Enteric Vaccines: Rotavirus and Norovirus Vaccines - Vaccine Development for Low- and Lower-Middle Income Countries

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ADVAC Alumni Refresher course (ARVAC)

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Gates Foundation

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

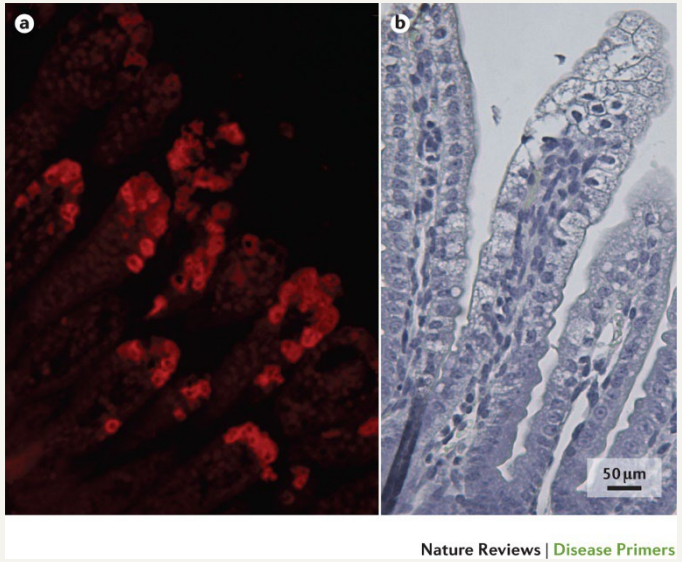
Rotavirus vaccines introduced in 127 countries (43/54 Gavi-eligible countries) (December 2024)

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.

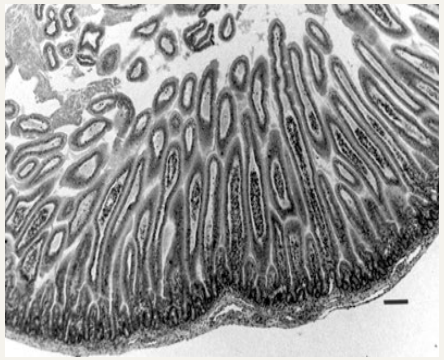
	Global	African Region	Region of the Americas	Eastern Mediterranean Region*	European Region	South-East Asian Region	Western Pacific Region
All-cause	582295 (493241, 683788)	396459 (321310, 482064)	10483 (7385, 14682)	79661 (56853, 108689)	1623 (1069, 2597)	84565 (70943, 101038)	8175 (6057, 10868)
Rotavirus	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.

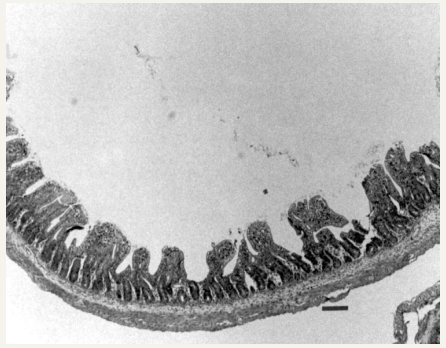
Histopathology of piglet intestine infected with rotavirus shows extensive damage to gut



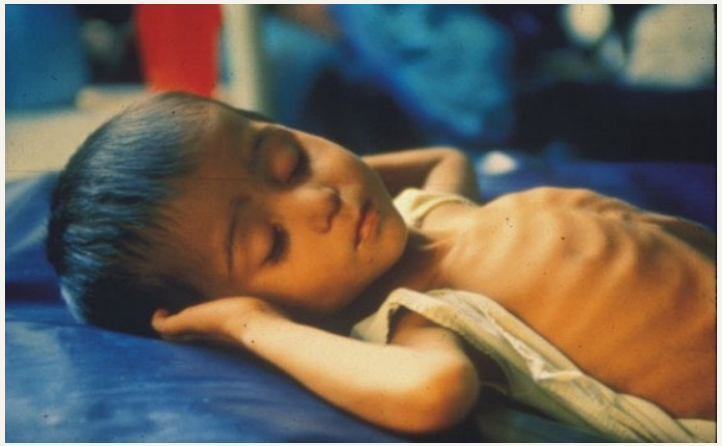
Duodenum histology of mice with rotavirus infection. Histopathological images of the duodenum of a mouse pup infected with a murine rotavirus strain (EDIM), 48 hours after infection. a | Rotavirus predominantly infects mature enterocytes at the middle and top of intestinal villi indicated by immunofluorescent labelling of rotavirus antigen viral protein 6. b | Vacuolization of enterocytes in the top and middle of intestinal villi can be observed with rotavirus infection, but crypt cells are unaffected.



Normal piglet villi



Rotavirus infected villi showing denuded micro-villi



Villous atrophy = malabsorptive diarrhea

Crawford SE *et al. Nat Rev Dis. 2017;* Saif L, Ward LA, Yuan L, *et al. Arch Virol 1996*

Efficacy against severe rotavirus gastroenteritis in the first year of life

Clinical protection against RVGE (≥11 on the Vesikari scale) in Africa and Asia

Region	Vaccine	Countries	Vaccine Efficacy	95% CI
Africa	Rotarix™	Malawi, South Africa	61.7	44.0, 73.2
Africa	RotaTeq™	Ghana, Kenya, Mali	64.2	40.2, 79.4
Africa	RotaSIIL™	Niger	66.7	49.9, 77.9
Asia	Rotavac™	India	56.4	36.6, 70.1
Asia	RotaSIIL™	India	36.9	11.7, 53,6
Asia	RotaTeq™	Bangladesh, Vietnam	51.0	12.8, 73.3

Madhi SA, Cunliffe NA, Steele AD et al. NEJM 2010; 362: 346-357; Zaman K, Anh DD, Victor CV et al. Lancet 2010; 376: 615-23; Armah GE, Sow S, Breiman RF et al. Lancet 2010; 376: 606-614; Bhandari N, Rongsen-Chandola T, Bavdekar A et al. Lancet. 2014; 383: 2136-43; Isanaka S, Ousmane G, Langendorf C, et al. NEJM 2017; 376:1121-30; Kulkarni PS, Desai S, Tewari T, et al. Vaccine 2017; 35: 6228-6237

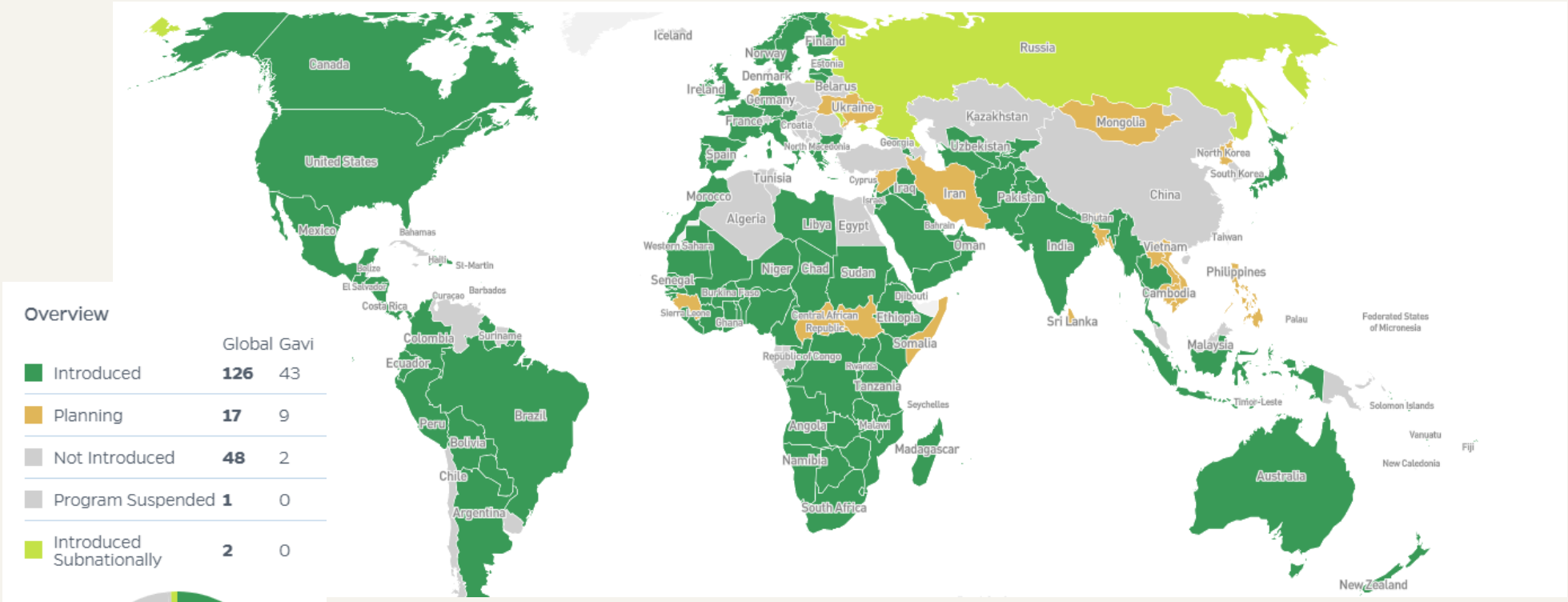
WHO Pre-qualified Oral Rotavirus Vaccines

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 dose, 1 dose, in plastic / BFS	'frozen' & 'liquid', 0.5ml dose, 1 & 5 dose presentation vials	lyophilized & liquid 2ml dose, 1 & 2 dose presentation	Does not supply GAVI Liquid, 2ml dose Plastic squeeze tube

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.
- 2-dose (Rotarix) or 3-dose schedule (RotaTeq, RotaSiil, RotaVac) administered with routine childhood vaccines.
- Not recommended for children >24 months of age.

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 in LMICs.

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

… 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

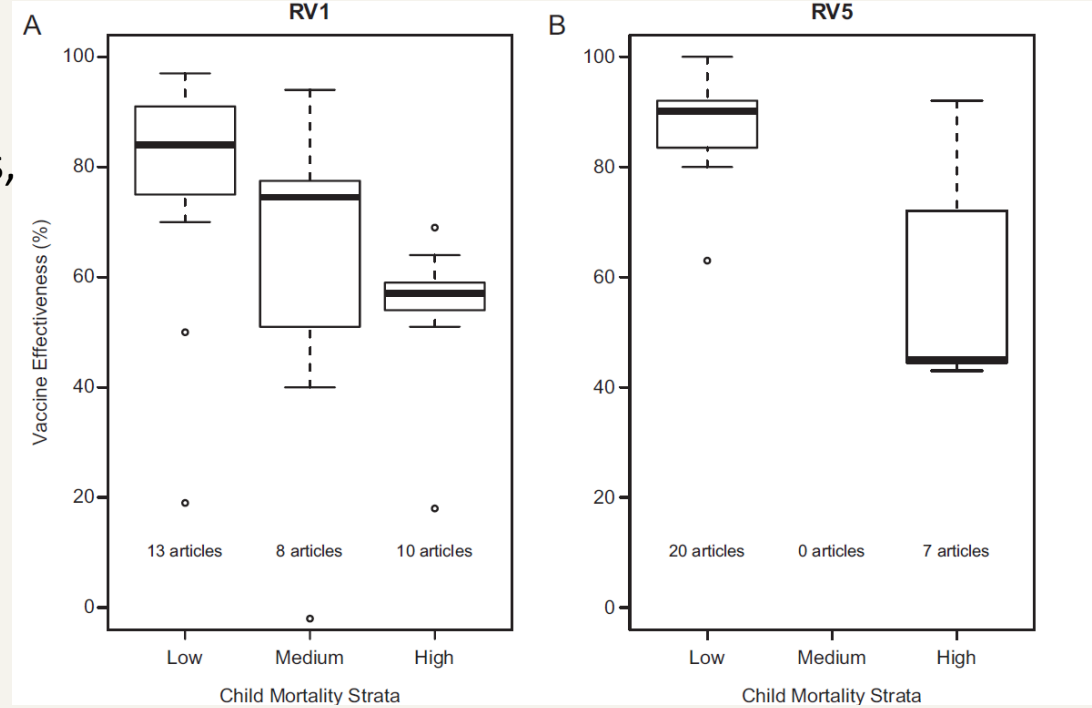
However, Rotarix and RotaTeq vaccine effectiveness against rotavirus hospitalizations differs based on mortality strata:

- 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 where the burden of moderate-to-severe rotavirus diarrhea predominates

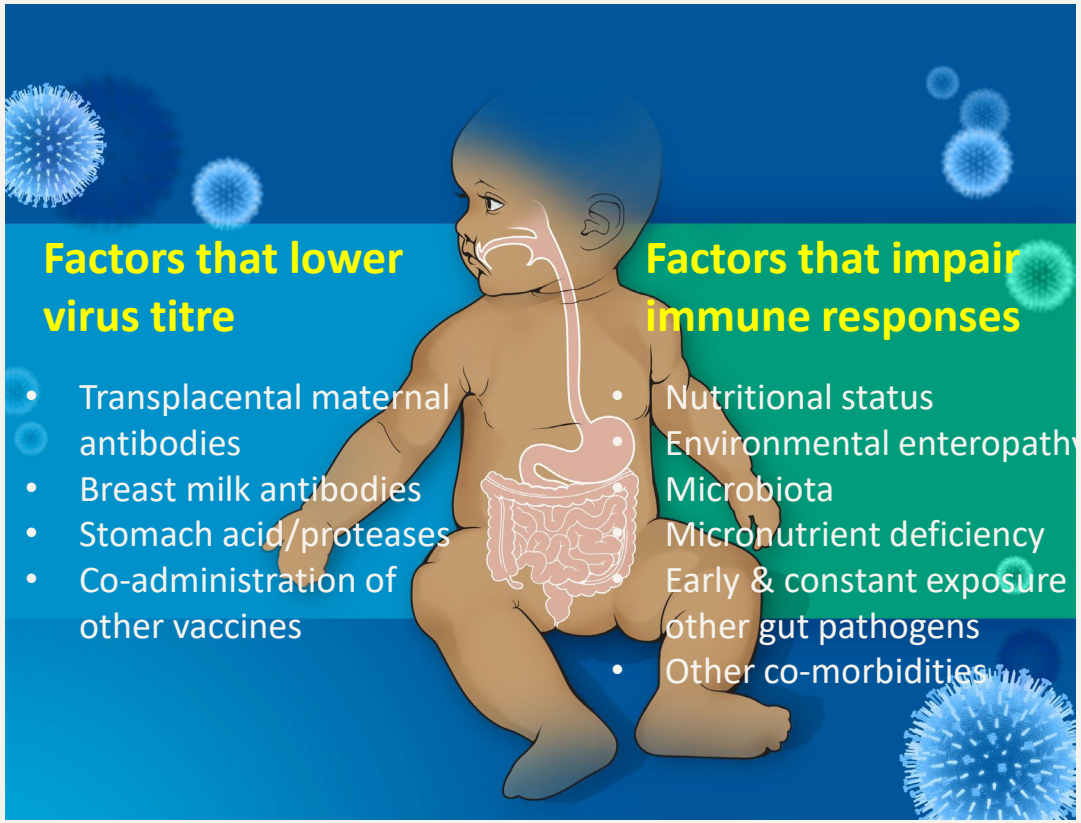
2. Rotavirus remains major cause of AGE, despite vaccine introduction.

Rotarix; VE 84% low U5 mortality countries
VE 75% in medium U5 mortality countries
VE 57% in high U5 mortality countries

RotaTeq: VE 90% low U5 mortality countries
VE 45% in high U5 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

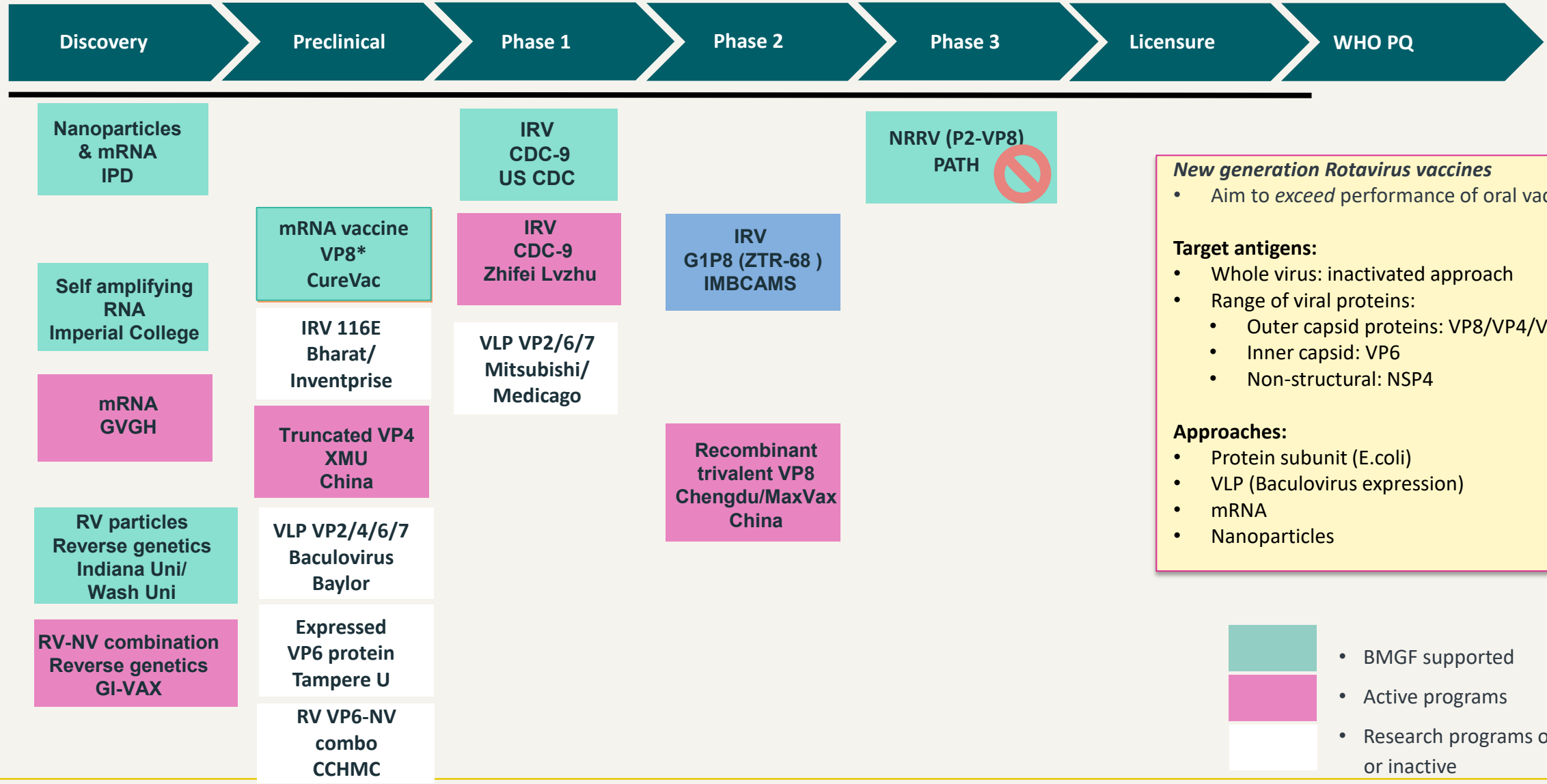
Eventual move away from oral vaccines??

Rotavirus Vaccine pipeline:

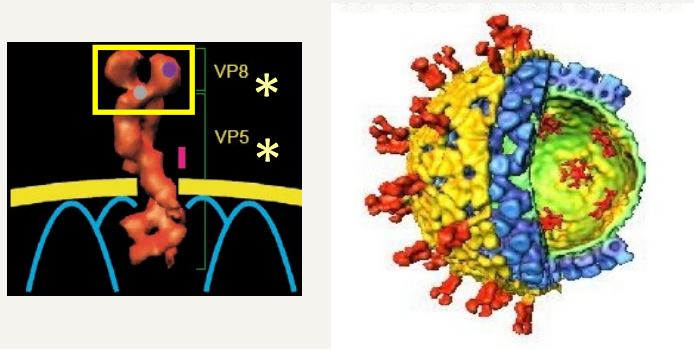
- Development of non replicating candidates

What is next in terms of rotavirus vaccines?

Next-generation non replicating rotavirus vaccine pipeline

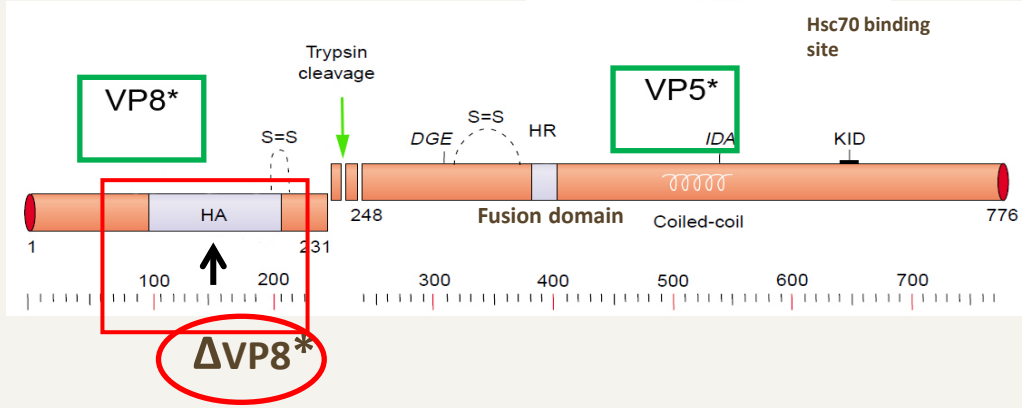


Non-replicating Rotavirus Vaccine (NRRV)



- 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



- Phase 1 and 2, dose ranging studies demonstrate safety and good immunogenicity.
- Sufficient to progress to Phase 3 studies

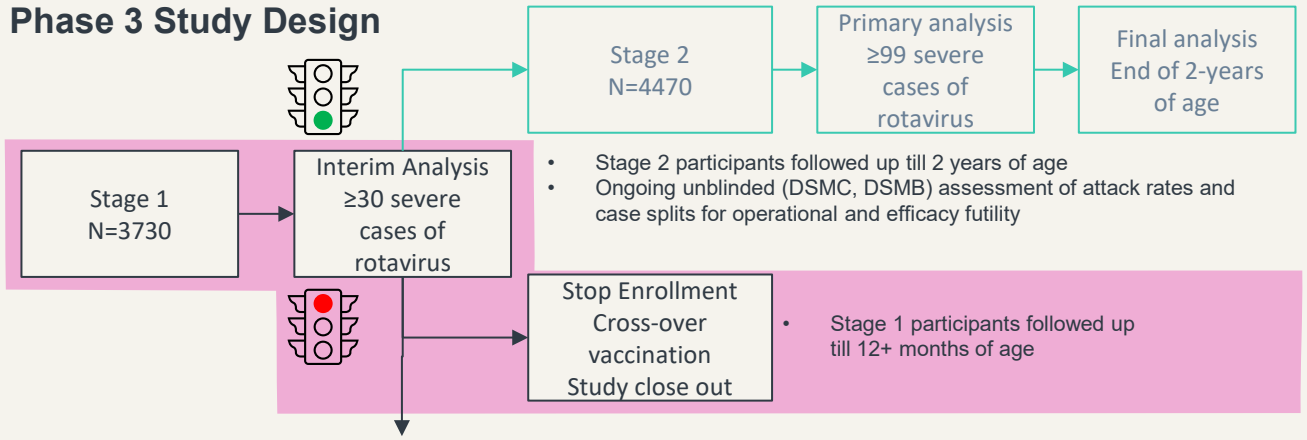
Intervention Target Product Profile	
Indication	Prevention of severe rotavirus gastroenteritis in infants
Target population	3 immunizations at approximately 6, 10, and 14 weeks of age
Efficacy	≥ 75%
Safety	Clinically acceptable safety profile
Route Of Admin.	IM
Cost	<$0.75/dose

Wen X et al. Vaccine 2014; Wen X et al. HVI 2015; Fix A et al. Vaccine 2015; Groome M et al. Lancet Infect Dis 2017 & 2020

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 and should be stopped.

Current activities

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

Possible explanations for trial outcome

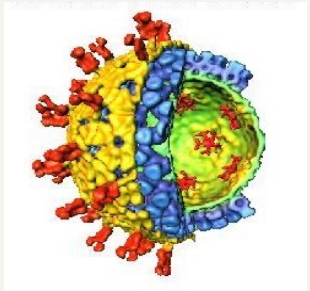
- Immune responses to VP8 subunit alone are not enough to elicit improved protection against severe disease from wildtype infection

- 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

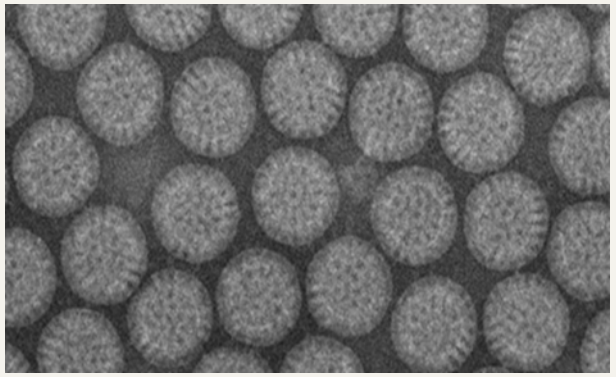
Cryz S and colleagues, unpublished data. Presented at WHO PDVAC meeting, December 2022

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

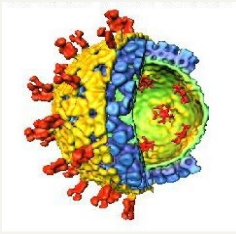
  Vaccine candidate:
  - Heat inactivated
  - Adjuvanted with aluminum hydroxide (2%)
  - Extensive animal testing showed highly immunogenic and proof of concept in gnotobiotic piglets (IgA and IgG)
  - 3 doses delivered via parenteral administration route (0.5ml)



Phase 1a safety and immunogenicity study underway at Emory University (USA)

- 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. Several IRVs in development in China



Zhifei LvHu Biopharmaceutical (licensed strain from CDC).

- Formalin inactivation
- Adjuvanted with aluminum hydroxide (2%)
- Delivered by IM (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.

Phase 1a safety and immunogenicity study

Dose escalation, age-descending, controlled study in 375 subjects:

Institute of Medical Biology, Chinese Academy of Medical Science (ZTR-68 strain).

- Grown in Vero cells
- Formalin inactivation
- Adjuvanted with aluminum hydroxide (2%)
- Delivered via parenteral administration route (0.5ml)

Phase 1a safety and immunogenicity study

Dose escalation, placebo-controlled study in 96 subjects

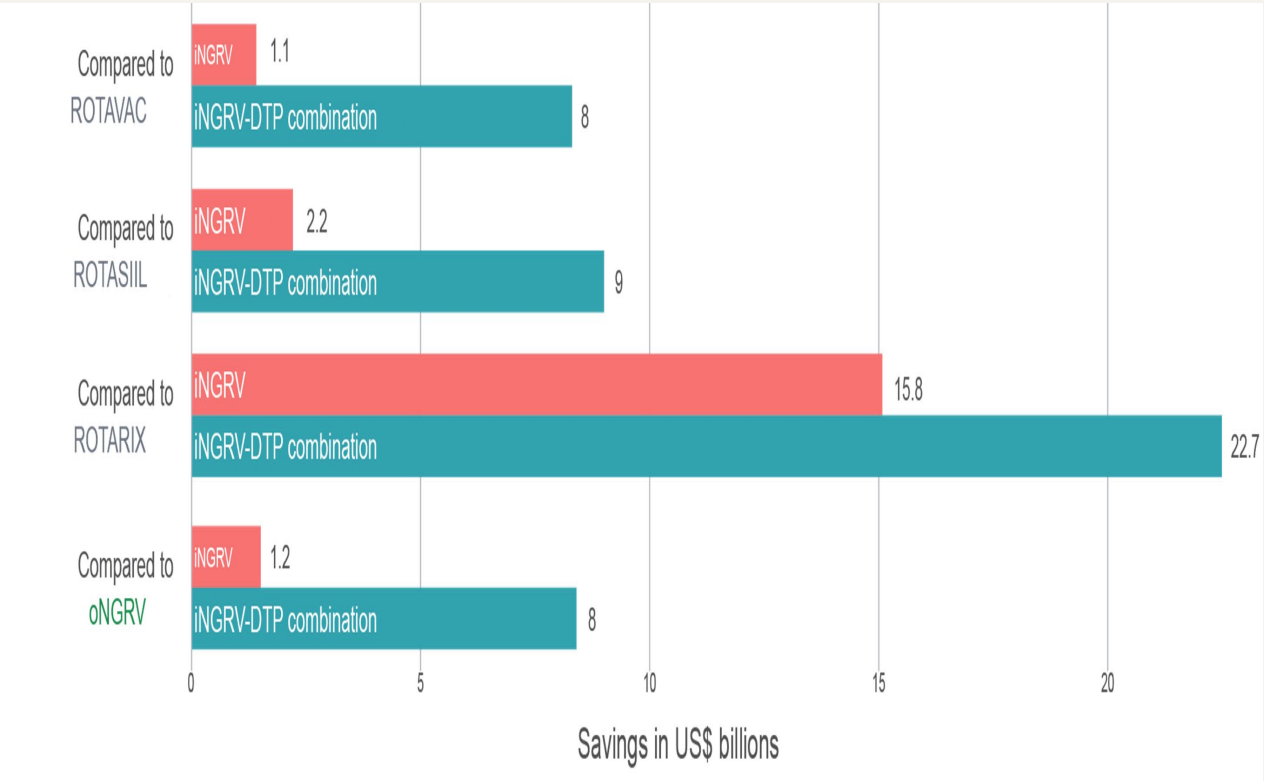
- Safety: No SAE vaccine associated.
- Immunogenicity: Good IgG, IgA, neutralizing ab responses

Wu et al, Vaccine 2024; 42: 4030-4039

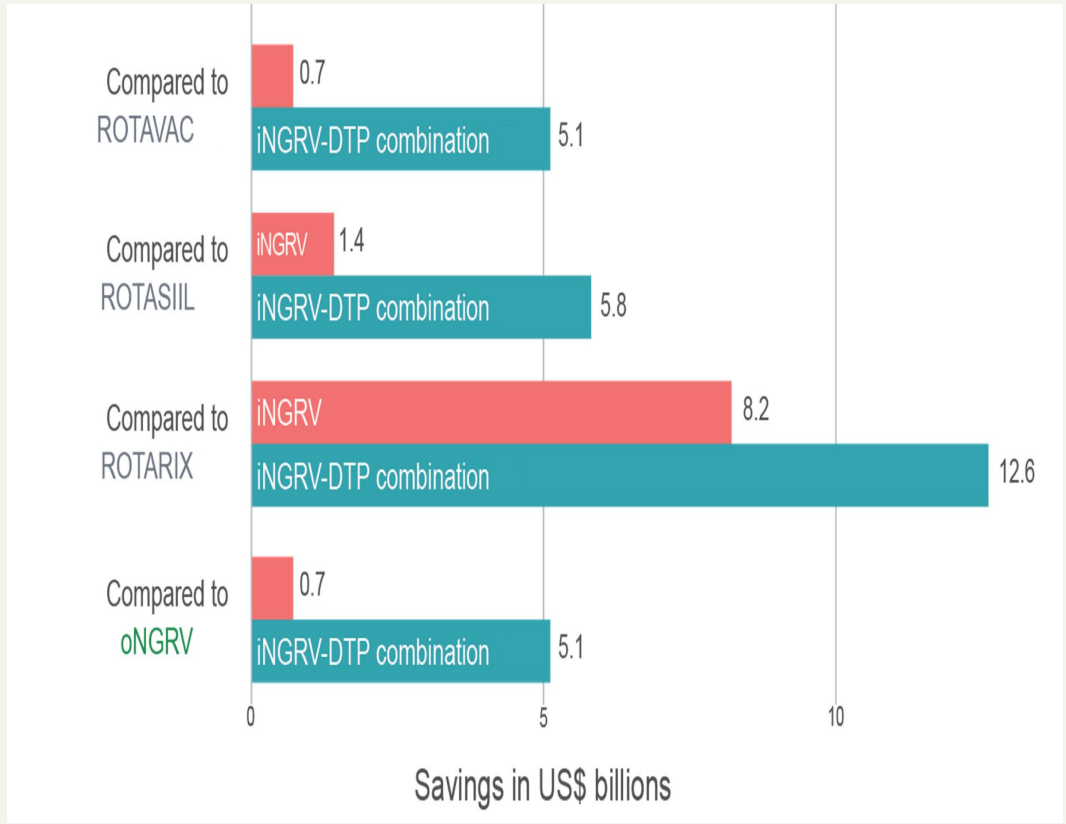
Impact and cost-effectiveness of injectable next generation rotavirus vaccines in 137 LMIC countries.

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

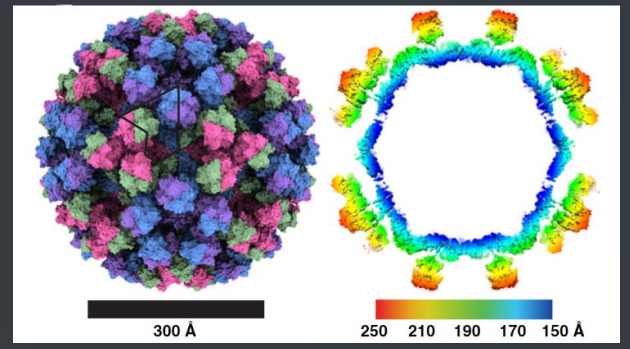
- Improve efficacy and duration of protection
- Enhance magnitude, onset and functionality of immune response by stimulating both cell-mediated and humoral immunity

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

Norovirus Vaccines



Burden: emerging as a recognized pathogen of significant impact

Significant global norovirus burden annually:

- 685 million cases; 200 million in <5 yrs
- 212,489 deaths; 54,214 in <5 yrs
- 85% of illnesses and 99% of deaths occur in developing countries

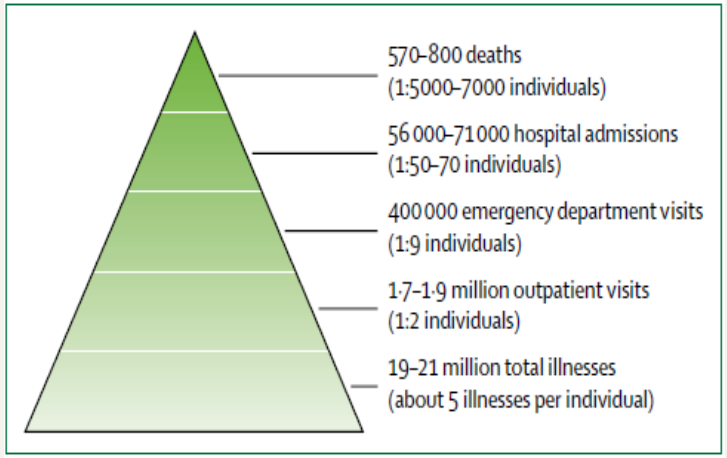
Global distribution of Norovirus:

- Many global epidemics of NoV in past decade (GII.4 strains)
- Significant impact: Outbreaks are common in schools, hospitals, congregate settings, cruise ships
- Epidemics attributed to contaminated food sources are common

Globally, the economic burden of norovirus is estimated to be $4.2 billion (95% UI: US$3.2–US$5.7 billion) in direct health systems cost. (Bartsch, ‘16)

Meta analysis (1990 – 2016) conducted using studies performed in developing countries, estimated prevalence of Norovirus was 17%.

Norovirus is responsible for ~12% of severe diarrhea in children in developed setting.



USA norovirus disease burden

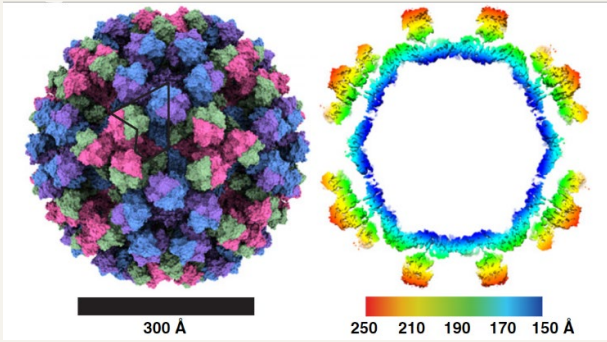
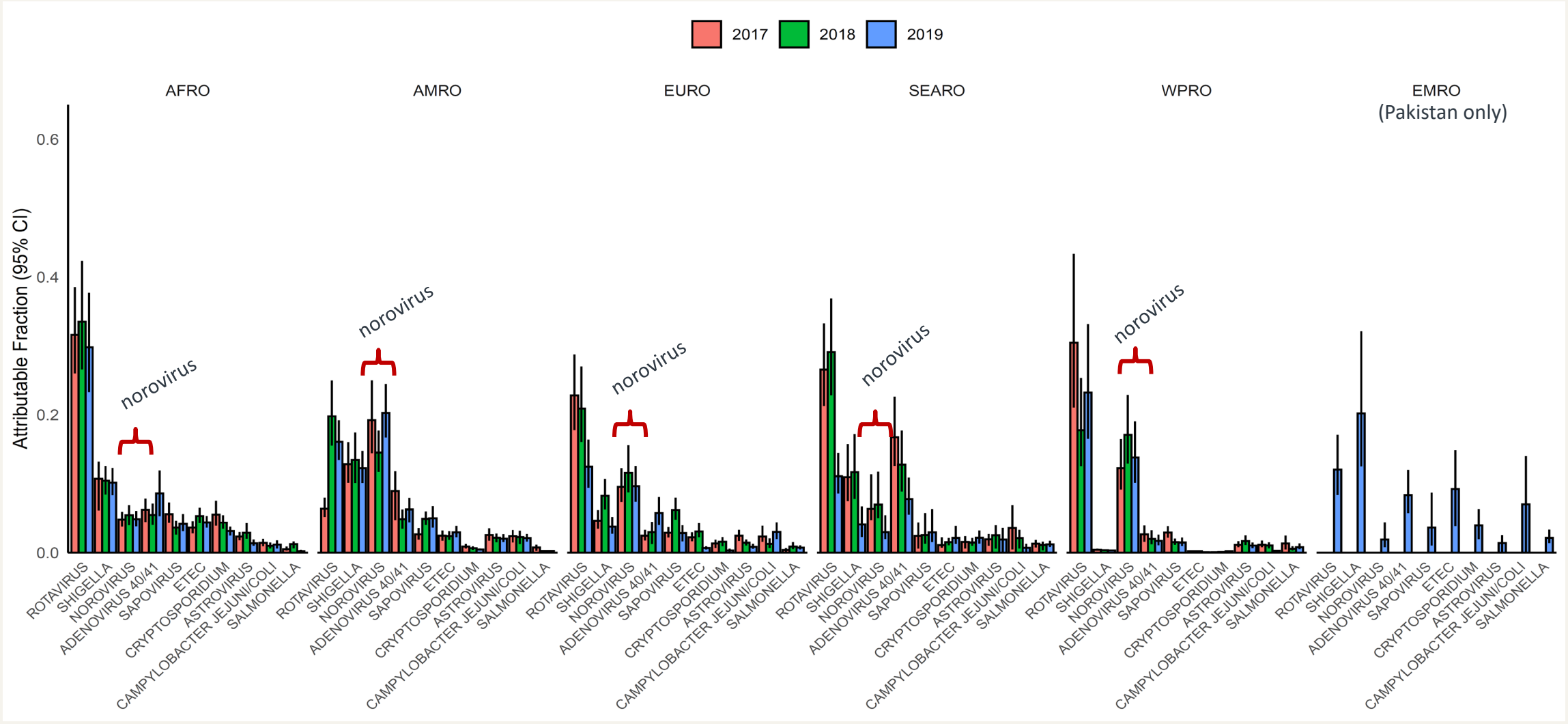


Image of norovirus GII.4 Minerva strain colored by subunit type (left), and a slice view of a GII.4 cryo-EM map colored by distance to center (right)

SOURCES: GBDS 2017-2018; Ronsman et al. Lancet 2010; 375:2041-31

GPDS 2017-2019: Attributable fractions of diarrheal hospitalization by pathogen by geography



SOURCES: GBDS 2017-2018 James Platts-Mills on March 23, 2022; Arowolo (2019) *J Med Virol*; Platts-Mills, Liu, et al (2018) *Lancet Glob Health*; Akdag (2020) *J Med*

Burden of Norovirus on other populations

In addition to burden in infants/children norovirus poses a significant burden to the elderly, military, traveler, and immunocompromised populations - added benefit for vaccine development.

Population of interest	Rates / Burden	Rationale for interest
Elderly / congregate living settings	• 1.2-4.8m NoV-associated illnesses, 40k-763k inpatient visits, 2000-13,000 NoV-associated deaths[2] • 10-20% of GE hospitalizations and 10-15% of GE deaths among older adults in high income and upper-middle income countries[2] • In the US, adults ≥65 yo experienced the highest rate of medically attended AGE due to NoV, after children <5 yo (4.5 episodes per PY, vs 20.4)[3]	• NoV causes a large number of AGE outbreaks globally among the elderly, especially those in congregate living settings
Military	• 40% of 2000 individuals deployed for 6 months to the Mediterranean reported acute diarrhea; 29% of those tested with diarrhea had a ≥4-fold rise in Norwalk-like virus (NLV) antibody titers, vs 14% of those tested without diarrhea[4] • Multiple outbreaks of AGE aboard US Navy aircraft carriers	• Active duty individuals living in close quarters are at higher risk of NLV infection and illness, impacting routine operations
Travelers	• Many cruise ships experience NoV-triggered AGE outbreaks[5], • 24% of diarrheal and AGE samples tested from OECD member country travelers to non-OECD countries were positive for either NoV GI or GII[7], and those infected with NoV are more likely to have severe AGE cases than many other pathogens[8]	• NoV is a frequently-detected pathogen in travelers' diarrhea • Travelers on cruise ships are susceptible to NoV illness, both due to close living quarters as well as common food sources
Immunocompromised	• 16.3% of immunocompromised children or children with hospital-acquired infection tested positive for NoV in a study in Atlanta[10] • Immunocompromised patients may experience chronic infection	• Immunocompromised patients, such as transplant and cancer patients, frequently experience significant NoV infection

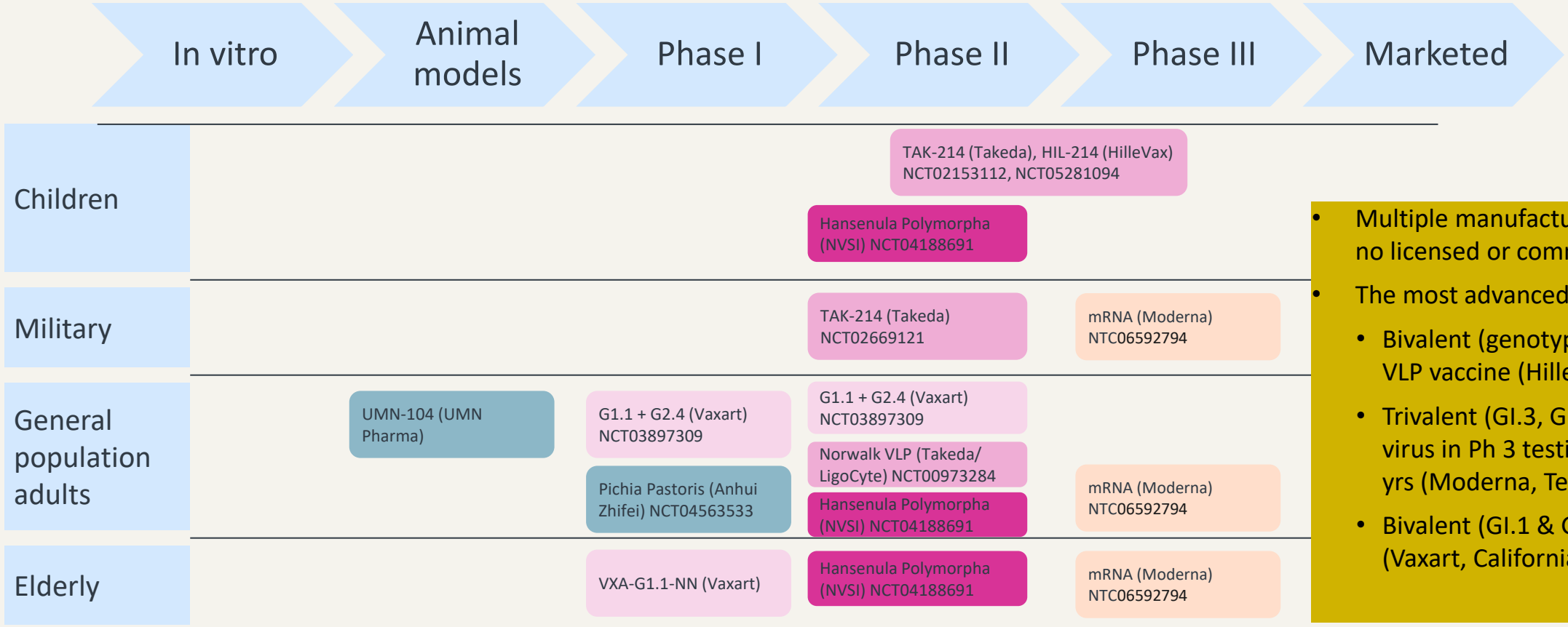
SOURCES: 1. Lee (2012) *Emerg Infect Dis*; 2. Lindsay (2015) *BMC Infect Dis*; 3. Burke (2021) *Clin Infect Dis*; 4. McCarthy (2000) *J Infect Dis*; 5. Wikswo (2011) *Clin Infect Dis*; 6. Isakbaeva (2005) *Emerg Infect Dis*; 7. Ashbaugh (2020) *Am J Trop Med Hyg*; 8. Ashbaugh (2021) *Trav Med Infect Dis*; 9. Apelt (2010) *BMC Infect Dis*; 10. Munir (2014) *J Med Virol*; 11. Bok and Green (2013) *NEJM*; 12. Green (2014) *Clin Microbiol Infect*; 13.

Norovirus Vaccine pipeline

Current Vaccine pipeline for Norovirus

NOT EXHAUSTIVE

- Several multivalent vaccines for norovirus are in clinical trials, and extensive research has been conducted *in vitro.*
- Current approaches use either a baculovirus-expressed viral like particle (VLP), mRNA LNP and an adenovirus vectored vaccine expressing VP1 proteins formulated in an oral tablet (GI.1/GII.4)
- Current studies in humans, suggest candidates to be safe and immunogenic in adults.



- Multiple manufacturers engaged, but no licensed or commercial product
- The most advanced vaccines are:
  - Bivalent (genotypes GI.1 & GII.4) VLP vaccine (HilleVax, Boston, USA)
  - Trivalent (GI.3, GII.4, GII.3) mRNA virus in Ph 3 testing in adults >18 yrs (Moderna, Texas, USA)
  - Bivalent (GI.1 & GII.4) oral vaccine (Vaxart, California, USA).

Last updated: September 9, 2025

1. Vaxart, CA – Adenovirus-vectored, oral vaccine

- Developed by Vaxart, biotech company.
  - Bivalent – GI.1 and GII.4
  - Adenovirus 5 vector platform (used for their influenza vaccine)
  - Formulated as an oral vaccine for delivery to gastro-intestinal tract.

Vaccine candidate:

- Adenovirus 5 vectored recombinant vaccine
  - VP1 gene of norovirus
- Adjuvanted with dsRNA
- Heat stable indication

- Intended as oral tablet for adults with a liquid formulation projected for children

A Phase 2 Double-Blind, Placebo-Controlled Study Showing Oral Tableted Norovirus Vaccine VXA-G1.1-NN is Immunogenic, Efficacious, and Reduces Viral Shedding Following Norovirus Challenge

Dr Sean Tucker, Vaxart. Presented at IDWeek, October 2024

Preliminary results of the Phase II trial (NCT05626803) of the oral pill bivalent showed robust immune responses across all doses at day 29. Both doses showed a similar increase in antibody responses with no statistical difference between the arms.

Increased serum IgA, IgG, and BT50 levels for both the GII.4 and GI.1 strains in the vaccine arms were comparable to those observed in previous norovirus studies conducted by Vaxart.

Results also showed that the oral bivalent vaccine candidate was well tolerated, with a favorable safety profile and no vaccine-related adverse events.

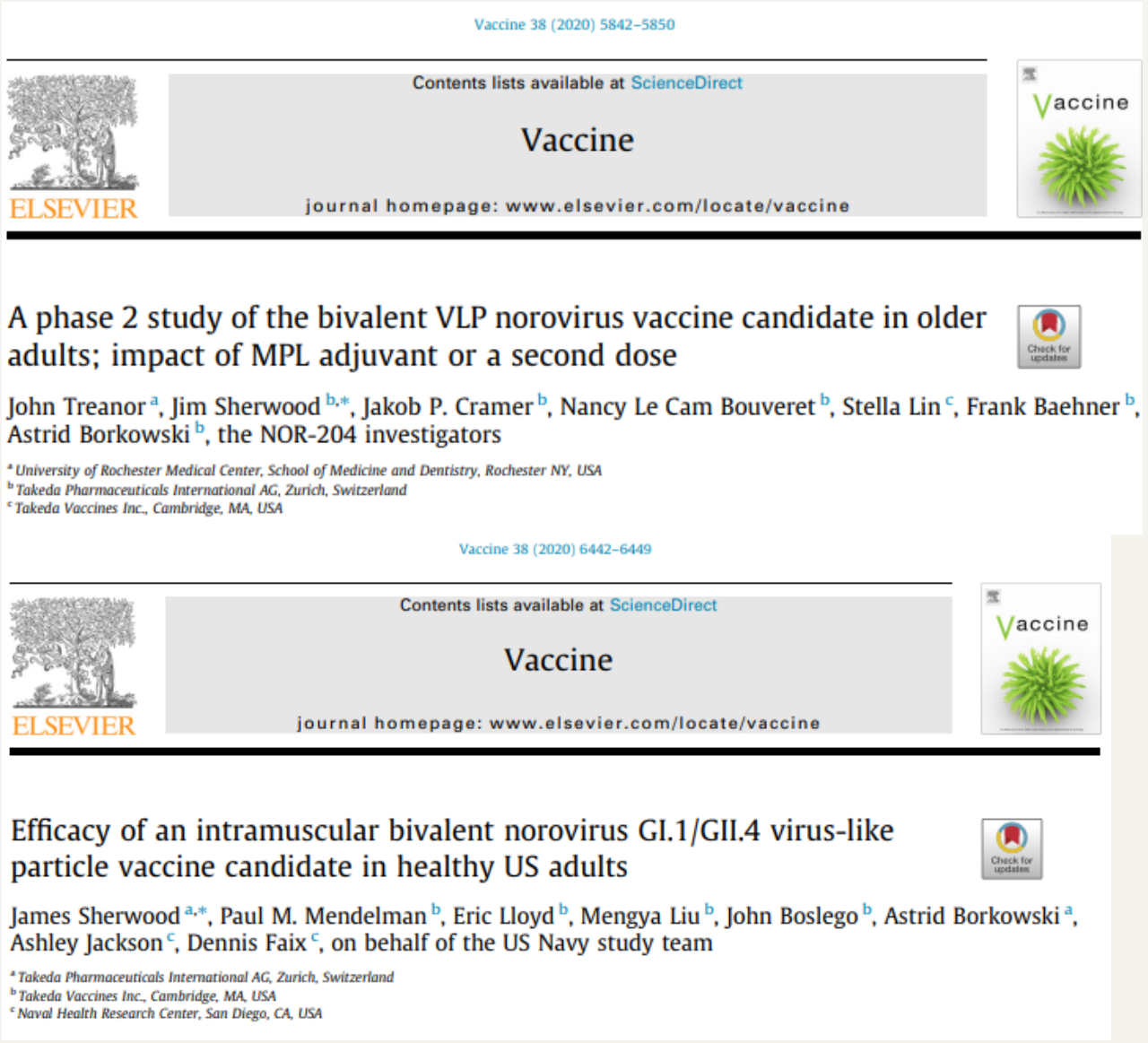
The study enrolled 135 healthy adults at three sites in the US. It was a multicentre, randomised, double-blind, placebo-controlled, single-dose, dose-ranging study to determine the safety and immunogenicity of the oral pill bivalent.

2. Takeda, Cambridge, MA – bivalent VLP vaccine

- Developed by Takeda.
  - Bivalent – GI.1 and GII.4
  - Baculovirus expressed VLPs
  - Norwalk GI.1 VLP cross reacts with other GI.1 strains
  - Strain GII.4c (derived from three GII.4 strains) to provide broad cross protection

Vaccine candidate:

- Vaccine had significant efficacy against all-type norovirus acute gastroenteritis.
- Some GII.2 cases in placebo recipients had immunity against vaccine GII.4c genotype.
- Candidate vaccine induces cross-protection against heterotypic norovirus strains



Vaccine 38 (2020) 5842–5850

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

A phase 2 study of the bivalent VLP norovirus vaccine candidate in older adults; impact of MPL adjuvant or a second dose

John Treanor [a], Jim Sherwood [b,*], Jakob P. Cramer [b], Nancy Le Cam Bouveret [b], Stella Lin [c], Frank Baehner [b], Astrid Borkowski [b], the NOR-204 investigators

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Efficacy of an intramuscular bivalent norovirus GI.1/GII.4 virus-like particle vaccine candidate in healthy US adults

James Sherwood [a,*], Paul M. Mendelman [b], Eric Lloyd [b], Mengya Liu [b], John Boslego [b], Astrid Borkowski [a], Ashley Jackson [c], Dennis Faix [c], on behalf of the US Navy study team

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Hillevax, Boston, MA – bivalent norovirus VLP vaccine (HIL-214)

Dr David Swerdlow, Hillevax at the 5th Chinese Meeting on Rotavirus and Norovirus Vaccines, Shanghai, May 2024

HIL-214 is a bivalent vaccine candidate consisting of VLPs representing two common genotypes (GI.1 and GII.4) and is co-formulated with an aluminum hydroxide adjuvant.

Clinical Experience from the Development of a Norovirus VLP Vaccine

- To date, HIL-214 has been studied in 9 completed human clinical trials with safety data from ~4,500 subjects and immunogenicity data from ~2,000 subjects.
- Two challenge studies:
  - LV01-103 with healthy volunteers with GI.1 Norovirus challenge
  - LV03-105 with healthy volunteers with GII.4 Norovirus challenge
- Ph 3 efficacy study (NOR-211 in US Navy recruits) has been done to support clinical efficacy of HIL-214 (NCT02669121).
  - **showed clinical proof of concept in 4712 adults in preventing norovirus-caused moderate-to-severe AGE**

Phase 2a program in infants and young children demonstrated poor efficacy (NCT05836012).

- The vaccine showed an efficacy of 5% in the 2,800 infants enrolled in the study aged four months of age at the time of enrolment in the US and Latin American countries, who had norovirus-related acute gastroenteritis.
- **The study did not meet the key endpoint of demonstrating efficacy against moderate or severe AGE events caused by the GI.1 or GII.4 norovirus genotypes**.

Current progress for Hillevax's VLP norovirus vaccine program

News report January 8, 2024

Collaboration leverages HilleVax's leading norovirus vaccine development expertise and adds a Phase 1-ready next-generation program to HilleVax's pipeline

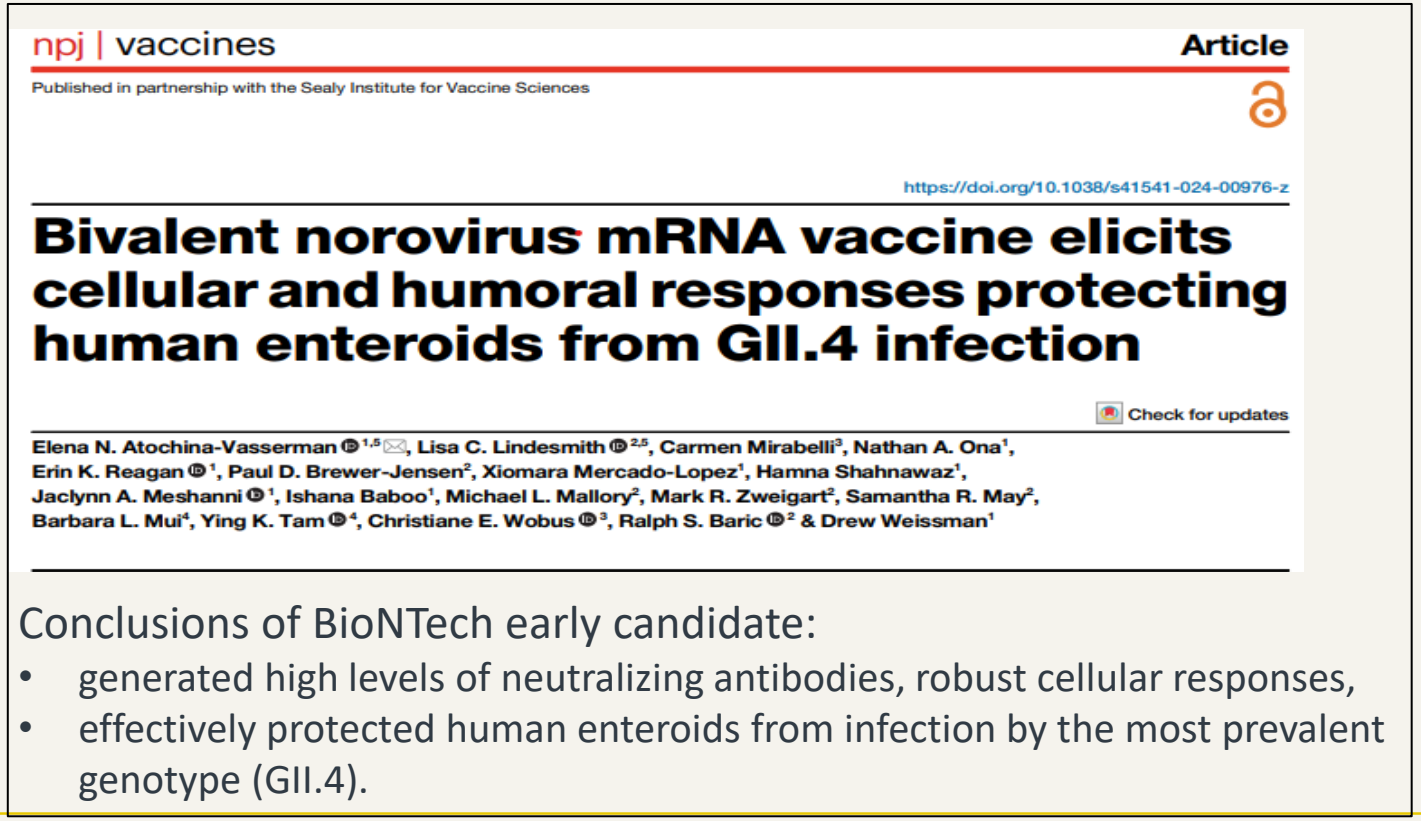
BOSTON and CHENGDU, China, Jan. 08, 2024 (GLOBE NEWSWIRE) -- HilleVax, Inc. (Nasdaq: HLVX), a clinical-stage biopharmaceutical company focused on developing and commercializing novel vaccines, and Chengdu Kanghua Biological Products Co., Ltd. (Kangh) (SHE: 300841), a biopharmaceutical company engaged in the research, development, production, and sale of bioproducts, today announced the entry into an exclusive license agreement for rights to Kangh's hexavalent virus-like particle (VLP) vaccine candidate for norovirus, referred to by HilleVax as HIL-216, outside of Greater China.

HIL-216 includes **VLPs for six of the most common norovirus genotypes, including GI.1, GII.2, GII.3, GII.4, GII.6, and GII.17**. The Investigational New Drug (IND) application for HIL-216 was cleared by the U.S. FDA in September 2023. As part of the exclusive license agreement, Kangh will supply HIL-216 for use in HilleVax's near-term clinical trials, including a Phase 1 trial that HilleVax expects to initiate in 2024

3. Moderna, TX – mRNA-1403 norovirus vaccine

Developed by Moderna

- Trivalent – GII.4, GI.3 and GII.3
- LNP technology used for Spikevax®/mRESVIA®
- Self-assembly of particles into VLPs



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Article

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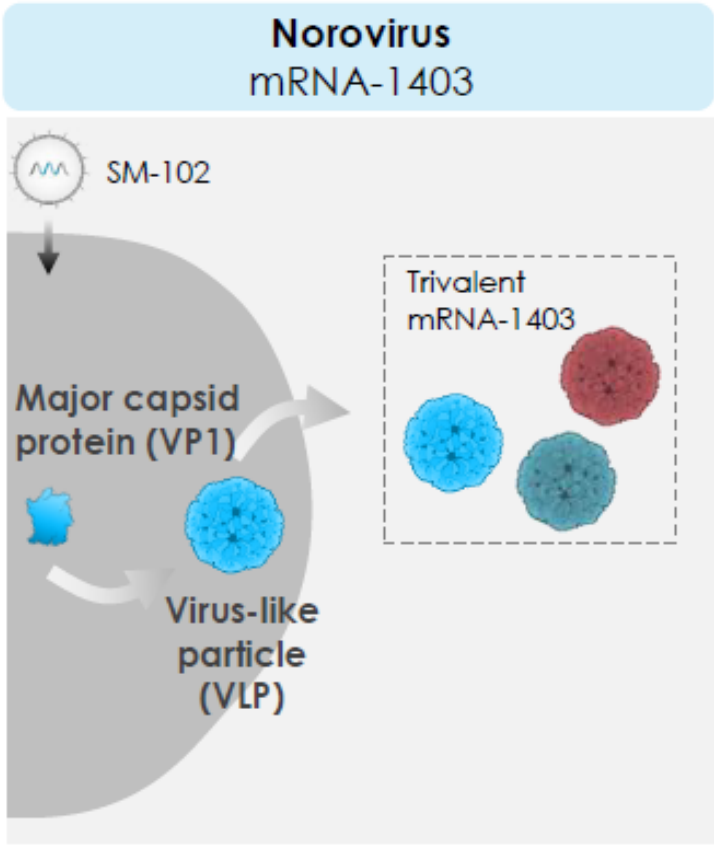
Bivalent norovirus mRNA vaccine elicits cellular and humoral responses protecting human enteroids from GII.4 infection

Check for updates

Elena N. Atochina-Vasserman[1,5], Lisa C. Lindesmith[2,5], Carmen Mirabelli[3], Nathan A. Ona[1], Erin K. Reagan[1], Paul D. Brewer-Jensen[2], Xiomara Mercado-Lopez[1], Hamna Shahnawaz[1], Jaclynn A. Meshanni[1], Ishana Baboo[1], Michael L. Mallory[2], Mark R. Zweigart[2], Samantha R. May[2], Barbara L. Mui[4], Ying K. Tam[4], Christiane E. Wobus[3], Ralph S. Baric[2] & Drew Weissman[1]

Conclusions of BioNTech early candidate:

- generated high levels of neutralizing antibodies, robust cellular responses,
- effectively protected human enteroids from infection by the most prevalent genotype (GII.4).



Dr Till Schoofs, Moderna. Presented at IDWeek, October 2024

Moderna's mRNA-1403 Ph 1/2 interim results

Dr Till Schoofs, Moderna. Presented at IDWeek, October 2024

Conclusions

- **Immunogenicity of mRNA-1403 in adults:**
  - A single injection of mRNA-1403 elicited robust serum HBGA-blocking antibody responses against all three NoV vaccine genotypes, across all dose levels evaluated in both younger and older adults
  - Similar findings were observed with serum VLP-binding antibody responses

- **Reactogenicity and safety of mRNA-1403 in adults:**
  - A single injection of mRNA-1403 was well-tolerated and showed a favorable reactogenicity profile across dose levels in both younger and older adults
  - No safety concerns identified through 8 months of follow-up in Ph1 and 1 month of follow-up in Ph2

Available data supported initiation of a Phase 3 study (NCT06592794) evaluating efficacy of a single dose primary schedule of mRNA-1403 in prevention of moderate to severe NoV AGE in adults

SOURCE: Slides with permission from Meklit Workneh, Moderna

Moderna's mRNA-1403 is in Phase 3 efficacy study

Recruiting

A Study to Investigate the Safety and Efficacy of mRNA-1403 in Participants ≥18 Years of Age for the Prevention of Acute Gastroenteritis (Nova 301)

ClinicalTrials.gov ID NCT06592794

Sponsor ModernaTX, Inc.

Information provided by ModernaTX, Inc. (Responsible Party)

Last Update Posted 2024-11-12

A Phase 3, Randomized, Observer-blinded, Placebo-controlled Study to Evaluate the Safety and Efficacy of mRNA-1403, a Multivalent Candidate Vaccine to Prevent Norovirus Acute Gastroenteritis in Adults ≥18 Years of Age.

The primary objectives of this study are to evaluate the safety and reactogenicity of mRNA-1403, and to demonstrate the efficacy of mRNA-1403 to prevent protocol-defined moderate or severe norovirus acute gastroenteritis (AGE) associated with vaccine matched genotypes.

Source: clinicialtrials. gov

National Vaccine and Serum Institute, Hebei, China

Hansenula polymorpha yeast-based expression system

Completed

A Clinical Trial to Evaluate the Safety and Immunogenicity of Norovirus Bivalent Vaccine

ClinicalTrials.gov ID NCT04188691

Sponsor National Vaccine and Serum Institute, China

Information provided by National Vaccine and Serum Institute, China (Responsible Party)

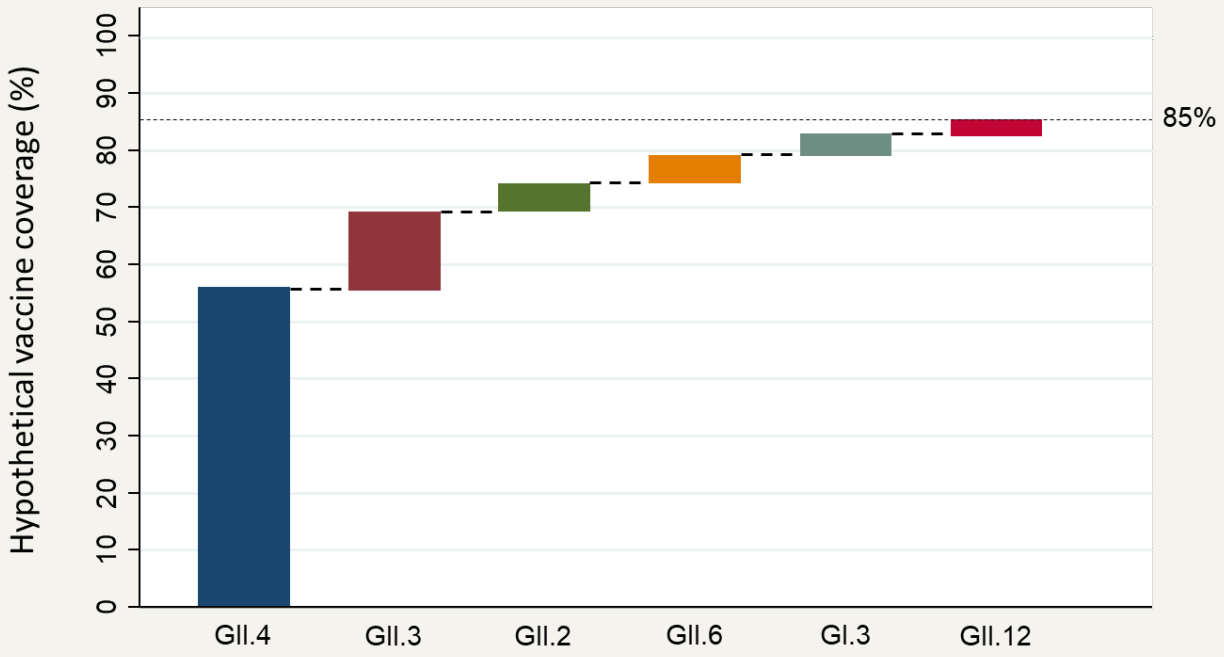
Last Update Posted 2021-04-22

- A total of 450 subjects were enrolled, divided into four age groups - 18-59 years, 6-17 years, 3-5 years, and 6-35 months.
- Three dosages of the test vaccine component in each age group. A total of 30 people in each dose group were vaccinated with the test vaccine or placebo 1 (saline) or placebo 2 (Al adjuvant), respectively, in a ratio of 3: 1: 1.
- The 18-59-year-old, 6-17-year-old, and 3-5-year-old age groups were vaccinated 2 times at a time interval of 28 days.
- The 6-35-month age group is divided into two groups
  - Group 1 is inoculated with 2 doses interval of 28 days each, and
  - Group 2 is inoculated with 3 doses interval of 28 days.

CROSS PROTECTION – challenge to NV vaccine success

Norovirus immunity is short-lived and does not generally provide good cross-strain immunity. This means that one can get norovirus multiple times in a short period of time if exposed to different strains. Most natural history studies have found that immunity to the same norovirus strain lasts less than six months. How long will vaccine protect?

Figure Step-coverage Assessment for a Hypothetical Norovirus Vaccine by Genotype



Classification of Noroviruses: ten genogroups (GI-GX) and 48 genotypes; only viruses from GI (n=9), GII (n=23), GIV (n=1), GVIII (n=1) and GIX (n=1) are known to cause human infections

- The level of cross-protection afforded to VLP-based vaccine against non-included genotypes is an important area of discovery. (HilleVax – Ph2 data suggests yes)
- Approximately 6 genotypes (GI.3, GII.2, GII.3, GII.4, GII.6, and GII.12) would be needed to achieve 85% coverage of the dominant genotypes circulating.
- Among the four candidates, all four target GII.4, but only one targets GII.3. Whether a GII.4 / GII.3 provides enough coverage and protection to provide a useful too is uncertain.

Summary: Disease Burden justifies development programs, however...

- Current vaccine pipeline although not extensive, is promising. Still significant challenges - immunity/cross protection
- While there are a number of promising vaccines under development, achieving a high level of strain coverage may be difficult with genotype-specific vaccines lacking heterologous neutralization. However, a vaccine may not require high levels of coverage to be of value.
- Recent epitope knowledge and mapping may open doors to novel and broadly protective norovirus vaccine designs.

- Many needs exist -> Full Public Health Value Proposition; Policy and regulatory pathway unknown.