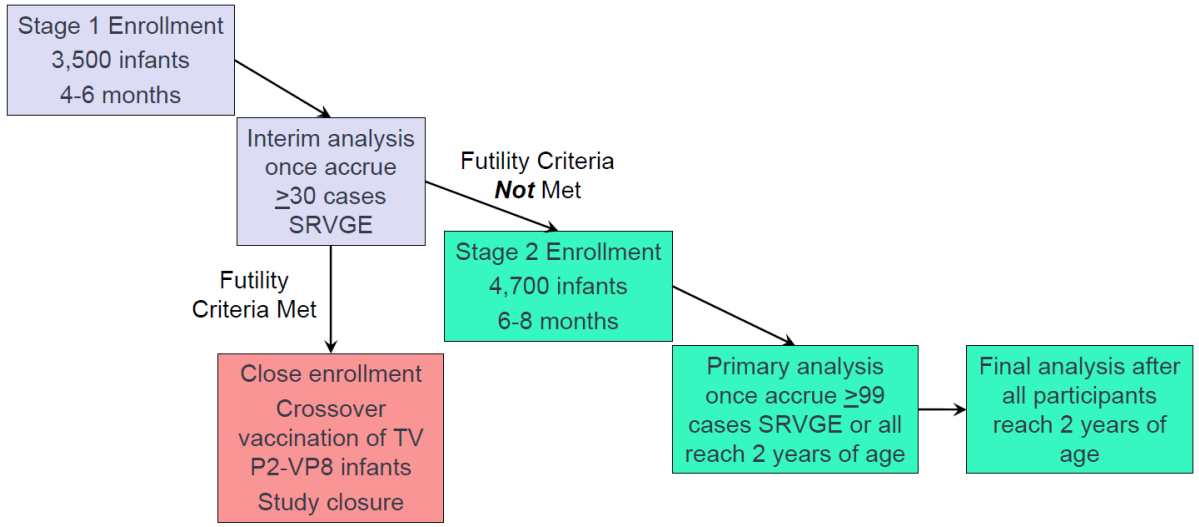
- Rotarix vaccine administered post 3rd dose of monovalent P2-VP8 or placebo
- Significant reduction in shedding of Rotarix virus in vaccinees (90ug – 40.5% reduction)
- Suggests that NRRV has an impact on rotavirus present in the gut mucosa and may mediate a potentially protective effect at the local gut surface.

Good immune responses & indication of functional protectional in gut – proceed to Ph3 efficacy study

Fix A et al. Vaccine 2015; 33:3766-72; Groome MJ et al, Lancet Infect Dis 2017; 17:843-53; Groome MJ et al. Lancet Infect Dis 2020; 20: 851-63

NRRV P2-VP8 Ph3 Efficacy study

CVIA 061 Study Outline



African sites: Zambia, Ghana, Malawi enrolled participants:

Zambia – commenced recruitment prior to COVID.

Ghana/Malawi – had not commence recruitment prior to COVID.
delayed approvals, but all sites actively recruited

A Phase 3 double-blind, randomized, active comparator-controlled, group-sequential, multinational trial.

- to assess the safety and efficacy of a trivalent P2-VP8 subunit rotavirus vaccine in prevention of severe RV diarrhea in healthy infants.
- 8,200 infants: randomized 1:1 - 90µg trivalent NRRV IM plus oral placebo or Rotarix plus IM placebo.
- three doses: monthly intervals (starting at 6-8 weeks of age)
- administered concomitantly with EPI vaccines.
- Follow-up through 2 years of age

Study plan undertake enrollment in two stages:

Stage 1, Futility component: ~3,500 infants will be enrolled at sites located in three African countries, with interim assessment of relative efficacy after at least 30 SRVGE

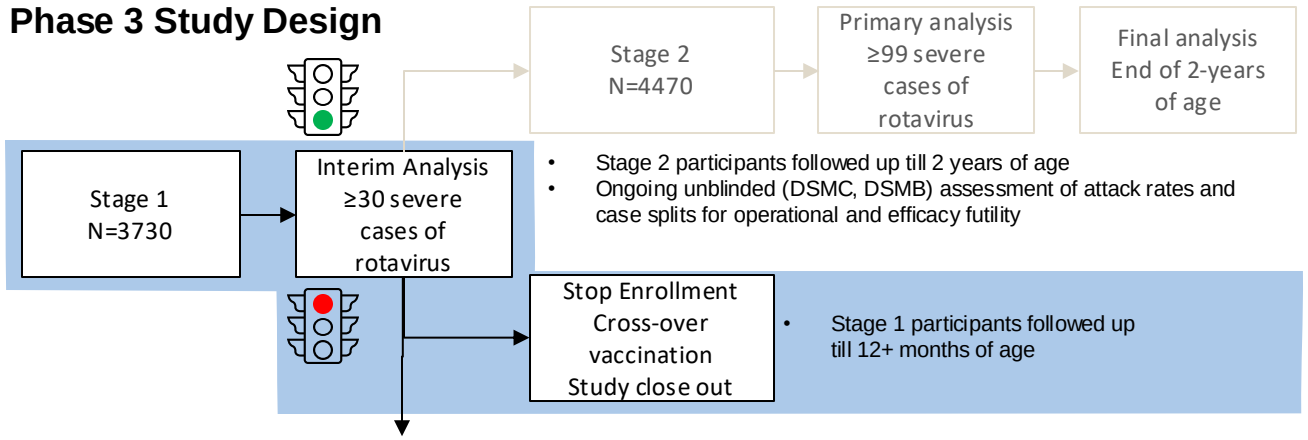
Stage 2, Expanded Efficacy: if do not meet futility, proceed to full study population (8500), final analysis after 100 events.

- Interim analysis is to detect early futility (RVE≤0%)
- Final analysis designed to detect relative VE (>0%)

NRRV met futility criteria in Ph3 efficacy study - stopped at stage 1

Following an interim analysis, the NRRV P3 study's independent DSMB determined that the Phase 3 NRRV trial should not continue as planned because it did not meet agreed upon pre-specified futility criteria

Phase 3 Study Design



Interim Analysis:

- Based on analysis of 36 severe cases, DSMB indicated the study met futility criteria.

Current activities

Relative vaccine efficacy is being determined.
- NRRV versus Rotarix (March 2024)

Possible explanations for trial outcome

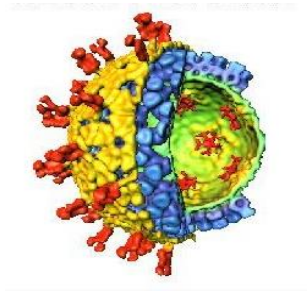
- Immune responses to VP8 subunit alone are not enough to elicit improved protection against severe disease from wildtype infection

- Novel circulating rotavirus strains present in the community are not protected by the immune responses generated by the vaccine

Correlation between reduction in shedding of Rotarix challenge seen in Ph2 study and protection against wild-type disease is not a suitable correlate for efficacy

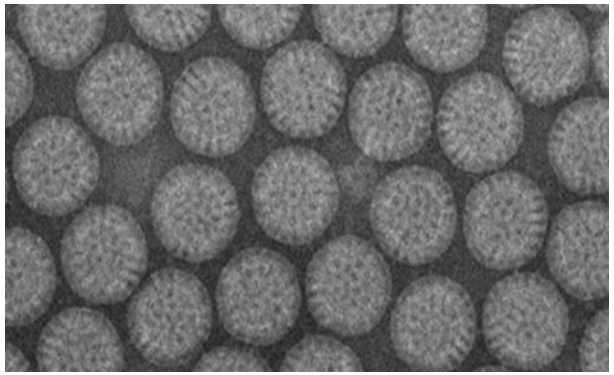
Cryz S and colleagues, unpublished data. Presented at WHO PDVAC meeting, December 2022

1. CDC- Inactivated Rotavirus Vaccine (IRV)



- Developed by CDC.
  - CDC-9 strain – G1P8 (single gene from DS-1 backbone)
  - Grows well in vero cells (10^7-10^8)
  - Predominant triple layered

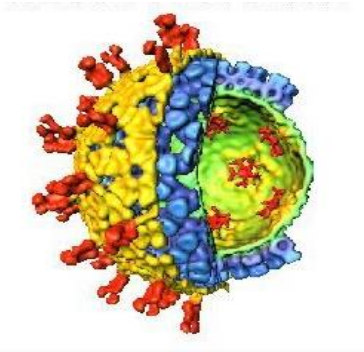
  Vaccine candidate:
  - Heat inactivated
  - Adjuvanted with aluminum hydroxide (2%)
  - Extensive animal testing showed highly immunogenic and proof of concept in gnotobiotic piglets (IgA and IgG)
  - 3 doses delivered via parenteral administration route (0.5ml)



<u>Phase 1a safety and immunogenicity study underway at Emory University (USA)</u>

- Dose escalation, placebo-controlled study in 50 adults (18-45 years of age)
- Administered IM, as either a 3.75ug or 7.5 ug dose (20 IRV & 5 placebo/arm)
- Schedule delivered as 3 doses given 28 days apart
- Safety follow–up 6 months after last dose

2. Zhifei Lyzhu - Inactivated Rotavirus Vaccine (IRV)

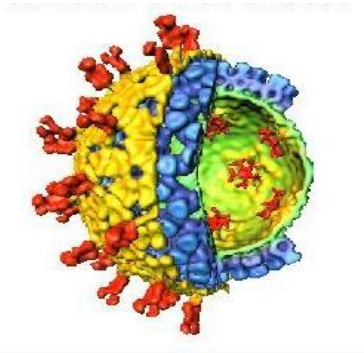


- **Licensed strain from CDC** (Beijing Zhifei Lvhu Biopharmaceutical Co).
  - CDC-9 strain – G1P8 (single gene from DS-1 backbone)
  - Grown in vero cells (10^7-10^8)
  - Predominant triple layered
- **Vaccine candidate**:
  - Formalin inactivation
  - Adjuvanted with aluminum hydroxide (2%)
  - Vaccine dose - 0.5ml
    - Compared IgG GMT dose (2.5/5/10) and schedule (2 or 3 doses) in mice
    - No difference 5/10 ug, 3 doses better than 2.
- **<u>Phase 1a safety and immunogenicity study (2021 -)</u>**

Dose escalation, placebo-controlled study in 375 subjects:

- 50 adults (18-49 yrs); 50 children (1-5 yrs) 275 infants (6-12 weeks)
- 3 doses 30 days apart delivered via parenteral administration route
- Administered IM, as either a low (2.5ug) or high dose (5.0ug) (20 IRV & 5 placebo/arm)
- Infant participants: low dose 20/5, high dose 20/5 after data review expanded to additional 100/100/25
- Safety follow–up 6 months after last dose – no vaccine related SAE.
- Immunogenicity results expected Q2 2024.

3. IMBCAMS- Inactivated Rotavirus Vaccine (IRV)



- Developed by Institute of Medical Biology, Chinese Academy of Medical Science.
  - ZTR-68– G1P8
  - Grown in vero cells

  Vaccine candidate:
  - Formalin inactivated
  - Adjuvanted with aluminum hydroxide (2%)
  - Delivered via parenteral administration route (0.5ml)

Phase 1a safety and immunogenicity study (China).

- Dose escalation, placebo-controlled study in 96 adults (18-49 years of age)
  - Administered IM, as either as 80Eu/160Eu & 320EU, as 3 dose schedule 28 days apart (28 vaccine/8 placebo)
- Outcomes:
- Safety: No SAE vaccine associated; AE significantly higher in mid-dose group than low-dose group, no difference mod-high (grade 1 or 2).
- Immunogenicity: good immunogenicity that stimulates IgG, IgA and neutralizing ab responses
  - high dose produced better IgG & IgA responses than low and intermediate dose.
  - IgA seroconversion rates: low 20%, mid 54%, high 45% 28 days post full immunization.

IMBCAMS IRV Ph2a Immunogenicity study underway

Aim: To evaluate the immunogenicity, safety, and persistence of immunity of IRV administered on a 2 dose schedule (0, 28-days) and on a 3 dose schedule (0, 28, 56-day).

Vaccine : IRV – IM administration 0.5mL/dose

Two dose schedule in infants/children - 7 to 71 months
Three dose schedule in infants - 2 to 6 months.

Study cohort - 600 participants

Rotavirus NSP4 is potentially a vaccine candidate

CLINICAL AND DIAGNOSTIC LABORATORY IMMUNOLOGY, Oct. 2005, p. 1157–1163 Vol. 12, No. 10
1071-412X/05/$08.00+0 doi:10.1128/CDLI.12.10.1157–1163.2005

Evaluation of Serum Antibody Responses against the Rotavirus Nonstructural Protein NSP4 in Children after Rhesus Rotavirus Tetravalent Vaccination or Natural Infection

Esmeralda Vizzi,[1]* Eva Calviño,[1] Rosabel González,[2] Irene Pérez-Schael,[2] Max Ciarlet,[3]†
Gagandeep Kang,[3]‡ Mary K. Estes,[3] Ferdinando Liprandi,[1] and Juan E. Ludert[1]

Laboratorio de Biología de Virus, Centro de Microbiología y Biología Celular, IVIC, Caracas, Venezuela[1]; Instituto de Biomedicina, MSDS, UCV, Caracas, Venezuela[2]; and Department of Molecular Virology and Microbiology, Baylor College of Medicine, Houston, Texas[3]

ELISA with rNSP4$_{(85\text{-}175)}$,-GST affinity purified from SA11, Wa and RRV (genotypes A, B, C) expressed in *E. coli* (*structure of antigen not known*)

Seroconversion to NSP4: 54% (42/78) of children after natural infection
8% (2/26) of RRV-TV vaccine recipients

Antibody levels were modest (titers of $\leq$ 200) in most infected and vaccinated children. Previous exposures to rotavirus did not affect the NSP4 seroconversion rate.

A heterotypic NSP4 response was detected in 48% of naturally infected children with a detectable NSP4 response

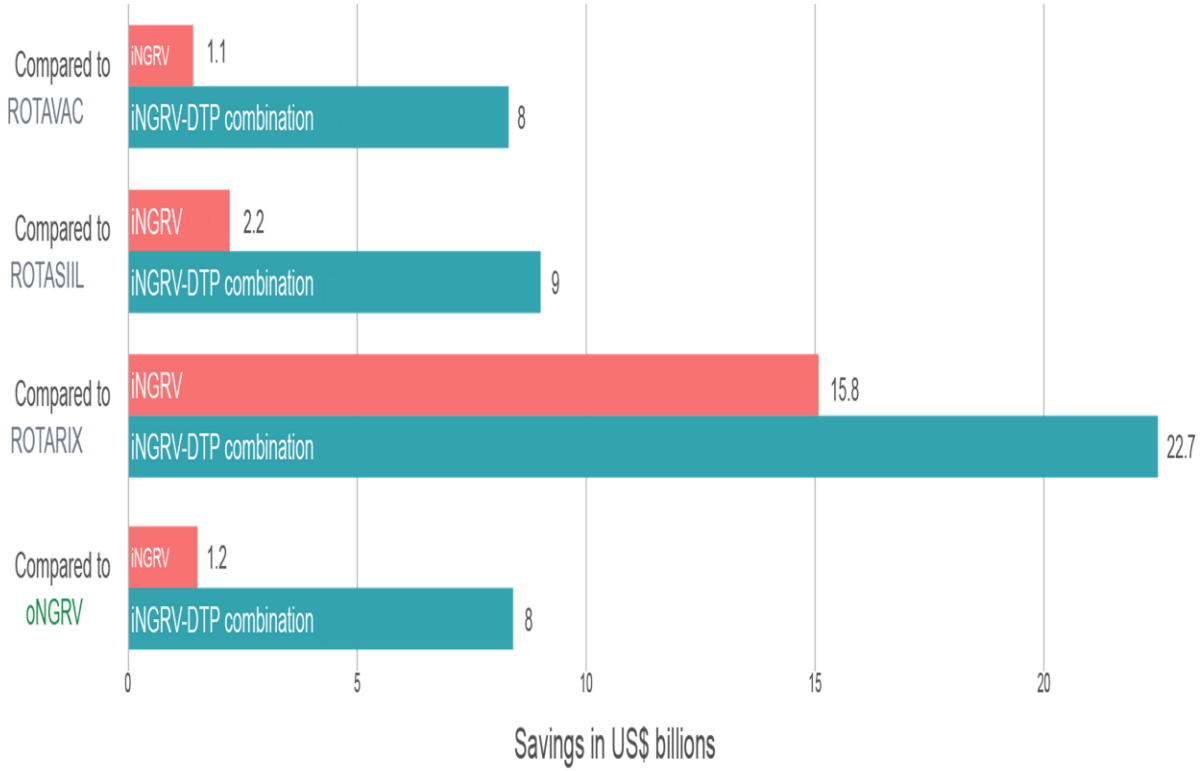
NSP4 was less immunogenic than the VP6 protein measured independently by ELISA

A significant proportion of children who had antibodies to NSP4 in acute-phase serum did not develop RV-associated diarrhea, suggesting that antibodies against NSP4 might **correlate with protection** from RV diarrhea

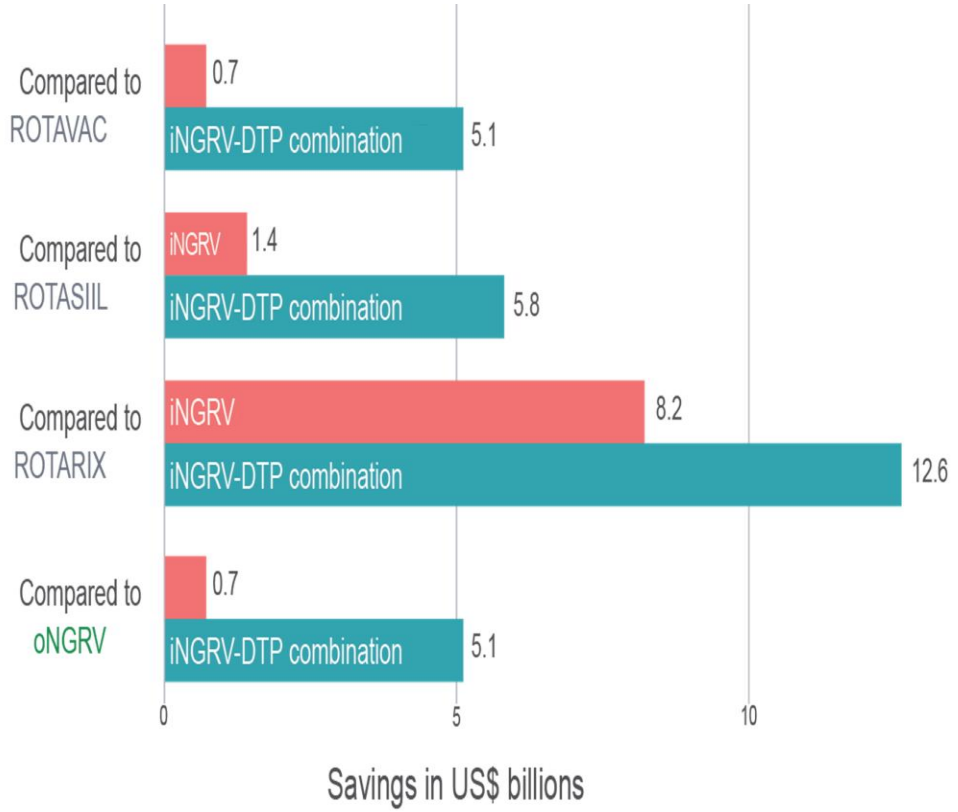
Impact and cost-effectiveness of injectable next generation rotavirus vaccines in 137 LMIC countries.

Economic cost savings with iNGRV in LMICs / Gavi-eligible countries over 10 years starting from 2025 if all countries were using LORVs

N = 137 LMIC countries



N = 73 Gavi eligible countries



Debellut F et al. HVI 2022

Potential use scenarios for non-replicating rotavirus vaccines:

Non-replicating, parenterally delivered rotavirus vaccines provide viable alternative to improve impact.
The potential benefits of non-replicating vaccine candidates include:

- Lower COGs
- Higher efficacy profile
- Avoid maternal ab, breast milk, microbiome, other pathogens, gut enteropathy
- Decreased signal of intussusception

Potential scenarios:

Stand-alone vaccine strategy:

- Replace oral vaccines only if efficacy improved significantly
- Parenteral immunization: challenge to delivery/uptake

Prime boost strategy:

Potential for alternative immunization schedules

- Improve efficacy and duration of protection
- Enhance magnitude, onset and functionality of immune response by stimulating both cell-mediated and humoral immunity

Combination vaccine:

Opportunity for combination vaccines with routine childhood vaccines

- Provides opportunity to increase coverage
- Reduce the number of clinic visits and number of injections

Summary: Residual rotavirus disease burden justifies development programs, however .....

- Reasonable pipeline of non-replicating rotavirus vaccines, however, likely require expanded target proteins to meet required effectiveness.
- Several scenarios where non-replicating rotavirus vaccine candidates could provide improved impact:
  - Stand alone / Prime boost / Combination approach
  - Are there scenarios for which there would be merit in developing a stand-alone parenteral rotavirus vaccine?
- Significant challenges to succeed: Clinical development program/ Manufacturing and formulation development
  - What studies remain to be done to evaluate the potential demand and acceptability, and critical parameters for these next-gen vaccines?
  - Is there a need to develop a TPP for a next generation rotavirus vaccine?

- ➢ How does PDVAC consider the merit of developing a parenteral rotavirus vaccine for infants as a stand-alone vaccine, vs a combination, for LMIC use?
- ➢ Does PDVAC agree that the next-gen rotavirus candidates should be considered in the vaccine combination framework, under development by WHO and PATH?