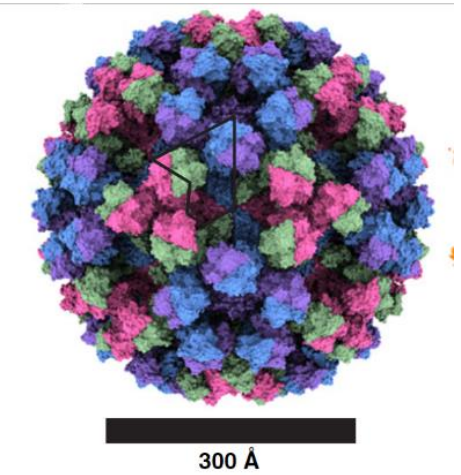
Norovirus Vaccine Pipeline

Carl Kirkwood & Duncan Steele

Bill & Melinda Gates Foundation

WHO PDVAC Meeting, Geneva.

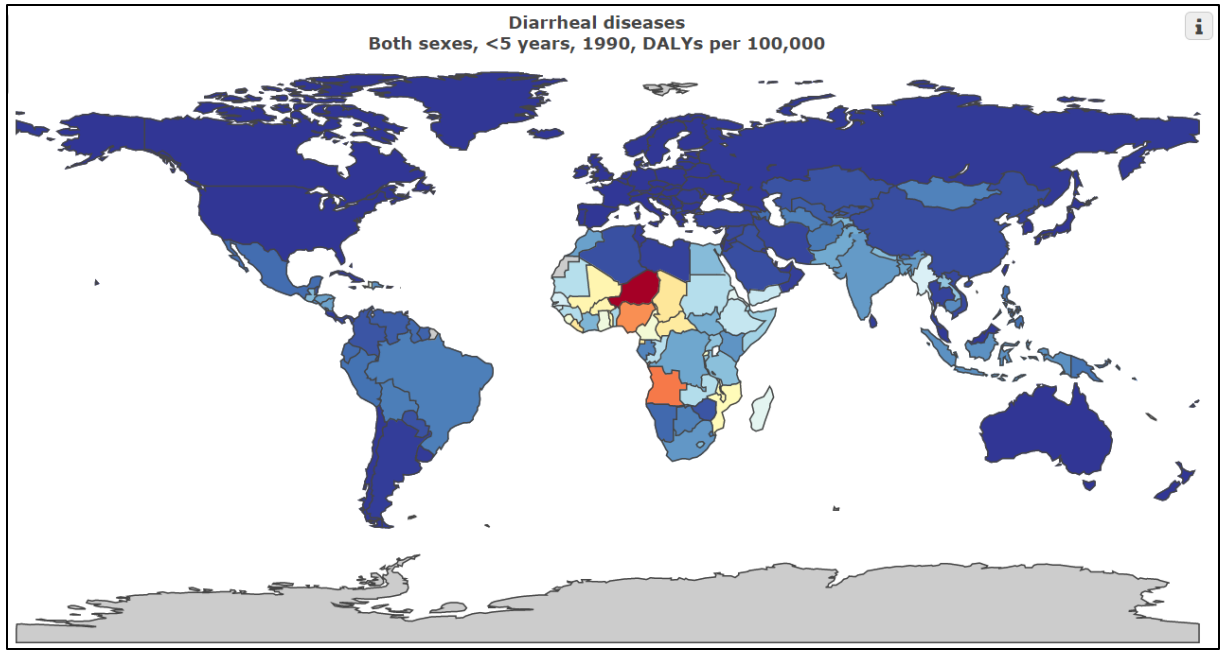
11 December 2024.

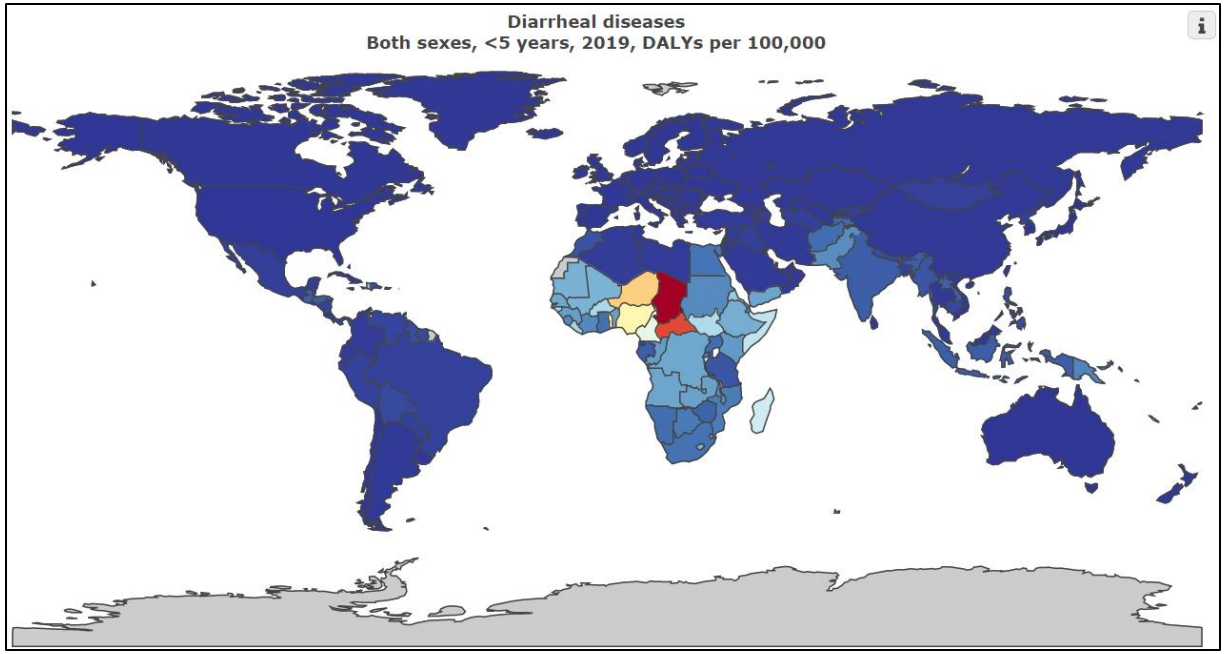


Diarrhea contributes to ~500k deaths in children under 5 every year

Although the burden of diarrheal diseases has decreased in most countries over the past two decades, it remains a leading cause of disability-adjusted life years in the under-5 population (~10%)

Despite progress in childhood vaccinations, there were 5.3 million deaths among children under 5 years in 2019, 9.1% of which was attributable to diarrhea (est. 480,000 deaths)





SOURCES: Global Burden of Disease 2019, 1. Perin (2022) *Lancet Child Adolesc Health;*

Last updated: December 17, 2024

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

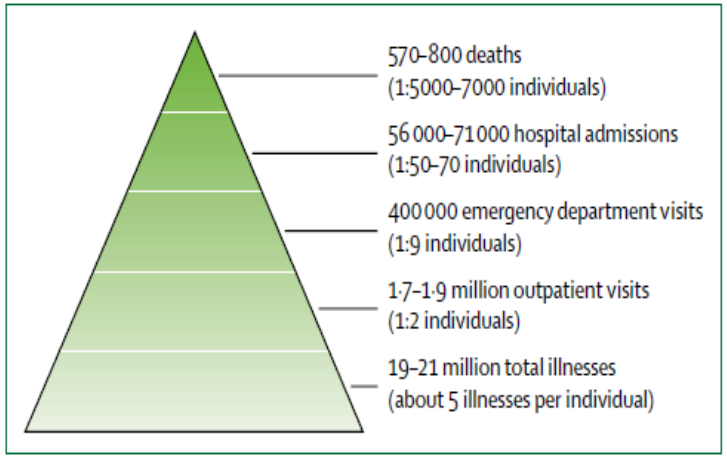
Global distribution of Norovirus:

- 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

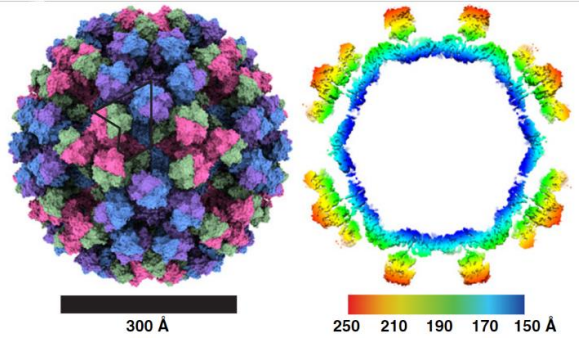
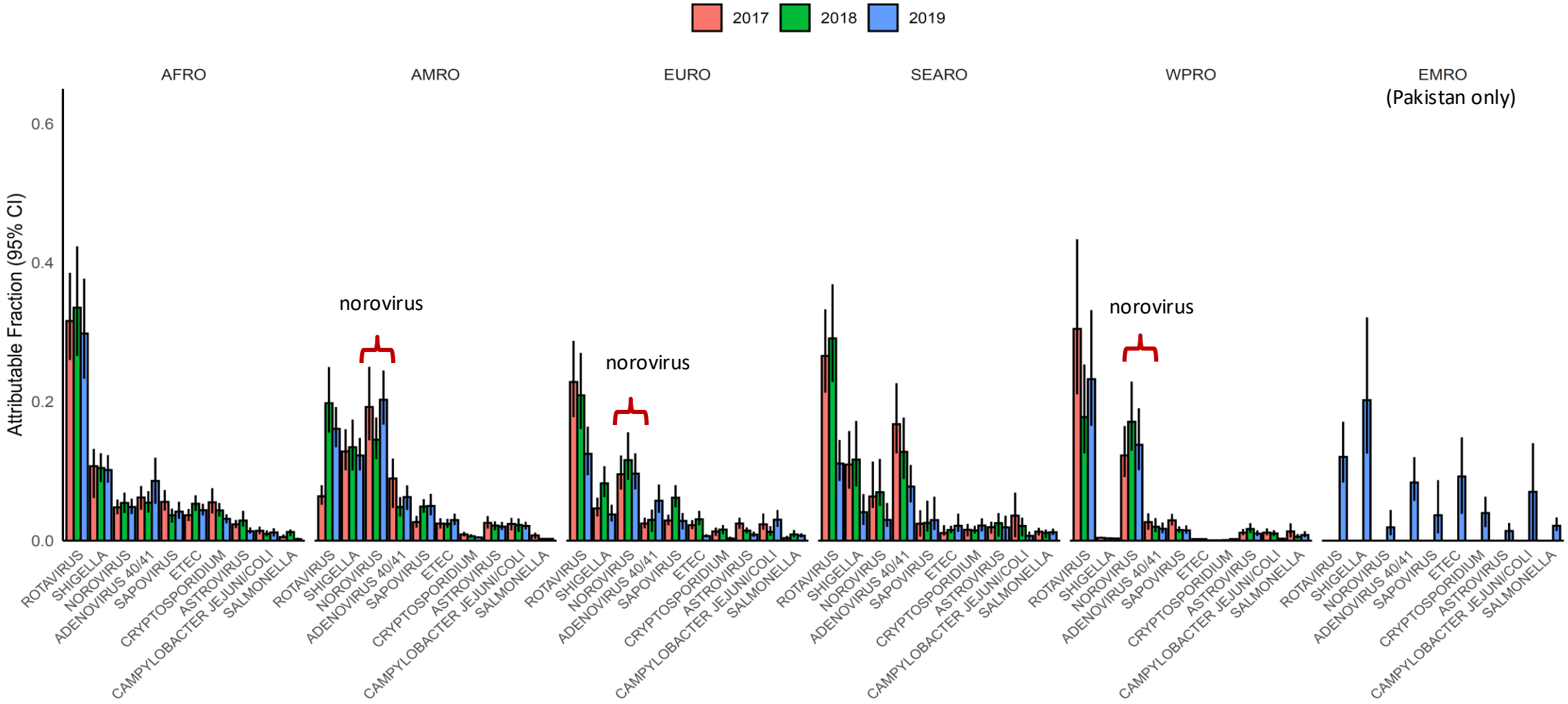


Image of norovirus GII.4 Minerva strain colored by subunit type (left), and a slice view of a GII.4 cryo-EM map colored by distance to center (right)

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

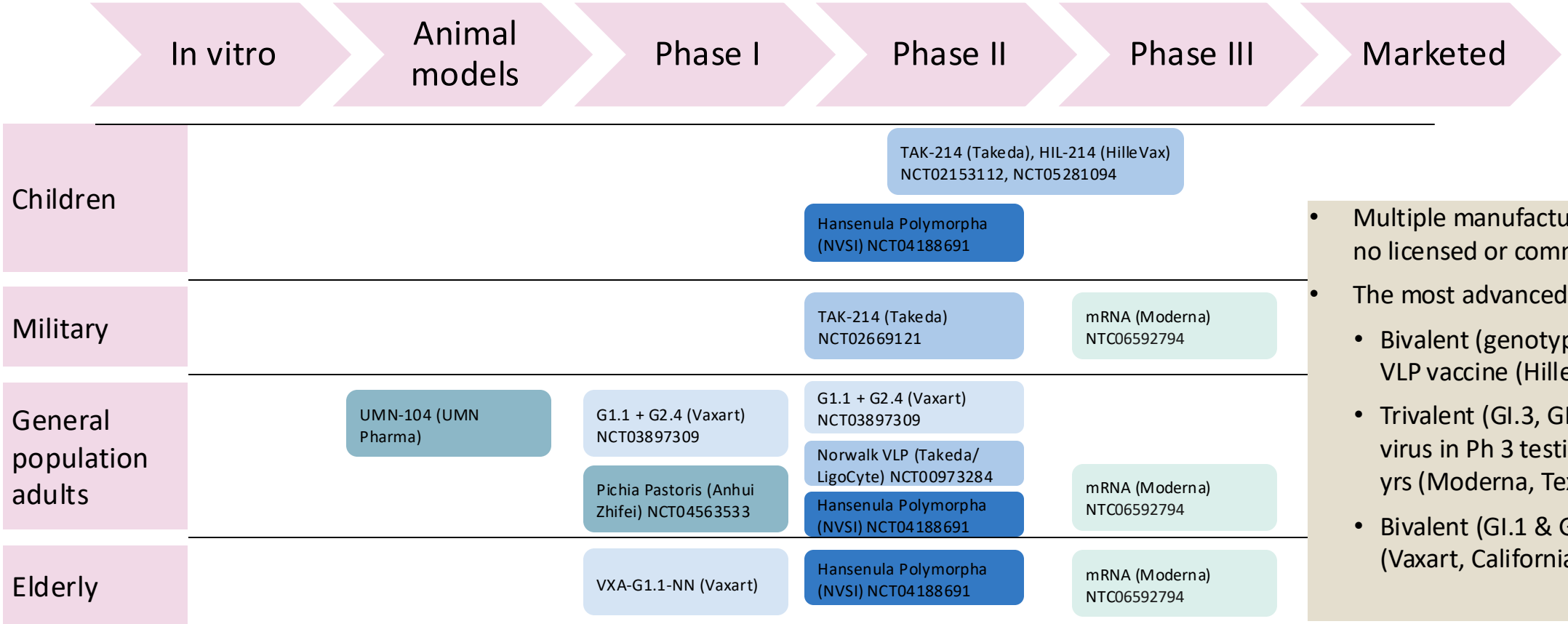
SOURCES: 1. Lee (2012) *Emerg Infect Dis*; 2. Lindsay (2015) *BMC Infect Dis*; 3. Burke (2021) *Clin Infect Dis*; 4. McCarthy (2000) *J Infect Dis*; 5. Wikswo (2011) *Clin Infect Dis*; 6. Isakbaeva (2005) *Emerg Infect Dis*; 7. Ashbaugh (2020) *Am J Trop Med Hyg*; 8. Ashbaugh (2021) *Trav Med Infect 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) or novel Pichia expression system, 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).

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

NOT EXHAUSTIVE

Vaxart – Adenovirus 5 vectored bivalent norovirus vaccine candidate

A Phase 1, Open-label, Safety and Immunogenicity Study of an Oral Multi-dose Administration Regimen With an Adenoviral-vector Based Tablet Norovirus Vaccine (VXA-G1.1-NN) Expressing GI.1 VP1 Administered to Healthy Adult Volunteers. **NCT05213728 / 8**

A Phase 1b, Open-label, Boost-optimization Study of an Adenoviral- Vector Based Oral Norovirus Vaccine (VXA-G1.1-NN) Expressing GI.1 VP1 Administered Orally to Healthy Adult Volunteers. **NCT04875676 / 30**

A Phase 1b, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Determine the Safety and Immunogenicity of an Adenoviral-vector Based Oral Norovirus Vaccine Expressing GI.1 VP1 Administered Orally to Health Stable Older Adult Volunteers 55-80 Years of Age. **NCT04854746 / 66**

A Ph 1b, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Safety and Immunogenicity Study of Adenoviral-vector Based Oral Norovirus Vaccines Expressing GI.1 or GII.4 VP1 With Monovalent or Bivalent Dosing. **NCT03897309 / 86**

A Phase 2b Double-Blinded, Randomized, Placebo-Controlled, Human Norovirus GI.1 (Norwalk Virus Inoculum) Challenge Study Following Administration of an Oral, Single-dose Norovirus Vaccine Expressing GI.1 VP1 and dsRNA Adjuvant to Protect Against Norovirus Gastroenteritis (NVG) in Healthy Adult Volunteers. **NCT05212168 / 165**

A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled, Single Dose, Dose-ranging Study to Determine the Safety and Immunogenicity of Bivalent GI.1 and GII.4 Vaccine Administered Orally to Healthy Volunteers Aged Greater Than or Equal to 18 Years and Less Than or Equal to 80 Years Old. **NCT05626803 / ongoing 135**

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.

A Phase I, Multicenter, Randomized, Double-blind, Placebo-controlled Single Dose, Dose-ranging Study to Evaluate the Safety, Tolerability, and Immunogenicity of Orally Administered Bivalent GI.1/GII.4 Norovirus Vaccine in Healthy Lactating Females ≥ 18 years Old and Their Breast-feeding Infants

Dr Lam Nguyen, Vaxart. Presented at IDWeek, October 2024

2. Takeda, Cambridge, MA – bivalent VLP vaccine

- Developed by Takada.
  - 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

[a] University of Rochester Medical Center, School of Medicine and Dentistry, Rochester NY, USA
[b] Takeda Pharmaceuticals International AG, Zurich, Switzerland
[c] Takeda Vaccines Inc., Cambridge, MA, USA

Vaccine 38 (2020) 6442–6449

Contents lists available at ScienceDirect

Vaccine

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

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

[a] Takeda Pharmaceuticals International AG, Zurich, Switzerland
[b] Takeda Vaccines Inc., Cambridge, MA, USA
[c] Naval Health Research Center, San Diego, CA, USA

NOT EXHAUSTIVE

Takeda clinical trials of bivalent norovirus vaccine candidate

A Phase II, Randomized, Double-blind, Safety and Immunogenicity Trial of Norovirus GI.1/GII.4 Bivalent Virus-Like Particle Vaccine in Healthy Elderly Adults. **NCT02661490 / 325**

A Phase II, Randomized, Double-Blind, Dosage, Safety and Immunogenicity Trial of Intramuscular Norovirus GI.1/GII.4 Bivalent Virus-Like Particle Vaccine Combined With Aluminum Hydroxide Adjuvant in Children, Toddlers, and Infants. **NCT02153112 / 840**

Phase II, Randomized, Placebo-controlled, Double-blind, Safety and Immunogenicity Trial of Intramuscular Norovirus GI.1/GII.4 Bivalent Virus-Like Particle Vaccine in Healthy Adults. **NCT02142504 / 450**

A Phase 2, Long-Term Immunogenicity Follow-up Trial of Adult and Elderly Subjects Who Have Previously Received an Intramuscular Injection of Norovirus GI.1/GII.4 Bivalent Virus-Like Particle Vaccine. **NCT03039790 / 575**

Phase 1-2, Randomized, Multi-Center, Double-Blind, Placebo-Controlled, Safety, Immunogenicity, and Efficacy Study in Healthy Adults of Intramuscular Norovirus Bivalent Virus-like Particle Vaccine in Experimental Human Norovirus GII.4 Disease. **NCT01609257 / 132**

A Phase II, Randomized, Controlled, Double-Blind, Dosage and Adjuvant Justification, Safety and Immunogenicity Trial of Intramuscular Norovirus GI.1/GII.4 Bivalent Virus-Like Particle Vaccine Adjuvanted With or Without Monophosphoryl Lipid A and Aluminum Hydroxide in Adults. **NCT02038907 / 420**

Phase 2b, Double-Blind, Randomized, Placebo-Controlled Trial to Evaluate the Efficacy and Immunogenicity of the Intramuscular Norovirus GI.1/GII.4 Bivalent Virus-like Particle Vaccine in Healthy Adults Aged 18 - 49 Years. **NCT02669121 / 4748**

clinicaltrials.gov

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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 (AGE). 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

npj | vaccines

Article

Published in partnership with the Sealy Institute for Vaccine Sciences

https://doi.org/10.1038/s41541-024-00976-z

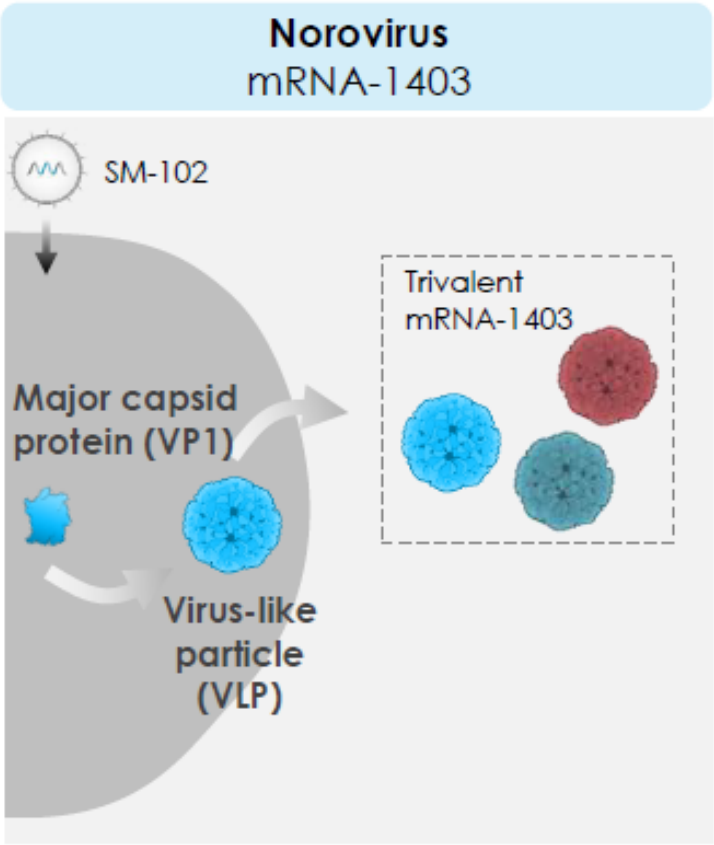
Bivalent norovirus mRNA vaccine elicits cellular and humoral responses protecting human enteroids from GII.4 infection

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).

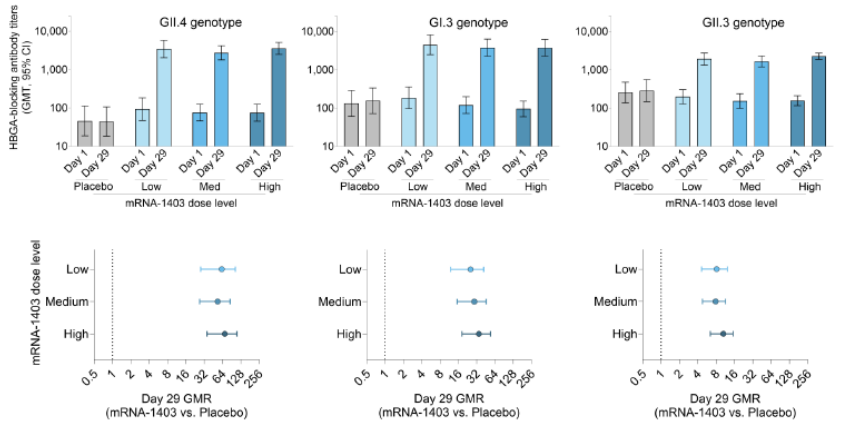


Dr Till Schoofs, Moderna. Presented at IDWeek, October 2024

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

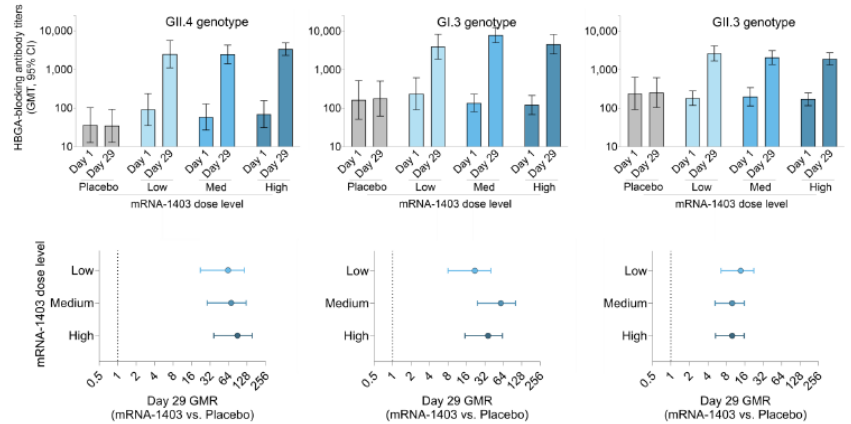
Dr Till Schoofs, Moderna. Presented at IDWeek, October 2024

Immunogenicity of single injection mRNA-1403 in Phase 2: Serum HBGA-blocking antibodies in younger adults (18-59 years of age)



- A single injection of mRNA-1403 elicited robust HBGA-blocking antibody titers against all three vaccine-matched NoV genogroup I and II genotypes in younger adults across all dose levels

Immunogenicity of single injection mRNA-1403 in Phase 2: Serum HBGA-blocking antibodies in older adults (60-80 years of age)



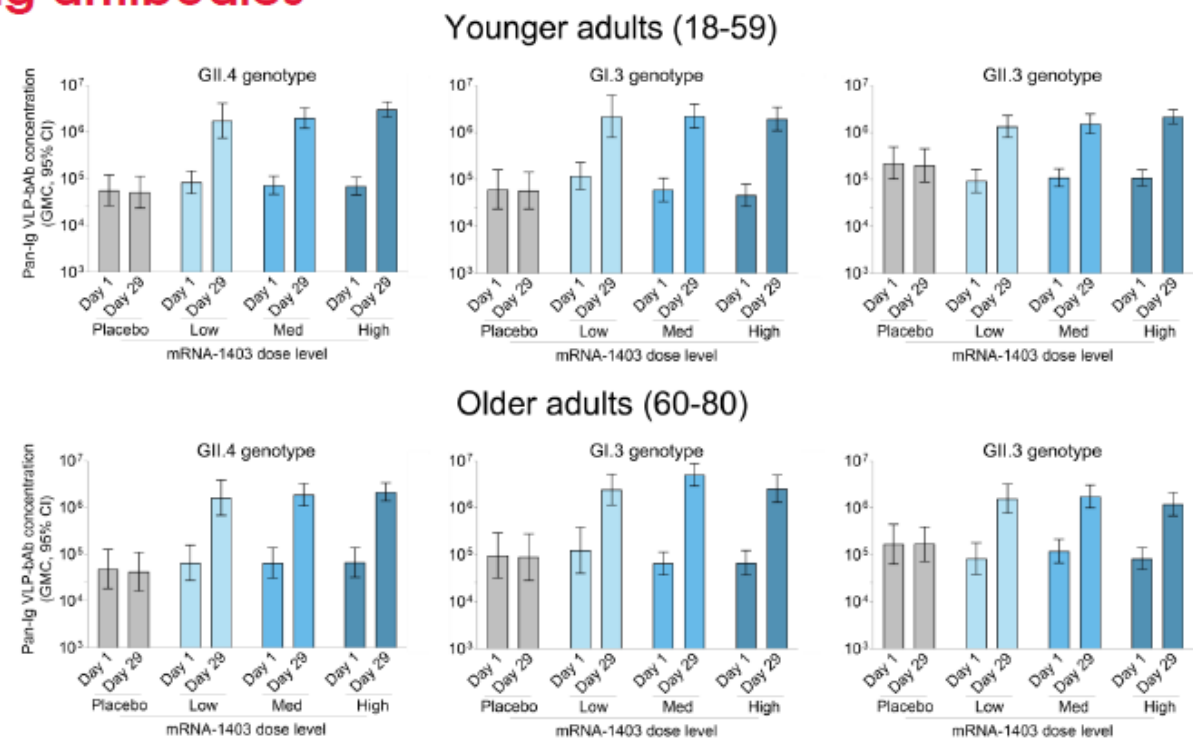
- A single injection of mRNA-1403 elicited robust HBGA-blocking antibody titers against all three vaccine-matched NoV genogroup I and II genotypes in older adults across all dose levels (similar to responses elicited in younger adults)

SOURCE: Slides with permission from Meklit Workneh, Moderna

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

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

Immunogenicity of single injection mRNA-1403 in Phase 2: Serum VLP-binding antibodies



- A single injection of mRNA-1403 also elicited robust Pan-Ig NoV VLP-binding antibody levels against vaccine-matched NoV genogroup I and II genotypes in both younger and older adults

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.

Clinical Investigation of Quadrivalent Human Recombinant Noroviruses Vaccine (Pichia Pastoris)

Dr. En-Qi Huang, Anhui Zhifei Longcom Biopharmaceutical Co., Ltd presented at the 5th Chinese Meeting on Rotavirus and Norovirus Vaccines, Shanghai, May 2024

The Quadrivalent Human Noroviruses Vaccine (*Pichia Pastoris*) utilizes gene recombination engineering technology and features the antigen protein which was rationally selected from four norovirus strains GI.1, GII.3, GII.4, and GII.17.

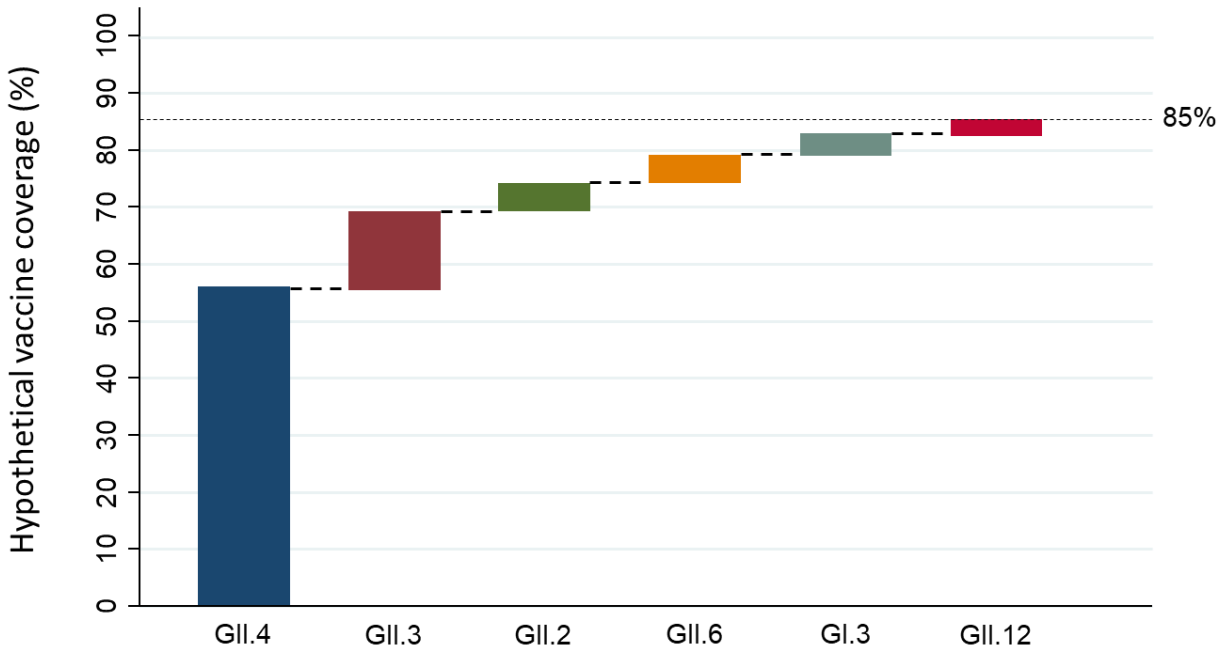
Phase I and IIa demonstrate good safety and immunogenicity of the vaccine, with the high-dose vaccine group exhibits superior immunogenicity, particularly in the population aged 6 weeks to 13 weeks. There's a good correlation between HBGA blocking antibodies and IgG binding antibodies.

Phase III study is being planned.

CROSS PROTECTION – challenge to NV vaccine success

Norovirus immunity is short-lived and does not generally provide good cross-strain immunity. This means that you can get norovirus multiple times in a short period of time if you're exposed to different strains. Most 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.

Are any existing non-vaccine treatment options feasible?

It is unlikely that any non- vaccine treatments for norovirus will replace the use case for a vaccine, given the likely cost and lack of proof of efficacy in infants.

Treatment	Details
Probiotics	• There is a possibility that probiotics will have an impact on norovirus-specific gastroenteritis, although clinical trials thus far have shown limited, and at best conflicting evidence on probiotics' impact on rotavirus- and norovirus-caused diarrhea[1,2,3,4,5] • A study of vitamin A in mice suggests it stimulates Lactobacillus sp. and has antiviral effects on murine norovirus[6]
Oral rehydration solutions	• Effect on Nov-specific diarrhea is likely to be similar to that of all-cause diarrhea[7]
Nitazoxanide (NTZ, Alinia)[8]	• Currently undergoing phase 2 clinical trials for treatment of norovirus in transplant patients (NCT03395405); Has undergone phase 2/3 trials for treatment of diarrhea in children (NCT00302640), with results indicating shortening of disease duration[9]; inhibits replication *in vitro*[10]; has been approved for use in *Crytosporidium* and *Giardia* treatment, currently in clinical trials for SARS-CoV-2[8,11]

SOURCES: 1. . Freedman (2018) *NEJM*; 2. Huang (2014) *J Clin Gastroenterol*; 3. Grandy (2010) *BMC Infect Dis*; 4. Freedman (2021) *Clin Infect Dis*; 5. Oberhelman (1999) *J Pediatr*; 6. Lee (2017) *Gut Microbes*; 7. Munos (2010) *Int J Epidemiol*; 8. ClinicalTrials.gov; 9. Rossignol (2006) *Lancet* for rotavirus only, Rossignol (2006) *Ailment Pharmacol Ther* for norovirus and rotavirus; 10. Dang (2018) *Antimicrob Agents Chemother*; 11. Accessdata.fda.gov; 12. Hanajiri (2020) *J Infect Dis*; 13. Van Dycke (2018) *J Infect Dis*

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

NOROVIRUS:

- 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 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.

- ➢ How does PDVAC consider the merit of developing a parenteral norovirus vaccine for infants as a stand-alone vaccine, vs a combination, for LMIC use?
- ➢ Does PDVAC agree that the Norovirus candidates should be considered in the vaccine combination framework, under development by WHO and PATH?
- ➢ Given interest in 'life-course' vaccination, is the elderly indication encouraging or is this paused?