

Vaccine value profile for norovirus

George Armah^a, Ben A. Lopman^b, Jan Vinjé^c, Miguel O’Ryan^d, Claudio F. Lanata^e, Michelle Groome^f, Jared Ovitt^g, Caroline Marshall^h, Elizabeth Sajewski^b, Mark S. Riddle^{g,*}

^a Noguchi Memorial Institute for Medical Research, University of Ghana, Legon, Ghana

^b Department of Epidemiology, Emory University Rollins School of Public Health, Atlanta, GA, USA

^c Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA

^d Microbiology and Mycology Program, Faculty of Medicine, University of Chile and Instituto de Sistemas Complejos de Ingeniería (ISCI), Santiago, Chile

^e Instituto de Investigación Nutricional, Lima, Peru

^f National Institute for Communicable Diseases, National Health Laboratory Services, Johannesburg, South Africa; School of Pathology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

^g Office of Medical Research, University of Nevada, Reno School of Medicine, Reno, Nevada, USA

^h World Health Organization, Geneva, Switzerland

ARTICLE INFO

Article history:

Available online 6 October 2023

Keywords:

Vaccines
Policy
Global Health
Vaccine value

The development of this Vaccine Value Profile has been commissioned by WHO’s Immunization, Vaccines and Biologicals (IVB) department on the recommendation of IVB’s Product Development for Vaccines Advisory Committee, to the Bill & Melinda Gates Foundation. All authors are independent subject matter experts and the authors alone are responsible for the views expressed in this manuscript.

ABSTRACT

Norovirus is attributed to nearly 1 out of every 5 episodes of diarrheal disease globally and is estimated to cause approximately 200,000 deaths annually worldwide, with 70,000 or more among children in developing countries. Noroviruses remain a leading cause of sporadic disease and outbreaks of acute gastroenteritis even in industrialized settings, highlighting that improved hygiene and sanitation alone may not be fully effective in controlling norovirus. Strengths in global progress towards a Norovirus vaccine include a diverse though not deep pipeline which includes multiple approaches, including some with proven technology platforms (e.g., VLP-based HPV vaccines). However, several gaps in knowledge persist, including a fulsome mechanistic understanding of how the virus attaches to human host cells, internalizes, and induces disease.

© 2023 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

1. The global public health need for a vaccine

Norovirus is attributed to nearly 1 out of every 5 episodes of diarrheal disease globally and is estimated to cause approximately 200,000 deaths annually worldwide, with 70,000 or more among children in developing countries [1]. While norovirus is ubiquitous among all populations in high-, middle-, and low- income settings, incidence is highest in young children and at an earlier age among children in low-and-middle-income countries (LMICs). In regions where rotavirus vaccine has been introduced, norovirus-associated illness are often the leading cause of medically-attended visits for acute gastroenteritis in pediatric populations, likely via replacement [2–5] An individual will experience an average of three to eight nor-

ovirus illness episodes in their lifetime, of which at least one will occur by age of 5 years. Noroviruses are transmitted by multiple routes, but person-to-person spread predominates. Noroviruses remain a leading cause of sporadic disease and outbreaks of AGE in industrialized settings [1], highlighting that improved hygiene and sanitation alone may not be fully effective in controlling norovirus. Current infectious disease priorities are largely based on the burden associated with medically attended health events. However, based on current models, the overwhelming cost of norovirus is due to productivity losses resulting from acute illness. Productivity losses tend to go unrecognized but make up 94 % of the global economic burden of norovirus [6]. From a full public health value approach, focusing only on medically attended outcomes substantially underestimates the total economic impact of infections, particularly norovirus. In summary, due to the ubiquitous nature of norovirus and the substantial health and economic impacts across

* Corresponding author.

E-mail address: markriddlemd@gmail.com (M.S. Riddle).

high-, middle-, and low-income countries, norovirus gastroenteritis should be considered a global health problem which cannot be addressed by hygiene and infrastructure alone. Table 1 and Table 2 provide a summary of the epidemiology, potential indirect public health impact, key populations and associated delivery strategies relevant to a norovirus vaccine.

1.1. Current methods of surveillance, diagnosis, prevention, and treatment

Surveillance – Many HICs such as Japan, the United States, Germany, and parts of China have implemented active and passive systems for monitoring norovirus infections and outbreaks [31,40–42]. However, most LMICs and regions of the world do not include assessing for norovirus at present. Although the Middle East and North Africa (MENA) region employ active and passive surveillance to monitor a number of disease pathogens, they currently do not include assessment for norovirus [43]. Similarly, in Latin America, there is no active surveillance of norovirus, and all data on disease distribution and determinants are collected through epidemiologic field studies [44,45].

Diagnosis – Methods vary by country and geographic region based on available resources. In HICs, diagnosis is generally presumptive due to the appearance of one or more norovirus related symptoms such as loose stool or vomiting and occurrence during the winter months. When routine clinical laboratory diagnosis is sought, it is usually tested via realtime (RT)-PCR platforms. However, due to most cases not presenting to medical services and the lack of RT-PCR availability and testing generally, norovirus cases often go undiagnosed. This is an important problem, since most physicians and pediatricians in LMIC are unaware of norovirus as an important agent, and therefore, they do not see the need for a norovirus vaccine, which might limit its use once it becomes available (Riddle et al, manuscript in preparation).

Prevention – Individual protection against norovirus (and other enteric viruses) occurs through routine practice of hygiene measures such as proper hand hygiene, safe food handling and preparation, surface cleaning and disinfection, and thorough laundry washing. From a population health perspective, identification and mitigation during outbreaks are important to mitigate spread with in communities.

Treatment – Current standard of care for norovirus infection remains supportive, with focus on hydration and electrolyte replenishment. Antiemetics and antimotility agents may play a role in some patients [46].

1.2. Summary of knowledge and research gaps in epidemiology, potential indirect public health impact and economic burden

Epidemiology

- Data underlying the illness burden estimates in adults and children over 5 years of age are sparse and subject to important under-reporting bias, especially in LMIC. Current estimates are significantly challenged by the fact that norovirus infections and detection of outbreaks largely go unrecorded as most people do not contact health care services because of the nature of the infection.
- There is a need to genotype norovirus strains associated with more severe AGE in different parts of the world, specifically in pediatric populations, to select the best combination of antigens for an effective norovirus vaccine that could be used globally.
- Data are lacking on the potential chronic health effects due to norovirus (e.g., post-infectious irritable bowel syndrome, constipation, dyspepsia, and gastroesophageal reflux disease).

- There are significant gaps in global norovirus surveillance that impose barriers for accurate estimation of global norovirus disease burden.
- Current observations on outbreak activity reflects the bias of information attainment from settings in congregate settings, and therefore may underestimate other important outbreak activity due to norovirus.

Indirect public health impact

- Societal costs include direct and indirect (i.e., productivity losses due to absenteeism from work or school and mortality) costs.
- Modelling suggests that productivity losses due to absenteeism is a large driver of total disease burden.
- There is an important need to measure indirect effects of norovirus infections in LMIC in nutrition (growth velocity) and cognitive development, as seen with AGE in general.
- For HIC (and LMIC as well), the impacts on work-force absences in healthcare and education settings, hospital infection control and isolation costs, as well as impacts on immunocompromised individuals also need evaluation.

Economic burden

- Current estimates of the economic burden include studies that exclude vomiting-only norovirus episodes, which may represent 13 %–27 % of cases in the community [16,47], and thus likely underestimate the true cost burden of all norovirus illnesses.
- There are limited data on treatment administered outside the formal health system (e.g., local pharmacy over the counter, traditional healers, oral rehydration) but would likely be substantial in the societal and individual costs of disease.
- More reliable data on health care seeking behavior, hospitalization rates for norovirus, and missed productivity, especially for LMICs and older children and adults would be particularly useful.

2. Potential target populations and delivery strategies

2.1. High-income countries

While no formal target product profiles exist, from an epidemiological perspective, likely population segments for a norovirus vaccine could include all age-groups given the epidemiology of infection and disease burden associated with infection. Priority groups in HICs would likely include children, the elderly, and travelers as well as certain industries such as food-handling, health care and education systems where outbreaks are frequently known to occur and cause substantial disruptions. Of interest, Bartsch and co-workers employing modelling techniques, have suggested that the greatest potential economic and health benefits of a norovirus vaccination programme will be young children (under 5 years old) and the elderly (over 65 years old) [48]. Within HICs a norovirus vaccine could be integrated into the routine childhood vaccine schedule as well as routine adult immunization schedules. Traveler populations could be identified and immunized as part of routine pre-travel counselling.

2.2. Middle-income countries

As with HIC, norovirus is likely to impact all segments of the population in middle-income countries. Immunization systems are robust, and a pediatric vaccine would likely be able to be integrated into EPI schedules. However, many MICs have not intro-

Table 1

Summary of epidemiology and potential indirect public health impact.

Feature	Summary and evidence
<i>Epidemiology</i>	
Reservoir	- Reservoir is human. Transmission is primarily through person-to-person and an estimated 10–15 % through contaminated food (e.g., grown or harvested from contaminated water (individual, municipal, recreational), or infected by preparer/handler, water, infected people and contaminated surfaces. - Despite the ability of noroviruses to infect and cause disease in a broad range of animal species, to date there is no evidence that supports the transmission of norovirus from animals to humans. A few studies report evidence of human serological exposure to bovine and canine norovirus, but cross-reactivity might explain observations [7,8].
At-risk populations	- Norovirus is ubiquitous, associated with 18 % (95 % CI: 17 %–20 %) of diarrheal disease worldwide, with significant burden of disease in high-, middle-, and low-income settings. - Norovirus affects individuals across all age groups; however, the highest rates have been identified among young children. - For a person with an average life expectancy of 80 years, norovirus will cause illness three to eight times [9–12].
Mortality	- Globally, norovirus is estimated to cause a median number of 219,000 deaths each year (95 % Uncertainty Interval [UI]: 171,000–277,000) across all ages [6]. 97 % of mortality is attributed in LMIC [6]. - Its case fatality has been estimated to be 0.25 per 1000 cases (95 % CI 0.03–8.99), which is higher than rotavirus disease [13].
Morbidity	- Globally, norovirus is estimated to cause a median number of 699 million illnesses each year (95 % Uncertainty Interval [UI]: 489–1,086 million) across all ages [6,14–16]. - Norovirus is a leading cause of medically attended pediatric acute infectious GI illness, particularly in areas where rotavirus vaccine has been introduced [2–5]. 82 % of all illnesses are in LMIC countries [6]. - There are research studies that indicate an increased risk of functional gastrointestinal disorders (e.g. functional dyspepsia, irritable bowel syndrome) among HIC populations. No data exists on such post-infectious sequelae in the LMIC populations.
Geographical and seasonal distribution	- Norovirus has a world-wide distribution. - In the northern hemisphere, seasonal trends have well established norovirus as a wintertime phenomenon, whereas seasonal patterns for norovirus in the southern hemisphere are less established, and it remains unclear if the lack of an observed trend is due to differences in epidemiologic factors or a lack of adequate data [17].
Gender distribution	- Norovirus infections demonstrate a sex-switch preponderance at puberty (Male:Female IRR = 1.10, 95 % CI 1.02–1.19 in age = 5–14 years; Male:Female IRR = 0.75, 95 % CI 0.71–0.79, age 15–59 years). - Adult women have higher exposure to foodborne infection due to the frequency in which they visit hospitals and day cares, and more frequently cook and prepare meals. - It is likely that women of reproductive age represent more secondary cases than men due to infection directly from their children [18,19].
Socio-economic status vulnerability(ies) (equity/wealth quintile)	- In LMICs limited access to potable water, access to health care, rotavirus vaccination coverage, poor sanitation, inadequate hygiene, and food contamination represent key drivers for norovirus infections. - Household density may place a disproportionate burden of norovirus infections among households where there are more than 1 person living in a single room per room. - Within HICs, children living in high income households had higher norovirus antibody titers at age 3 years compared to those in lower income households [20–22].
Natural immunity	- In LMICs, children < 6 months of age are less frequently infected by norovirus than infants and older adults due to antibodies passed through breastmilk and limited opportunities for person-to-person and foodborne exposure. - While the data are limited and reliant on outbreaks which may not represent sporadic infections, mathematical modelling estimates suggest that the duration of norovirus gastroenteritis immunity is 4.1 (95 % CI 3.2–5.1) to 8.7 (95 % CI 6.8–11.3) years [19–23].
Pathogenic types, strains, and serotypes	- Noroviruses have been classified into ten genogroups (GI–GX) and 48 genotypes, though only viruses from GI (n = 9), GII (n = 23), GIV (n = 1), GVIII (n = 1) and GIX (n = 1) are causing infections in humans. - GII.4 noroviruses are associated with higher frequency and more severity in all age groups, while in children GII.3 viruses are the most frequent genotype second to GII.4 viruses. - GI.1 noroviruses have been identified as important in some settings, but overall is a rare genotype. - Other genotypes may be important in other settings, particularly in LMIC, where few studies have been conducted - Repeat infections with norovirus are common, but repeat infections with the same genotype are rare, suggesting that genotype-specific immunity is important [24,25].
<i>Potential indirect impacts</i>	
Anti-microbial resistance (AMR) threat	- There are no antiviral treatments for norovirus, though this is an area of active development (Nettler et al. 2019) - Many viral infections are inappropriately treated with antibiotics. Therefore, prevention of norovirus infections with vaccination could reduce antibiotic use and the development of attendant AMR (theoretical). - There is an important proportion of norovirus-positive AGE episodes where other enteropathogens are also present (mixed infections), including bacterial agents like ETEC or <i>Shigella</i> sp, where antibiotic treatment may be needed. There is a need to identify which organism is the cause of AGE in episodes where more than one enteropathogen is present, to reduce un-needed antibiotic treatments.
Epidemic and outbreak potential	- Outbreaks are commonly found in settings involving semi-closed populations and are particularly common in health care settings such as long term care facilities (LTCF) as well as school settings among young children of primary school and kindergarten ages. - Additional studies have indicated outbreaks on ships and military camps - Impacts on hospitals operations in many countries have been described [20,26–28].

Table 1 (continued)

Feature	Summary and evidence
Transmission route/potential	- Noroviruses are transmitted through the fecal-oral route but can also spread through fomites and airborne vomitus droplets. - Noroviruses are highly contagious, and outbreaks occur from direct person-to-person contact but can also be transmitted through contaminated food or water. - Typically, transmission occurs from humans to foods which can then act as vehicles of infection [26,29–35].
Acquired/herd immunity	- Compelling data on acquisition of natural immunity comes from volunteer challenge studies and observational birth cohorts. - Natural infection appears to confer short term protection against similar strains, lasting on the order of months to a few years. - Observational data from birth cohort studies demonstrate decreasing attack rates with age as well as lower rates of infection and/or gastroenteritis following one or more infections. - Empirical data on the duration of immunity is lacking; a modelling study estimated a range from about 3 to 9 years. [19,23,25,36–38]
Co-associated mortality	- Estimates on the proportion of childhood death associated with noroviruses are extrapolated from proportions of norovirus identified in more severe AGE episodes requiring hospital treatment. - The true role of norovirus on childhood mortality will be obtained by vaccine-introduction studies, as seen with rotavirus vaccine introduction.
<i>Economic burden</i>	
Health facility costs/out of pocket costs/productivity costs	- Globally, norovirus accounts for an estimated \$4.2 billion dollars (95 % UI: \$3.2–5.7 billion) in direct health systems cost and approximately \$60.3 billion in societal cost each year (including productivity losses). - Children < 5 years old account for the majority of societal cost at 39.8 billion per year compared to 20.4 billion in societal cost for all other age groups combined. - Productivity losses associated with norovirus resulted in an annual economic burden of 56.2 billion dollars per year; half of which were due to mortality (Bartsch et al. 2016) - There is a need to do cost-effectiveness analyses of norovirus vaccines including cost to society, which may have important variations by regions/countries in the world. Such cost-effectiveness analyses should consider all relevant and important outcomes comprehensively. These could include studies of different (older) age groups, vulnerable populations, and the impact of prolonging or deteriorating underlying conditions in immunocompromised individuals. Other important considerations may be the indirect effects for society including education and military readiness impacts. Traditional cost-effective studies without these indicators in countries with low infant mortality may make the vaccine too costly for DALY averted [6,39].

duced rotavirus vaccines with which a new norovirus vaccine may compete. From an adult vaccine preventable disease perspective, a recent review has captured current challenges broadly for adult

Table 2
Overview of potential target and key population(s) and associated delivery strategy (ies).

Target and key population(s)	Delivery strategy(ies)
LIC - Adult	Very difficult; adult VPD burden and surveillance systems to support vaccine programs lacking; no comprehensive WHO recommendation for adult immunization; vaccine delivery systems are not optimized.[49]
LIC - Pediatric	Key population of interest and established vaccine programs. Vaccine series would be ideally introduced prior to six months of age given epidemiology [31].
MIC - adult	Very difficult; high risk groups of HIV-infected populations and access to vaccine care is more robust. Growing elderly population and traveler markets may exist. Norovirus may be an important vaccine to introduce into these populations and thus could be a pathway [49].
MIC - Pediatric	Vaccination systems are in place for introduction in pediatric populations. Likely alignment with schedule of rotavirus vaccination.
HIC - Adult	Vaccination systems are in place for adult immunizations and high-risk target populations (elderly, hospital workers, education systems, travelers, etc).
HIC - Pediatric	Vaccination systems in place for introduction in pediatric populations.

vaccine introduction in middle- (and low-) income countries [49]. In the next decades, the number of adults over 65 years of age will grow to be more than the under-5 population, heavily concentrated in low- and middle-income countries. Current adult vaccine programs targeted at pneumococcal disease, influenza, and herpes zoster provide prescient examples of gaps and considerations for adult immunization programs in these countries. Lack of burden of disease in adults limits the potential public and governmental assessment of adult immunization program value. The few countries reporting adult immunization programs generally focus on high-risk groups, and a norovirus vaccine may not compete well with the other aforementioned vaccines. There is also a general lack of appropriate delivery platforms. Thus, a robust system for norovirus vaccination in adults may not be easily integrated into many MICs that could benefit from a norovirus vaccine, except for high-risk adult populations that some MICs target.

2.3. Low-income countries

Approximately 70 % of norovirus cases worldwide are known to occur in children between the ages of 6 and 23 months with the median age of infection in LMICs, where the burden of norovirus infection is highest, being between 6 and 16 months of age [31]. A vaccine should also provide protection before the peak of infection. Pediatric immunization could be implemented within the existing EPI or immunization schedule. Since the burden of it is greatest during the first year of life, immunizing early will have the greatest impact. It is estimated that a norovirus vaccine schedule completed by 6 or 12 months of age could prevent up to 85 % or 50 % of pediatric cases, respectively. The introduction of any new vaccine into routine vaccination programs in most LIC require a complex set of activities including mobilization and leverage of

political will and country leadership; advocacy and communications; advanced planning for all aspects of vaccine introduction including processes, standard operating procedures, preparation of the cold chain, logistics, training, and monitoring and evaluation. Most countries in the LMIC, where the burden of disease is quite high, currently deliver vaccines against 13 vaccine preventable diseases (VPDs) at regular schedules within their immunization programme. The current *EPI* schedule is contact at birth, 6 weeks, 10 weeks, 14 weeks, 6 months, 9 months, 12 months and 18 months. Immunization could be implemented within this schedule. It should be noted that the success of a pediatric vaccine will depend very much on how it can be integrated into the current immunization programmes of countries. As stated above, issues with adult immunization programs in MIC would be the same for LIC.

While the above considerations have been broken out by socioeconomic strata, these likely have applicability across all settings. Other target population and use-case considerations across all socioeconomic strata are important to consider including situations when a novel pandemic strain might arise, utilization of the vaccine as part of an outbreak response in congregate, health care and educational settings, as well as the potential value of a norovirus vaccine in maternal vaccination programs.

3. Norovirus and its consideration as a public health priority by global, regional or country stakeholders

Norovirus vaccine stakeholders are thought to include global health organizations, low-income countries where mortality and morbidity are considerably high, and high-income countries in which burden of disease has been substantially defined and vaccine markets may support early introduction, as well as non-governmental philanthropic organizations (Table 3). For countries who have introduced rotavirus vaccines into their national immunization programs, norovirus would likely be a pathogen (along with shigella) for a vaccine target of interest. However, such an assessment is largely hypothetical as there is little documented evidence that defines the prioritized interest in global health intuitions and stakeholders. At the country-level there is better evidenced interest by the United

States as well as China, though formal estimates of demand and vaccine uptake are lacking. Within the United States, health economic analyses have been conducted for US general population as well as the US Department of Defense.

A norovirus vaccine should have a dual market potential with pediatric populations in LMIC and HIC, as well as adult populations in HIC and MICs. Private markets in MICs may be sizeable given the burden of disease of this pathogen in all segments and potential demand for such a vaccine. However, formal market analyses are clearly needed.

4. Existing guidance on preferences/preferred product attributes for vaccines against norovirus

Neither the WHO nor any other global priority setting body has developed a preferred product characteristic or target product profile for a norovirus vaccine.

5. Vaccine development

5.1. Probability of technical and regulatory success (PTRS):

There are a number of features currently known about a norovirus vaccine that are favorable towards development of successful norovirus vaccine. These include a diverse though not deep pipeline which includes multiple approaches, and some with technology platforms that have proven successful for other vaccines (e.g., VLP-based HPV vaccines). (Tan 2021) In addition, there is evidence for acquisition of immunity from natural exposure [53,54]. A fairly clear development pathway exists for pediatric populations in LMIC (e.g., rotavirus vaccine development), and there is a human challenge model that could provide opportunity for de-risking, though this model has not been extensively used [55–58].

However, development of a norovirus vaccine is not without challenges. Mechanistic understanding of how the virus attaches to human host cells, internalizes and induces disease is not fully elucidated, and which genotypes to include may rely on future emerging new strains as well as the level of cross-protection against different genotypes that are not included in the vaccine for-

Table 3
Overview of non-commercial stakeholders engaged, their interest and potential demand.

Stakeholders engaged	Summary of position/interest	Potential demand and uptake
WHO	No stated position: however, the present effort demonstrates that the WHO has interest in defining the value of a potential vaccine for global use.	No WHO-derived global demand or uptake forecasts.
China	No stated position on norovirus vaccine, though research advances in candidate vaccines and establishment of national surveillance systems suggest that this is a priority pathogen. Scientists from the Chinese Centers for Disease Control state that these efforts are essential to provide information about the evolving strain distribution and epidemiologic characteristics of norovirus outbreaks which contributes to the development of effective vaccines.	No formal demand or uptake estimates are available. Unclear the target populations that might be of interest. Given size, demand forecasts likely to be large [50].
Centers for Disease Control and Prevention (CDC) / US	Not a stated position; however, interest is clear given activity and leadership in norovirus surveillance and epidemiology in the US (and globally).	No-CDC based demand forecasts, though economic analysis and burden of disease description efforts point towards important populations of interest including pediatrics, adult and the elderly [10].
Bill & Melinda Gates Foundation	Norovirus is on a learning agenda but is not in the BMGF's active enteric vaccine portfolio.	No demand forecast/uptake assessments described.
Department of Defense/US	No specific requirement for a norovirus vaccine articulated, however DoD has provided industry support (Ligocyte/Takeda) for norovirus vaccine development and testing.	No formal DoD vaccine demand/uptake forecast though economic analysis has described potential vaccine dose requirements and cost-effectiveness of a vaccine strategy (relative to other leading enteric pathogens) [51,52].

mulation [59,60]. Hence, the frequency of possible reformulation of a norovirus vaccine is currently unknown. There are no good animal disease models that recapitulate human disease, though the recently developed human intestinal enteroid system may provide newer tools to better understand biology and vaccine design optimization.[61].

Table 4 outlines the current expert assessment of the PTRS for a norovirus vaccine with a standardized rating provided according to Appendix A. Table 5 provides an overview of parameters that inform scientific feasibility of developing an effective vaccine for LMIC public market use.

5.2. Overview of the vaccine candidates in the clinical pipeline:

There are currently-three VLP-based platform vaccine candidates and one adenovirus vector-based platform which have undergone clinical studies (Fig. 1 and Table 6). The most advanced candidate has produced several publications, from its early stage (Ligocyte) and later stages (Takeda) including phase I and II trials as well as formulation and dosing adjustments and active search of immune correlates of protection. This vaccine, currently under development by HilleVax, is the only candidate reporting clinical efficacy to date, and is moving forward to phase III trials in adults and children from 5 months of age. The other two VLP candidates, from Chinese manufacturers are in earlier stages, and peer-review results of the phase I trials have not yet been reported. The adenovirus vectored GI.1 vaccine using oral tablets was reported to be safe and immunogenic (using several immunologic parameters).

6. Health, social and economic impact of a norovirus vaccine on burden of disease and transmission

A norovirus vaccine would have a number of different target populations and thus a variety of potential health, social and economic impacts (Table 7). These populations include young children in LMICs as well as those in HICs. In addition, there are healthy adults, as well as older adults where there is substantial burden. Finally, there are also identified specific at-risk populations such as healthcare workers or food-handlers. As such, there are many potential and important impacts that a vaccine may have. The tables below provided substantial detail on what has been considered thus far. From an age-based perspective, the youngest will have the highest rates of overall healthcare utilization, as well as are considered primary drivers of transmission in communities. In HIC, more severe disease is also found in the older age groups, with a majority of deaths occurring in elderly individuals aged 65 years and older. Travelers from HIC to LMIC are at increased risk of itinerary disrupting illness which not only has individual health impacts but could also impact the local economies through reduction of purchases/expenditures during travel. Military personnel in garrison, on ships and deployed on the ground in overseas locations also have a high incidence of norovirus illness which could impact readiness and operational effectiveness. Other high-risk groups include health-care workers and food-handlers, the latter of which would be important given that norovirus accounts for a considerable amount of domestically-acquired foodborne illness in HIC.

Table 4

Summary of indicators supporting an assessment of the probability of technical and regulatory success for a norovirus vaccine candidate.

Probability of success theme	Indicator	Summary	Rating
Biological Feasibility	Most advanced vaccine candidate(s)	- Four candidates have undergone clinical trials with the most advance (HilleVax Bivalent GI.1/GII.4 VLP) heading into phase III trials in 2022. - Other three candidates in phase I/II.	Low-Moderate
	Existence of immunity from natural exposure	- Natural exposure causes asymptomatic and symptomatic infections, both of which are associated with both humoral and cellular immune responses. - Cohort studies conclude that prior infection confers protection against reinfection to the same genotype and potentially to the same serogroup/different serotype; duration is unclear. - Adult volunteer study results provide conflicting results, suggesting limited infection-related protection.	Moderate
	Understanding mechanisms of immunity	- Recent studies focusing on host differences (HBGA phenotypes for example) may partially explain early results of lack of protective immunity conferred by a prior infection. - Long term protection, mucosal/systemic immune response induction, and cross-protection against heterogeneous epitopes is not fully understood.	Low
	Likelihood of vaccine protection against the majority of pathogenic strains	- Strong evidence that protection is provided against the homologous genotype. - Less evidence that protection may also be against the homologous genogroup despite different genotype (although there may be differences for given serotypes). - Vaccine will need to include the most common genogroup/genotypes.	Low
Product Development Feasibility	Existence of animal models to facilitate vaccine development	- Mouse model and zebra-fish model are being increasingly explored. - Mouse models do not recapitulate human infection and appear to have different receptor/attachment mechanisms.	Low-Moderate
	Existence of in vitro assays to facilitate vaccine development	- Several antibody tests have been developed and are under evaluation. - HBGA blocking antibodies may prove most helpful for establishing correlates for future studies, but this is still under evaluation. - The exact host cell receptor molecule(s) necessary for attachment and invasion are not identified.	Moderate
	Ease of Clinical Development	- Clinical trials following the “rotavirus clinical trials model” are likely the norm and currently being implemented for Phase III trials. - Challenges will include dealing with genotype diversity and role of coinfections.	High
	Availability or need for human challenge models	- Human challenge models have been important for the “proof of concept” of vaccine associated protection. - Current efforts include the development of suitable genogroup/genotype candidates for human challenge. - Licensure in HIC adults/travelers through use of CHIM are reasonable given recent precedence	Moderate-High

Table 5

Overview of parameters that inform scientific feasibility of developing an effective vaccine for LMIC public market use.

Parameter	Issues and evidence
Diagnosis/case ascertainment	Most studies related to norovirus impact have focused on case definitions (acute diarrhea characterized by increase/unformed stools, with or without vomiting or fever) together with stool testing for norovirus using mostly real-time RT-PCR. This methodology is robust with the caveat that the specific etiologic role of norovirus can be questioned due to high coinfection rates in some studies and to high asymptomatic infection in others. In young children, studies evaluating multiple pathogens frequently detect norovirus together with other viral (mainly rotavirus) or bacterial (mainly diarrheagenic <i>E. coli</i>) pathogens, which makes an etiologic assignment difficult. Conversely, detection of norovirus in fully asymptomatic individuals (although at a lower percent when compared to diarrhea individuals), also suggests that the sole detection of the pathogen does not imply a pathogenic role [27,62–65].
Biomarkers/Correlates of risk and/or protection	While a number of correlates of protection have been explored, they have not allowed to consistently identify a correlate suitable for vaccine trials. HBGA-blocking antibodies have showed promising results, and together with studies in Human Intestinal Enteroids represent the most relevant advances in our understanding of virus diversity and their relationship with cell adhesion and infection [66,67].
Sero-epidemiological data	Population-based studies suggest that seroepidemiology may be used as a tool to measure force of infection within a given population, and that there is genotype-specific homologous protective effect after natural exposure, with some evidence of short-term cross-genotype functional anti-body responses. Number of infections need to induce broadly protective natural antibody responses are not known, nor is the full duration of homologous and heterologous protection after natural exposure [53,54].
Clinical endpoints	Clinical endpoints for vaccine studies are just recently being proposed. Following the “rotavirus model”, moderate to severe infection based on hospitalization and/or fluid replacement requirement, and/or Vesikari/modified Vesikari scores are being considered. Detection method will likely be realtime RT-PCR and protection against the clinical outcome caused by vaccine types will likely be the primary outcome.
Controlled Human infection model (CHIM)	Volunteer studies using a controlled human infection model have been developed and are used for early vaccine evaluations. Studies aiming to identify suitable challenge strains are in progress [55,56,68,69].
Opportunity for innovative clinical trial designs	Current vaccine trials for the most advanced candidates are being evaluated in adult and child populations (see below). Trial designs are conventional and will include populations followed for up to 2 years for the primary outcome as well as reinfections and potential herd protection for family members. Human challenge studies have also been considered and could be introduced into LMIC settings given the risk of infections in adults globally.
Regulatory approach(es), including potential accelerated approval strategies	- Several population segments would benefit from a norovirus vaccine and there will likely be different pathways towards licensure. From an LMIC perspective, clinical development pathways would largely follow those of current rotavirus vaccines and those under development. Primary endpoints would likely be medically attended vaccine-preventable norovirus acute gastroenteritis (e.g., moderate-severe). Study designs to demonstrate safety, efficacy and vaccine manufacturing consistency would be envisioned with a target for WHO pre-qualification, as well as developing world manufacturing. - From a HIC perspective, the multiple segments would include all age-groups. Given the potential demand for healthy adult traveler and military populations, a development could contemplate an initial licensure in this population through use of a CHIM to demonstrate efficacy (as well as ideally identify immune correlates of protection). If a correlate of protection is confidently identified, expanded safety and immunobridging studies in older age-groups as well as young age-groups could follow. Alternatively, efficacy studies may need to be done. - Given the establishment of a CHIM, licensure pathways could consider the use given the sporadic nature of disease particularly in travelers and healthy adults. Though, the traditional model of field trials in LMIC and HIC under 5 populations should be achievable given the disease incidence [1,9]
Potential for combination with other vaccines	Given the route of administration, schedule, number of doses and delivery strategy the combination of a norovirus vaccine with another respiratory and/or enteric pathogen, for example rotavirus would be attractive [1,9].
Feasibility of meeting presentation and stability requirements	Likely, yes as vaccines in development utilize similar constructs and formulation to existing vaccines in the LMICs.
Vaccine platform	Depending on the vaccine construct, a norovirus VLP vaccine would be similar to other vaccines that are manufactured by developing world manufactures.
Large scale Manufacturer capacity/interest	Uncertain. Current vaccines in the pipeline are not yet developed by large manufactures.

6.1. Summary of knowledge and research gaps in modelling health, social and economic impact on disease burden and transmission

Gaps in modelling literature include:

- Impact of norovirus vaccination in settings where vulnerable population are at risk such as long-term care facilities.
- Impact of norovirus vaccination across the whole population considering the role of and targeting vaccination among high transmission populations (e.g., healthcare workers, food workers and handlers).
- Comparison of vaccination schedules in young children, considering maternal antibody interference and norovirus infection rates.
- Impact of vaccination in LMICs. There are some models from middle income countries but few and none in LICs.

- Models that consider the multi-strain dynamics and vaccine valency.
- Models which consider the impact of COVID-19 and changes in underlying disease dynamics of norovirus, including the proportion of susceptible individuals in different age groups, and possible disruptions to inter-epidemic cycles.

Influential model inputs that need further definition to inform modelling studies include:

- Care seeking behaviors and health care utilization for norovirus across diverse age groups and populations (especially in LMIC settings).
- Protection and duration of protection of norovirus immunity following vaccination and/or viral infection.

Norovirus Vaccine Pipeline

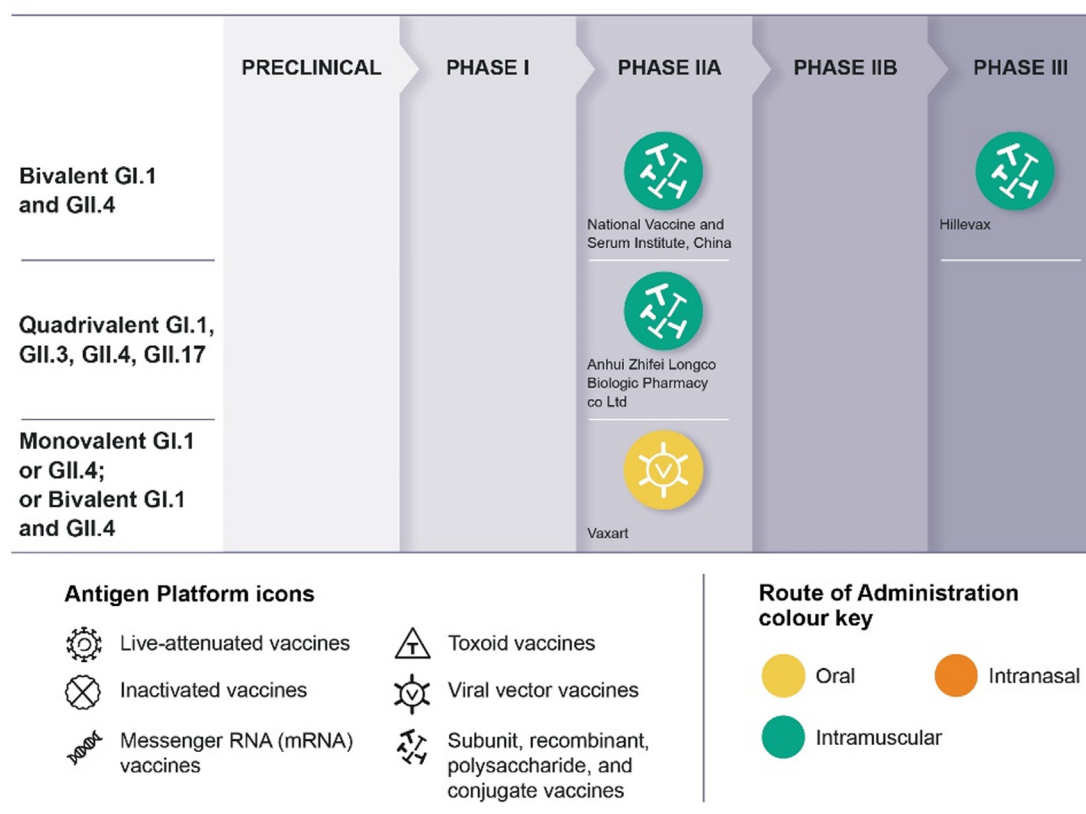


Fig. 1. Norovirus vaccine pipeline as of April 30th, 2022 (Credit: WHO).

Table 6

Overview of vaccine candidates in the clinical pipeline.

Candidate	Antigen platform	Developer/manufacturer	Phase of development, population, and location	Route of administration, no. of doses, schedule
Bivalent GI.1 and GII.4	Virus-like particles Baculovirus expression system	Ligocyte followed by Takeda, now Hillelax	Clinical: Phase IIb and norovirus challenge completed in US healthy adults; advancing to phase 2b trials in children under 5 in the US, Colombia, Dominican Republic, Mexico, Panama and Peru	First delivered by intranasal route, and currently developed for intramuscular administration in two doses separated by 28–57 days [51,57,58,70].
Bivalent GI.1 and GII.4	Virus-like particles Hansenula polymorpha expression system	National Vaccine and Serum Institute, China Collaborators: Lanzhou Institute of Biological Products Co., Ltd Beijing Zhong Sheng Heng Yi Pharmaceutical Technology Co., Ltd. Zhengzhou University	Clinical: Phase I completed in Healthy People Aged 6 Months to 59 Years; Phase II trials in progress among Healthy People Aged 6 Months to 59 Years. China.	Developed for intramuscular administration in 2–3 doses separated by 28 days [71,72].
Quadrivalent GI.1, GII.3, GII.4, GII.17	Virus-like particles Pichia pastoris system expression system	Anhui Zhifei Longcom Biologic Pharmacy Co., Ltd.	Clinical: Phase I/IIa ongoing in healthy people aged 6 weeks to 59 years (age-descending). China	Developed for intramuscular administration; doses under evaluation [73].
Monovalent GI.1 or GII.4; or Bivalent GI.1 and GII.4	Adenovirus vector-based vaccine platform including the VP1 gene; Co-expression with a double-stranded RNA adjuvant	Vaxart	Clinical: Phase I in adults completed (GI.1 vaccine); advancing to Phase II trials in the US.	Oral administration; currently evaluating number of doses [74].

Table 7

Overview of studies that address the potential value of a norovirus vaccine on health, social and economic impacts on disease burden and transmission.

Policy question	Assessment method/measure	Additional information specific to models	Assumptions	Outcomes/interpretation
Understand the transmission dynamics of norovirus and to predict the likely impact of vaccination.	Dynamic age-specific mathematical model of norovirus transmission and vaccination.	Model fitted to age-stratified time series case notification data available from Germany. Includes the use of a self-reporting Markov model to account for variation by age and over time in the statutory reporting of norovirus in Germany. The model uses a sequential Monte Carlo particle filter. The estimated model was then extended and applied to investigate the potential impact of a range of immunization strategies. Sensitivity analyses were performed on the mode of vaccine action and other vaccine-related parameters.	- SEIR-type model with maternal immunity and vaccinated classes - Asymptomatic contribute to transmission greater than 90 % coverage for children; 50 % for elderly 50 % VE for kids; 70 % for elderly - Duration of protection 5 years	- Routine immunization could reduce the incidence of norovirus by up to 70.5 % even when those vaccines do not provide complete protection from disease. - Relative efficiency of alternative strategies targeting different age groups are dependent on the outcome. - Results sensitive to assumptions on the mode of vaccine action [75].
Which age groups should be vaccinated to maximize population impact?	Deterministic, age-structured compartmental model of norovirus transmission and immunity in the U.S. population.	Model was fit to age-specific monthly norovirus-associated U.S. hospitalizations between 1996 and 2007 Simulated mass immunization of both pediatric and elderly populations	- Assumed coverages of 90 % and 65 %, for pediatric and elderly populations respectively. - Considered two mechanisms of vaccine action, resulting in lower vaccine efficacy (IVE) between 22 % and 43 % and higher VE (hVE) of 50 % - Maternal immunity is short-lived and negligible - Vaccine response was “take-type:”	- Pediatric vaccination was predicted to avert 33 % (95 % CI: 27 %, 40 %) and 60 % (95 % CI: 49 %, 71 %) of norovirus episodes among children under five years for IVE and hVE, respectively. Vaccinating the elderly averted 17 % (95 % CI: 12 %, 20 %) and 38 % (95 % CI: 34 %, 42 %) of cases in 65 + year old individuals for IVE and hVE, respectively. At a population level, pediatric vaccination was predicted to avert 18–21 times more cases and twice as many deaths per vaccine compared to vaccination of the elderly. - Potential benefits are likely greater for a pediatric program, both via direct protection of vaccinated children and indirect protection of unvaccinated individuals, including adults and the elderly [76].
Is pediatric norovirus vaccination cost-effective in daycare settings?	Transmission-model-based cost-effectiveness analysis	A dynamic SEIR-like transmission model of norovirus outbreaks in daycare settings was calibrated to NORS outbreak data and adapted to include vaccination. The model incorporated detailed dynamics of pediatric transmission within daycare settings (including infection via human-to-human and fomite-to-human contacts). The economic analysis utilized an incremental cost-effectiveness ratio to compare costs and QALYS of vaccination and no vaccination (observed standard of care only, in which symptomatic children are excluded from daycare). The model did not include secondary transmission outside of daycare centers.	Vaccination Assumptions 90% vaccination coverage - Compared 50% and 80% all-or-nothing vaccination efficacy - Vaccination in addition to standard of care (exclusion of symptomatic children from childcare) - Two-year modelling period Cost Analysis Assumptions - From a societal perspective (including child medical costs and loss of productivity to parents). - Two-year time horizon	Primary Outcomes: - Due to large burden of disease, vaccinating children in daycares would likely be cost-effective. - Norovirus vaccination is more costly than the standard of care but leads to more QALYs than the standard of care. - Vaccination leads to modest reduction in costs to manage norovirus infections, but primarily gains QALYS (gains 253 QALYS per 10,000 children). - Similar cost-effectiveness ratio to other recommender childhood vaccines. Health Outcomes: 50% efficacious vaccine averts 571.83 norovirus cases per 10,000 children and 0.003 norovirus-related deaths. Costs, incremental cost-effectiveness ratio (ICER):

Table 7 (continued)

Policy question	Assessment method/measure	Additional information specific to models	Assumptions	Outcomes/interpretation
				- o 50% efficacious vaccine at \$200/vaccination series results in net cost increase of \$178.10 per child, with an ICER of \$7028/QALY ■ Based on probabilistic sensitivity analysis, Willingness-to-pay \$100,000/QALY: 94.0% likely to be cost effective - o Even with cost of \$500 per child vaccinated and modest efficacy of 50%, vaccination is likely to be cost-effective (86.7%) at threshold of \$100,000 per additional QALY - o ICERs most sensitive to probability of norovirus introduction within the vaccination efficacy period, days in supportive care, and quality-of-life being in supportive care [77]
Clinical impact and cost effectiveness thresholds for vaccinating children or older adults in community settings	Age-structured compartmental transmission model and cost effectiveness analysis.	• Norovirus Model: Compartmental SEIR-like transmission model with 4 age groups: preschool-aged children (0–4 years), school-aged children (5–17 years), adults (18 – 64 years) and older adults (≥ 65 years) applied to the US • Cost estimates: Compared third payer perspective, including all direct medical costs, to societal perspective included direct and indirect (productivity losses) costs. Calculated ICER use of QALYs and DALYs. • Sensitivity analysis: Monte Carlo simulations of 2000 trials, sensitivity in terms of population size, vaccine cost, vaccine efficacy, and vaccine coverage (population of 2500 to 7500 people). • Model Calibration: Calibrated model to US population incidence and age-specific incidence trends.	• Vaccine and natural infection assumed to provide protection from symptomatic illness for one year. Assumed productivity losses for all symptomatic norovirus infections and modelled annual norovirus vaccination. • ICER based on willingness-to-pay threshold of \$50,000/QALY	• Vaccination coverage as low as 10% can provide clinical and economic benefits • Health outcomes with varying vaccine efficacy (25%–75%) and vaccination coverage (10%–80%): - o Vaccinating preschool-aged children averted 8–72% of symptomatic cases in community - o Vaccinating older adults averted 2% – 29% of symptomatic cases • Vaccine is cost effective at higher cost thresholds for vaccinating preschool-aged children compared to vaccinating older adults alone (cost thresholds below using societal perspective): - o Vaccinating children: Low efficacy (25%) vaccine was cost effective at ≤ \$445, cost saving at ≤ \$370; higher efficacy (75%) vaccine was cost effective at ≤ \$1600, cost saving at ≤ \$1300 per vaccinated person (including vaccine, administration and associated costs) - o Vaccinating older adults: Low efficacy (25%) vaccine was cost effective at ≤ \$42 and cost saving at ≤ \$30, higher efficacy (75%) vaccine was cost effective at ≤ \$165 and cost saving at ≤ \$100 per vaccinated person (including vaccine, administration and associated costs)

(continued on next page)

Table 7 (continued)

Policy question	Assessment method/measure	Additional information specific to models	Assumptions	Outcomes/interpretation
Cost effectiveness of norovirus vaccine compared to other enteric vaccines for military use	Modified version of an economic model developed to evaluate the cost-effectiveness of a vaccine acquisition strategy within the Department of Defense adapted to norovirus.	• Cost-effectiveness analysis for use of norovirus vaccine in the military using a previously developed model that evaluated vaccines for ETEC, Campylobacter, and Shigella for the prevention of non-outbreak associated travelers' diarrhea. • One-way sensitivity analysis performed using high and low values for each input variable.	• Duty days lost to acute gastroenteritis chosen as an outcome measure • Incidence of norovirus-attributable illness based on systematic review of incidence of sporadic travelers' diarrhea cases in a deployed military setting • Troops vaccinated prior to every deployment based on current pre-deployment vaccine coverage rates • Vaccine coverage: 75% • Vaccine efficacy: 80% • Did not consider potential for herd immunity or value of preventing domestically-acquired infection • Considered purchase price of vaccine (\$28.59/dose), administrative costs (\$2.96/dose), and costs of treating a vaccine-associated adverse event. • One-year time horizon chosen for this model and 2013 USD costs.	• Thresholds were substantially lower from the third-party payer perspective, given that the majority of savings from averted cases are a result of reduced productivity losses [78]. • Absolute cost-effectiveness of a norovirus vaccine appears to be favorable: ◦ Norovirus cost effectiveness equivalent to Shigella but not as favorable as an ETEC of Campylobacter vaccine. ◦ When adjusting case definition to account for vomiting predominant illness, the cost-effectiveness ratio per duty day lost to illness (CERDDL) for norovirus vaccine is \$572, which makes it the most cost effective. ◦ The CERDDL of \$1,344 compared to \$776 for ETEC, \$800 for Campylobacter, and \$1,275 for Shigella. • Norovirus vaccine adoption by the DoD could prevent 12,490 cases of gastroenteritis annually during deployment. ◦ After norovirus vaccine introduction, the number of duty days lost due to gastroenteritis predicted to drop from 4,930 to 986 per year. ◦ Annual total cost of care after norovirus vaccine introduction predicted to drop from \$1,952,500 to \$292,875. • Total annual cost of vaccination of \$6,956,775 at \$60.14/vaccine administered. • Sensitivity analysis: 48% of variation in the economic model accounted for by inverse relationship between duration of deployment and cost-effectiveness. Increasing duration of deployment to a year leads to norovirus vaccine cost-effectiveness

Table 7 (continued)

Policy question	Assessment method/measure	Additional information specific to models	Assumptions	Outcomes/interpretation
Cost effectiveness of norovirus vaccination in LMIC military population	Adapted economic model developed by the United States Department of Defense to evaluate cost-effectiveness of vaccine acquisition strategies utilizing a static decision tree model to compare cost-effectiveness of vaccine implementation.	- Evaluated the cost-effectiveness of vaccine acquisition and implementation for norovirus, <i>Campylobacter</i>, ETEC, and <i>Shigella</i> compared with current medical management. The cost effectiveness ratio was calculated based on (1) the pathogen-specific gastroenteritis prevalence, management approaches, and treatment costs; (2) the cost of administering the vaccine in the Peruvian military population, and (3) the duty days lost to gastroenteritis averted by vaccination. - Performed a one-way sensitivity analysis using high and low values for each parameter.	- Cost effectiveness analysis performed in the context of the Peruvian armed forces (population of LMIC adults with high incidence of infectious gastroenteritis) for a one-year time horizon in 2019 costs. Vaccine Assumptions: - Imperfect vaccine efficacy could protect from gastroenteritis or susceptibility to the pathogens - Assumed vaccine administration before each deployment to account for waning immunity - Vaccine Efficacy: 80% (minimal military parameter requirements) - Vaccine associated costs: purchase price of two dose vaccine, program administration costs, adverse event treatments - Vaccine cost: \$13 per vaccine series (estimated vaccine costs for Peruvian military based on prices of Rotarix)	approaches a cost-neutral threshold when medical treatment costs alone are considered - Other most influential parameters include pathogen prevalence, incidence, coverage, probability of seeking medical treatment [52]. - After <i>Shigella</i> vaccination, norovirus vaccination was most-cost-effective in preventing gastroenteritis-associated DDL (then ETEC and <i>Campylobacter</i>), suggesting that norovirus military vaccination should be prioritized. - Norovirus cost effectiveness estimates compare favorably to US estimates of norovirus vaccine cost effectiveness in the military, suggesting that norovirus vaccine may be cost effective in the Peruvian military. - Norovirus vaccination for the Peruvian military could prevent 3870 cases of gastroenteritis and decrease norovirus-associated duty days lost from 940 to 368 days. - Reduction in total annual cost of gastroenteritis care from \$25,942 to \$17,013 annually. - Cost per duty day lost averted: \$803; cost per diarrheal day averted: \$199 - Model outcomes were most sensitive to length and frequency of individual deployments, with longer, more frequent deployments resulting in more exposure and improving cost-effectiveness [79].
Cost-effectiveness of norovirus vaccination in children in LMICs (Peru)	Markov decision model to evaluate cost-effectiveness of a two-dose norovirus vaccine in Peru's routine childhood immunization schedule based on two recent estimates of NV incidence (one for <i>peri</i> -urban region, one for jungle region).	- Evaluated cost-effectiveness of a two-dose norovirus vaccine added to Peru's routine childhood immunization schedule using a probabilistic three-box Markov model for a Peruvian birth cohort. - Conducted a probabilistic sensitivity analysis using Monte Carlo simulation with 20,000 draws. - Model does not include the indirect costs of norovirus vaccination nor any additional direct costs of self-treatment or home care (which may be significant), also model does not account for indirect benefits attributable to reduced shedding in the community, reduced disease transmission	- Based health effects on norovirus diarrhea incidence data from community-level study in <i>peri</i>-urban area of Lima and rural jungle diarrheal surveillance site in the Amazon Basin. - Assumed diarrheal incidence at 5 years old was half that at 12 – 24 months and declined linearly with time. - For healthcare costs associated with norovirus, used weighted averages of urban and rural treatment costs. - Assumed 85% norovirus vaccination coverage with a two-dose vaccine with 47% efficacy against diarrhea within Peru's routine childhood immunization schedule (similar to the rotavirus vaccine).	Vaccinating young children against norovirus could offer economic value under the right conditions in Peru: - Potentially cost effective in scenarios with high norovirus incidence - In scenarios with higher norovirus incidence (jungle setting), more favorable cost-effectiveness estimates - Strongly dependent on vaccine price and efficacy based on sensitivity analysis - With varied incidence rates, cost per DALY averted ranged from \$15,616 to \$41,512 in <i>peri</i>-urban area and from \$4,483 to \$14,700 in rural jungle setting.

(continued on next page)

Table 7 (continued)

Policy question	Assessment method/measure	Additional information specific to models	Assumptions	Outcomes/interpretation
			- o Estimated cost of \$13.19 per dose (based on cost estimates for another VLP-based vaccination (HPV)) with no additional vaccination administration costs. • Ran model for 60 months, cost effectiveness calculated for children < 5 years old only • Costs reported in 2012 USD	• Using a willingness-to-pay threshold of the GDP per capita of Peru (\$6242 in 2012), the vaccine would have to be at least 70% effective at the lowest cost of \$8.50 per dose to be cost effective. If the vaccine cost \$11.20 per dose, vaccine effectiveness would have to be 91% to be cost effective. • The annual cost of vaccination would be 13.0 million, with \$2.6 million in treatment savings, resulting in the following outcomes: - o Vaccination could avert 473 DALYs, over 526,000 diarrheal cases, 153,735 outpatient visits, and 414 hospitalizations between birth and the fifth year of life. - o The ICER for norovirus vaccination would be \$21,415 per DALY averted, \$19.86 per diarrhea case averted, \$68.23 per outpatient visit averted, \$26,298 per hospitalization averted [39]
Potential economic value of human norovirus vaccine for the United States	Markov simulation model of vaccine cost-effectiveness from societal perspective (including direct medical costs and indirect costs)	• Markov model selected to determine potential impact of vaccine over time (compared to traditional decision tree model) • Probabilistic sensitivity analysis (i.e., Monte Carlo simulation) for all parameters • One-way sensitivity analysis for vaccine efficacy (25%, 50%, 75%), protection duration (12, 24, 48 months) and vaccine cost (\$25, \$50, \$75)	• Norovirus incidence based on community-based study of AGE from England and Wales to estimate age-specific norovirus incidence. • Healthcare utilization based on self-reported healthcare utilization for persons with acute diarrheal disease from the US Foodborne Diseases Active Surveillance Network. • Model simulations based on 1000 individuals ages 0 to 85. • Assumed 43% versus 95% vaccination coverage across every age group.	• Norovirus vaccination could be cost effective, depending on price, efficacy, and duration of protection: - o Vaccine cost-saving for young children with minimal vaccine cost (<\$25) - o Cost of <\$1,500/case averted with highest cost (\$75) vaccine with efficacy of ≥50% and protection of 24 months - o For vaccine providing 48 months protection, costs per case averted was <\$700 • Clinical outcomes and costs: - o Vaccination could avert 1.0–2.2 million cases (efficacy 50%, 12-month duration) - o Vaccine cost \$400 million - \$1.0 billion - o Vaccine savings ≤2.1 billion (48-month duration) • Protection duration is an important driver of cost-effectiveness. • Children under five are suggested as the most attractive target vaccination population, in terms of cases averted and costs, followed by older adults (≥65 years) [48]

- Impact of maternal antibodies on vaccine effectiveness in young children.
 - o Cost of norovirus vaccine and vaccine program implementation.
 - o In children.
 - o In older adults.
 - o In the military.
 - o Other targeted groups like HCWs.
- Vaccine uptake willingness of norovirus vaccine among priority populations.
 - o Children, older adults, the military.
- Established cost-effectiveness cut off value across settings (not norovirus specific).

7. Policy considerations and Financing

The evidence required to support a global policy recommendation and financing from Gavi are quite similar to other acute enteric vaccines, most notably rotavirus vaccines for which there are a number of oral rotavirus vaccines already pre-qualified and under the Gavi investment. In addition, new parenteral rotavirus vaccines are currently under development also provide an example pathway for development, licensure and lessons learned from policy development and financing perspectives.

In general, the pathway for a norovirus vaccine would be quite similar to a rotavirus vaccine, although given the epidemiology of norovirus the evaluation of the full public health impact of disease extends beyond childhood given that norovirus incidence and burden of diseases is present and quantifiable across older children, adolescents, adults and the elderly. Given that the severity of illness and under 5 mortality attributable to norovirus appears less in children compared to rotavirus, the full public health burden for those age greater than 5 needs to be considered and enumerated.

Experience also indicates that country level preferences need to be considered early in the process of development. For example, recent evaluation on the hypothetical introduction of injectable or oral next generation rotavirus vaccines (NGRVs) identifies that vaccine delivery considerations were the most important preference drivers for national stakeholders, followed by improved efficacy and cost [80]. Interestingly, while national vaccine program stakeholders preferred a higher efficacy stand-alone injectable NGRV or existing oral live-attenuated rotavirus vaccines, health care providers strongly opposed an injectable rotavirus vaccine to a vaccine schedule. From both immunization program and provider stakeholder perspectives, combination vaccine approaches are much preferred compared to stand-alone vaccines and thus early considerations of combination norovirus vaccines with existing vaccines or those in advanced development (Phase III) could be considered.

Finally, considerations of Gavi financing for new vaccines is critical to garner interest by industry partners, though the potential dual market of a norovirus vaccine may provide non-Gavi financing from high and middle-income countries based on the potential value of preventable disease burden by vaccines.

From a non-Gavi eligible country perspective (e.g., MICs and HICs), vaccine policy and financing considerations would be largely driven by identification of substantial disease burden, demonstration of efficacy in a country or region, approval by a national regulatory authority and consideration and endorsement by a national immunization policy making body. Financing of the vaccine would likely be a blend of private and public market procurement.

Table 8 outlines a number of policy and financing considerations from an LIC perspective that apply in large part to all vaccines but have been made specific to a hypothetical norovirus vaccine as appropriate. Many considerations cannot be known at the present due to the early development process of current norovirus vaccines.

8. Access and implementation feasibility

Vaccines only work if they are actually used. And getting vaccine manufacturers to pursue development and licensure of a vaccine requires a strong market and one that is sustainable long term. Thus, in identification of market strength and sustainability, issues of vaccine access and implementation are of critical importance to consider in prioritizing, developing and establishing policy and financing of novel vaccines such as norovirus. Pertinent to a novel norovirus vaccine, the rotavirus vaccine experience is instructive and provides perspective on what might be relevant to consider. While rotavirus vaccines have consistently been shown to save lives in many LMICs, and to be highly cost-effective or even cost-saving in many, 110 countries have introduced rotavirus vaccines into their national immunization programs, 53 have accessed support from Gavi, and 65 countries have not expressed plans to introduce rotavirus vaccines, including 8 that are eligible for Gavi support.[87]

Despite the clear evidence of mortality reduction by rotavirus vaccines, the high emphasis on infant mortality reduction by global vaccine financiers and regional immunization program authorities often presents a challenge for diseases where there is 'relatively' more morbidity than mortality. Such is the case with rotavirus and would appear to be even more of the case with norovirus. To offset the lesser case-fatality rate of norovirus and relevant to the situation of non-rotavirus adoption among many LMICs, a framework was used to consider the favorability of access and implementation and ultimately market strength and sustainability (Appendix B). While limited vaccine candidates are currently in the pipeline (and early stage at that), we considered both a parenterally delivered VLP-based vaccine construct (Hillevar, Boston, MA USA) and an oral adenovirus vectored- VLP-based construct (Vaxart, South San Francisco, CA USA) as prototype vaccines in the access and implementation framework. For simplicity we refer to these as oral novel norovirus vaccines and injectable novel norovirus vaccines.

Possibility of implementation within existing delivery systems

Both oral and injectable vaccines are common vaccine constructs on the market therefore theoretically implementing with existing delivery systems is possible. However, the unique product profiles and formulation characteristics of a vaccine would have important impacts on whether such a new vaccine could be integrated into existing systems. Cold storage requirements, shelf life, and package volumes would be important, but final formulations/-packaging for both constructs are not known at this time. Vaccines which do not require significant cold storage demands, have a long shelf life and are contained in environmentally friendly and space efficient packaging are optimum. Unique to a currently developed adenovirus-vectored norovirus vaccine by Vaxart, this vaccine is formulated as oral tablets (or liquid formulation for patients unable to swallow tablets) which are room temperature-stable. [88] While there are no existing systems which deliver tablet-based vaccines globally, such a formulation could be conceivably integrated and would be an alternative to the current crowded landscape of injectable vaccines.

Vaccine schedule is also an important feature to consider in this area of implementation feasibility. Current trials of available constructs are considering both single dose and two dose regimens separated by 1 or 2 months with boosters at 4 months (see vaccine section). Single dose regimens could be better accommodated in schedules, though multi-dose regimens may be required particularly in younger populations who are not already primed by natural history exposure.

Finally, potential for combinability with other licensed or near-to license vaccines is a consideration. An attractive combination

Table 8

Overview of expectations of evidence that are likely to be required to support a global/regional/national policy recommendation, or financing for LICs.

Parameter for policy/financing consideration	Assumptions	Guidance/reports available
Consensus building to define priority public health goals for the vaccine candidate	- Need to establish norovirus as a competitive global public health priority in the landscape of all enteric infections and other priority global health pathogens. - Formulate and promulgate a WHO Preferred Product Characteristics for Vaccines Against Norovirus.	WHO Technical document. From Vaccine Development to Policy: A Brief Review of WHO Vaccine-Related Activities and Advisory Processes (2017) [81]. WHO WHO Preferred Product Characteristics (PPCs) [82].
Facilitation and acceleration of product development to achieve WHO public health goals in accordance with WHO recommend norms and standards	- Improve global estimates of disease burden and better characterize the epidemiology of norovirus infection. - Support further description of the spectrum of natural disease history including post-infectious consequences. - Support vaccine antigen selection decisions to cover broad variation of global norovirus strains to assure adequate coverage. - Develop consensus guidance about the use of LMIC human challenge models to support regulatory considerations and approvals. - Support the characterization of immunological surrogates/correlates of protection. - Define appropriate clinical development pathways for vaccine approval in LMIC populations (children and adults).	WHO Technical Document. From Vaccine Development to Policy: A Brief Review of WHO Vaccine-Related Activities and Advisory Processes (2017) [81].
Registration of product by a functional National Regulatory Authority	Given the dual use potential of a norovirus vaccine for reduction of disease morbidity and mortality in a HIC, a norovirus vaccine would likely receive either a national regulatory authority approval.	
Review of key evidence inputs by SAGE working group (WG) to inform optimal use of vaccine from public health perspective, including safety, operational issues and implementation research, and programmatic suitability, as well as the quality of the evidence, values and preferences, equity, feasibility, etc.	- Detailed information on epidemiological features of norovirus disease burden globally and regionally to include age-specific mortality, morbidity, and social impact. Genotype distribution over time and the likelihood of vaccine coverage would be critical to review. - Clinical considerations of the norovirus may be important including challenges in clinical management, and long-term health complications (if any). - Analysis of alternatives for disease prevention and control such as emerging therapeutics, or improved strategies of ORS delivery and management of childhood diarrheal/vomiting. - Vaccine and immunization characteristics would be key considerations including efficacy, herd immunity, safety, cold chain, vaccine availability, schedule, and ability to reach target populations and monitor an impact of an immunization program. - Formal cost-effectiveness analyses would be beneficial, ideally at region and country level. Affordability of vaccine/cost key. - Evaluation of interactions with other interventions and control strategies as well as impact of vaccine introduction on the wider health system could be considered. - Social, legal, ethical considerations are entertained.	WHO Guidance for the development of evidence-based vaccination-related recommendations [83].
SAGE recommendations (from SAGE WG) to WHO are adapted into global policy published as Vaccine Position Paper	- Vaccine position paper development at the World Health Organization based on SAGE recommendation is a complex, rigorous, multifaceted process involving many stakeholders and occurring over roughly a two-year timeline. - SAGE accepts or modifies the proposed WG recommendations or states the need for revisiting steps in the process. In the latter case, the issue is revisited at a later SAGE meeting. SAGE decisions are reached by consensus as opposed to using a voting mechanism, thus promoting in-depth discussion of the evidence and careful weighing of benefits and harms. SAGE is the arbiter with respect to the recommendations included in the position paper and is independent of WHO. - Initial draft is subject to an iterative process with multiple stakeholder reviews (both internal and external) and revisions with final publication in the Weekly Epidemiological Record.	WHO Supplement to WHO Vaccine Position Papers. Guideline Development Group [83].

Table 8 (continued)

Parameter for policy/financing consideration	Assumptions	Guidance/reports available
Concurrent with or following SAGE recommendation for widespread use, companies can submit their dossier for WHO prequalification	- While HIC countries are likely to develop a norovirus vaccine, vaccine supply will likely require production from a non-HIC country vaccine manufacturer. To be eligible for prequalification, the NRA of record would need to meet certain requirements defined by WHO. Currently, common global suppliers of prequalified vaccines for low-income country markets include those based in India and China. - Partnership with the International Federation of Pharmaceutical Manufacturers Association (IFPMA) and the Developing Country Vaccine Manufacturer Network (DCVMN) regarding norovirus vaccines may be helpful. - Combination vaccine approaches with IFPMA and DCVMN rotavirus manufactures may be strategic.	FDA. WHO Vaccine Pre-qualification Program. 2018 [84,85]. WHO Guidance Documents. WHO - Prequalification of Medical Products (IVDs, Medicines, Vaccines and Immunization Devices, Vector Control) [86].
Develop a package of information to meet Gavi's approach to prioritizing adoption of support of new vaccines	Gavi's approach to prioritizing new vaccines for investment include the following categories would need to be addressed through consultations with in-country stakeholders, peer-reviewed literature, expert and partner input, health impact modelling and analytics developed for the VIS process. - Rigorous assessment of health impact to include the impact of immunization program on child mortality, overall mortality and overall morbidity. - Defining of additional impact considerations with norovirus to include epidemic potential, alignment with global/regional health priorities, herd immunity, analysis of alternatives, socio-economic inequity considerations, gender inequity, and/or disease of regional importance. - Development of implementation feasibility to include capacity and supplier base, GAVI market shaping potential, ease of supply chain integration, ease of programmatic integration, vaccine efficacy and safety. - Formal conduct of cost and value analysis which includes vaccine procurement cost, in-country operational cost, procurement cost per event averted.	Gavi Vaccine Investment Strategy [80].

would be a norovirus combined with rotavirus vaccine given the overlap in clinical condition, as well as the global epidemiology of norovirus. Oral and next generation parenteral rotavirus vaccines are currently being used or may be introduced into the near future. An alternative opportunity might also be to make a combined influenza-norovirus vaccine given the similar geographic distributions (global), strong overlap in seasonality, and the potential need to update the norovirus vaccine with prevailing genotypes as new genotypes emerge.

Thus, the possibility of implementation within existing delivery systems is seen as HIGH to VERY HIGH.

Commercial attractiveness

In support of favorability for this factor, based on our assessment there are large target populations in HIC and LMIC, both private and public markets. Though formal market assessments are needed, it would be likely that military and traveler markets would be quick to adopt such a vaccine, as well as food handlers and those working in congregate settings where norovirus outbreaks are known to frequently occur. In addition, given that norovirus is a recurrent illness among all age-groups and the potential that the vaccine might need to be readministered as genotype epidemiology changes, demand requirements may be higher than traditional pediatric vaccines. This may be seen as a downside as well if manufacturers are required to reformulate the vaccine at some frequency with safety and efficacy studies if correlates of protection are not established.

The potential downside for the attractiveness of a norovirus vaccine is whether the vaccine would meet considerations and

be prioritized under Gavi's Vaccine Investment Strategy. If non-mortality burden of disease is considered and augmented with broader population-based burden of disease estimates, the global public health value of a norovirus vaccine may be considerable and of high priority. If the vaccine has a large global market in HIC and middle-income countries who are willing to pay, this may also increase interest given the opportunity for cost-sharing of a high-volume vaccine with tiered pricing.

Given these reasons, the commercial attractiveness for a norovirus vaccine at present is assessed as MODERATE to HIGH.

Clarity of licensure and policy decision pathway

Rotavirus vaccines (and other acute diarrheal vaccines under development) have paved the way for clinical development, licensure and policy decision pathways. Given the attractiveness of a norovirus vaccine to HIC populations, it is highly likely that a recognized NRA would license the vaccine for their populations including pediatric age-groups. The WHO SAGE in working on rotavirus vaccines has an existing framework to consider a norovirus vaccine, though would need to be expanded to consider the full public health value of a vaccine that extends beyond children under 5 years.

Thus, we assess the clarity of licensure and policy decision pathway to be VERY HIGH for a norovirus vaccine.

Expected financing mechanism

A norovirus vaccine would likely have fairly expansive global interest in high income countries given the documented impact of disease burden and epidemiology. Less is known about the

potential interest in LMICs with competing demands for existing licensed vaccines and other novel vaccines entering the market. Given the potential dual use market for a norovirus vaccine, large volume and tiered pricing strategies could provide cost of vaccine offsets for LMICs with advanced market commitment incentives.

Therefore, the expected financing mechanism is considered LOW to MODERATE.

Ease of uptake

A pediatric vaccine would likely be able to be integrated into an EPI schedule. However, depending on the timing of introduction there may be concerns about another separate injection for norovirus vaccine. Combination of the vaccine with penta- or hexavalent vaccines, or a combined diarrhea vaccine (with inactivated rotavirus or shigella) may be attractive but would require other clinical and technical development. Alternatively, an oral formulation may also increase uptake given it would not require additional injection. Adult and pediatric dose formulations could present a challenge as well. Use of norovirus in the HIC should not present a major barrier.

Thus, it is assessed that the ease of uptake is considered HIGH.

9. Conclusion

The consideration of norovirus as a target for vaccine development as a priority pathogen is complex. On one hand, its incidence and impact are noted in all regions of the world as well as in both younger and older age-groups, thus making the potential value of preventing disease vast. This would also appear to be a driving factor to encourage multiple stakeholders who might want to see such a vaccine developed. However, in contrast to a number of other priority pathogens for which vaccines are being developed, the economic and health burden attributed to norovirus infections are generally due to milder disease and there is often a premium placed on vaccines that prevent infections that commonly lead to death. However, if one were to look at this infection from a holistic perspective, there is a considerable global disease burden that should place this vaccine as a priority pathogen. Furthermore, norovirus is one of a number of enteric pathogens for which there are current vaccines available and underutilized (e.g., rotavirus) as well as vaccines under development that provided competition for another enteric vaccine to develop (e.g., shigella, non-Typhoid salmonella and ETEC). Given these alternative interventions that are underutilized and under development, norovirus may not present as a global public health priority pathogen. However, to solve the current problem of enteric burden of disease as well as the important long-term health manifestations that accompanies populations with high disease burden caused by multiple infections, a 'this AND that' is needed perspective can be taken.

There are many positive considerations regarding the state of science, and vaccine development pipeline that encourage a positive outlook on the probability of success that a safe and effective norovirus vaccine could be developed. Burden of disease data (and ongoing public health surveillance) are broadly available to provide strong data that guides vaccine need, though measures of impact on work-force productivity and the accounting of impacts of mild-to-moderate disease need focus. There are currently-four different norovirus vaccines under development, relying on proven technology (VLPs) and currently in phase 2 field efficacy trials. Furthermore, there is a controlled human infection model that could be utilized to support or accelerate (e.g., in HIC adults) vaccine licensure. For LMIC pediatric indication, there is an existing 'playbook' on how to develop, test and approve enteric vaccines, particularly given the robust pathways that rotavirus vaccines have been advanced through.

More work is needed to understand how a norovirus vaccine might fit in the current payer models of Gavi, as well as middle-income and higher-income public and private markets.

Disclaimers

The conclusions, findings, and opinions expressed by authors contributing to this journal do not necessarily reflect the official position of the U.S. Department of Health and Human Services, the Public Health Service, the Centers for Disease Control and Prevention, the World Health Organization or the authors' affiliated institutions.

The current knowledge described in this document is largely based on studies from the pre-COVID-19-pandemic era. The impact of large-scale non-pharmaceutical interventions against SARS-CoV-2 on the underlying *epi* of norovirus, including potential changes in its disease dynamics, the proportion of susceptible individuals in different age groups, and possible disruptions to the cycles between epidemics is unknown.

Data availability

No data was used for the research described in the article.

Declaration of Competing Interest

BAL reports personal fees from Epidemiological Research and Methods, LLC. MO acknowledges financial support from ANID PIA/PUENTE AFB220003 and reports receiving grants and research support from Janssen Vaccines & Prevention B.V., Bharat Biotech International Limited, and HilleVax Inc. CFL declares that he receives research grant funding to his Institute from Takeda Vaccines Inc. and HilleVax Inc. for norovirus epidemiology and a norovirus vaccine phase II trial, respectively. All other authors declare no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The team would like to sincerely thank the Office of Medical Research staff Meghana Veeramachaneni and Amber Emerson for their invaluable editing and project management assistance. This work in part was also supported by the Bill & Melinda Gates Foundation Seattle, WA [INV029307].

This supplement was sponsored by the World Health Organization's Immunization, Vaccines, and Biologicals unit. The authors alone are responsible for the views expressed in each article and they do not necessarily represent the views, decisions, or policies of the institutions with which they are affiliated.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2023.03.034>.

References

- [1] Lopman B. Global burden of norovirus and prospects for vaccine development. CDC Foundation; 2015 Aug. 46 p. Available from: <https://www.cdc.gov/norovirus/downloads/global-burden-report.pdf>.
- [2] Burke RM, Mattison CP, Marsh Z, Shioda K, Donald J, Salas SB, et al. Norovirus and other viral causes of medically attended acute gastroenteritis across the age spectrum: results from the medically attended acute gastroenteritis study in the United States. *Clin Infect Dis* [Internet]. 2021;73:e913–20. Available from: Doi: 10.1093/cid/ciab033.
- [3] Ballard S-B, Requena D, Mayta H, Sanchez GJ, Oyola-Lozada MG, Colquechagua Aliaga FD, et al. Enteropathogen changes after rotavirus vaccine scale-up. *pediatrics* [Internet]. 2022;149. Available from: Doi: 10.1542/peds.2020-049884.

- [4] Tarr GAM, Pang X-L, Zhuo R, Lee BE, Chui L, Ali S, et al. Attribution of pediatric acute gastroenteritis episodes and emergency department visits to norovirus genogroups I and II. *J Infect Dis* [Internet]. 2021;223:452–61. Available from: [Doi: 10.1093/infdis/jiaa391](https://doi.org/10.1093/infdis/jiaa391).
- [5] Payne DC, Vinjé J, Szilagyi PG, Edwards KM, Staat MA, Weinberg GA, et al. Norovirus and medically attended gastroenteritis in U.S. children. *N Engl J Med* [Internet]. 2013;368:1121–30. Available from: [Doi: 10.1056/NEJMsa1206589](https://doi.org/10.1056/NEJMsa1206589).
- [6] Bartsch SM, Lopman BA, Ozawa S, Hall AJ, Lee BY. Global economic burden of norovirus gastroenteritis. *PLoS ONE* [Internet]. 2016;11:e0151219. Available from: [Doi: 10.1371/journal.pone.0151219](https://doi.org/10.1371/journal.pone.0151219).
- [7] Wikswo ME, Kambhampati A, Shioda K, Walsh KA, Bowen A, Hall AJ, et al. Outbreaks of acute gastroenteritis transmitted by person-to-person contact, environmental contamination, and unknown modes of transmission—United States, 2009–2013. *MMWR Surveill Summ* [Internet]. 2015;64:1–16. Available from: [Doi: 10.15585/mmwr.mm6412a1](https://doi.org/10.15585/mmwr.mm6412a1).
- [8] Villabruna N, Koopmans MPG, de Graaf M. Animals as reservoir for human norovirus. *Viruses* [Internet]. 2019;11. Available from: [Doi: 10.3390/v11050478](https://doi.org/10.3390/v11050478).
- [9] Lopman BA, Steele D, Kirkwood CD, Parashar UD. The vast and varied global burden of norovirus: prospects for prevention and control. *PLoS Med* [Internet]. 2016;13:e1001999. Available from: [Doi: 10.1371/journal.pmed.1001999](https://doi.org/10.1371/journal.pmed.1001999).
- [10] Lanata CF, Fischer-Walker CL, Olascoaga AC, Torres CX, Aryee MJ, Black RE, et al. Global causes of diarrheal disease mortality in children <5 years of age: a systematic review. *PLoS ONE* [Internet]. 2013;8:e72788. Available from: [Doi: 10.1371/journal.pone.0072788](https://doi.org/10.1371/journal.pone.0072788).
- [11] Pires SM, Fischer-Walker CL, Lanata CF, Devleeschauwer B, Hall AJ, Kirk MD, et al. Aetiology-specific estimates of the global and regional incidence and mortality of diarrhoeal diseases commonly transmitted through food. *PLoS ONE* [Internet]. 2015;10:e0142927. Available from: [Doi: 10.1371/journal.pone.0142927](https://doi.org/10.1371/journal.pone.0142927).
- [12] Kirk MD, Pires SM, Black RE, Caipo M, Crump JA, Devleeschauwer B, et al. World health organization estimates of the global and regional disease burden of 22 foodborne bacterial, protozoal, and viral diseases, 2010: A data synthesis. *PLoS Med* [Internet]. 2015;12:e1001921. Available from: [Doi: 10.1371/journal.pmed.1001921](https://doi.org/10.1371/journal.pmed.1001921).
- [13] Asare EO, Hergott D, Seiler J, Morgan B, Archer H, Wiyeh AB, et al. Case fatality risk of diarrhoeal pathogens: a systematic review and meta-analysis. *Int J Epidemiol* [Internet]. 2022. Available from: [Doi: 10.1093/ije/dyac098](https://doi.org/10.1093/ije/dyac098).
- [14] Pogreba-Brown K, Austhof E, Armstrong A, Schaefer K, Villa Zapata L, McClelland DJ, et al. Chronic gastrointestinal and joint-related sequelae associated with common foodborne illnesses: a scoping review. *Foodborne Pathog Dis* [Internet]. 2020;17:67–86. Available from: [Doi: 10.1089/fpd.2019.2692](https://doi.org/10.1089/fpd.2019.2692).
- [15] Porter CK, Faix DJ, Shiao D, Espirito J, Espinosa BJ, Riddle MS. Postinfectious gastrointestinal disorders following norovirus outbreaks. *Clin Infect Dis* [Internet]. 2012;55:915–22. Available from: [Doi: 10.1093/cid/cis576](https://doi.org/10.1093/cid/cis576).
- [16] Marshall JA, Hellard ME, Sinclair MI, Fairley CK, Cox BJ, Catton MG, et al. Incidence and characteristics of endemic norwalk-like virus-associated gastroenteritis. *J Med Virol* [Internet]. 2003;69:568–78. Available from: [Doi: 10.1002/jmv.10346](https://doi.org/10.1002/jmv.10346).
- [17] Ahmed SM, Lopman BA, Levy K. A systematic review and meta-analysis of the global seasonality of norovirus. *PLoS ONE* [Internet]. 2013;8:e75922. Available from: [Doi: 10.1371/journal.pone.0075922](https://doi.org/10.1371/journal.pone.0075922).
- [18] Walter F, Ott JJ, Claus H, Krause G. Sex- and age patterns in incidence of infectious diseases in Germany: analyses of surveillance records over a 13-year period (2001–2013). *Epidemiol Infect* [Internet]. 2018;146:372–8. Available from: [Doi: 10.1017/S0950268817002771](https://doi.org/10.1017/S0950268817002771).
- [19] Cannon JL, Lopman BA, Payne DC, Vinjé J. Birth cohort studies assessing norovirus infection and immunity in young children: a review. *Clin Infect Dis* [Internet]. 2019;69:357–65. Available from: [Doi: 10.1093/cid/ciy985](https://doi.org/10.1093/cid/ciy985).
- [20] Gruber JF, Bowman NM, Becker-Dreps S, Reyes Y, Belson C, Michaels KC, et al. Risk factors for norovirus gastroenteritis among Nicaraguan children. *Am J Trop Med Hyg* [Internet]. 2017;97:937–43. Available from: [Doi: 10.4269/ajtmh.16-0799](https://doi.org/10.4269/ajtmh.16-0799).
- [21] Violato M, Taylor-Robinson D, Hungerford D, Gray A, O'Brien S, Iturriza-Gómara M. Family income and exposure to norovirus in childhood: findings from the UK Millennium Cohort Study. *SSM Popul Health* [Internet]. 2019;8:100445. Available from: [Doi: 10.1016/j.ssmph.2019.100445](https://doi.org/10.1016/j.ssmph.2019.100445).
- [22] Kreidieh K, Charide R, Dbaibo G, Melhem NM. The epidemiology of norovirus in the Middle East and North Africa (MENA) region: a systematic review. *Virol J* [Internet]. 2017;14:220. Available from: [Doi: 10.1186/s12985-017-0877-3](https://doi.org/10.1186/s12985-017-0877-3).
- [23] Simmons K, Gambhir M, Leon J, Lopman B. Duration of immunity to norovirus gastroenteritis. *Emerging Infect Dis* [Internet]. 2013;19:1260–7. Available from: [Doi: 10.3201/eid1908.130472](https://doi.org/10.3201/eid1908.130472).
- [24] Rouhani S, Peñataro Yori P, Paredes Olortegui M, Sigua Salas M, Rengifo Trigos D, Mondal D, et al. Norovirus infection and acquired immunity in 8 countries: results from the MAL-ED Study. *Clin Infect Dis* [Internet]. 2016;62:1210–7. Available from: [Doi: 10.1093/cid/ciw072](https://doi.org/10.1093/cid/ciw072).
- [25] Saito M, Goel-Apaza S, Espetia S, Velasquez D, Cabrera L, Loli S, et al. Multiple norovirus infections in a birth cohort in a Peruvian Periurban community. *Clin Infect Dis* [Internet]. 2014;58:483–91. Available from: [Doi: 10.1093/cid/cit763](https://doi.org/10.1093/cid/cit763).
- [26] Jones TF, Yackley J. Foodborne disease outbreaks in the United States: a historical overview. *Foodborne Pathog Dis* [Internet]. 2018;15:11–5. Available from: [Doi: 10.1089/fpd.2017.2388](https://doi.org/10.1089/fpd.2017.2388).
- [27] Ashbaugh HR, Early JM, Johnson ME, Simons MP, Graf PCF, Riddle MS, et al. A multisite network assessment of the epidemiology and etiology of acquired diarrhea among U.S. military and western travelers (global travelers' diarrhea study): a principal role of norovirus among travelers with gastrointestinal illness. *Am J Trop Med Hyg* [Internet]. 2020;103:1855–63. Available from: [Doi: 10.4269/ajtmh.20-0053](https://doi.org/10.4269/ajtmh.20-0053).
- [28] Hungerford D, Jere KC, Bar-Zeev N, Harris JP, Cunliffe NA, Iturriza-Gómara M. Epidemiology and genotype diversity of norovirus infections among children aged <5 years following rotavirus vaccine introduction in Blantyre, Malawi. *J Clin Virol* [Internet]. 2020;123:104248. Available from: [Doi: 10.1016/j.jcv.2019.104248](https://doi.org/10.1016/j.jcv.2019.104248).
- [29] Hofmann FM, Olawumi E, Michaelis M, Stöfel U, Hofmann F. Significance of norovirus in occupational health: a review of published norovirus outbreaks in Central and Northern Europe. *Int Arch Occup Environ Health* [Internet]. 2020;93:911–23. Available from: [Doi: 10.1007/s00420-020-01543-4](https://doi.org/10.1007/s00420-020-01543-4).
- [30] Manuel CS, Moore MD, Jaykus L-A. Predicting human norovirus infectivity - recent advances and continued challenges. *Food Microbiol* [Internet]. 2018;76:337–45. Available from: [Doi: 10.1016/j.fm.2018.06.015](https://doi.org/10.1016/j.fm.2018.06.015).
- [31] Bucardo F, Reyes Y, Svensson L, Nordgren J. Predominance of norovirus and sapovirus in Nicaragua after implementation of universal rotavirus vaccination. *PLoS ONE* [Internet]. 2014;9:e8201. Available from: [Doi: 10.1371/journal.pone.0098201](https://doi.org/10.1371/journal.pone.0098201).
- [32] Biswas JS, Lentaing J, Hill NE, Harrison JJ, Mackenzie H, Akorli E, et al. Epidemiology and etiology of diarrhea in UK military personnel serving on the United Nations Mission in South Sudan in 2017: a prospective cohort study. *Travel Med Infect Dis* [Internet]. 2019;28:34–40. Available from: [Doi: 10.1016/j.tmaid.2018.12.004](https://doi.org/10.1016/j.tmaid.2018.12.004).
- [33] Bennett SD, Sodha SV, Ayers TL, Lynch MF, Gould LH, Tauxe RV. Produce-associated foodborne disease outbreaks, USA, 1998–2013. *Epidemiol Infect* [Internet]. 2018;146:1397–406. Available from: [Doi: 10.1017/S0950268818001620](https://doi.org/10.1017/S0950268818001620).
- [34] Neo FJX, Loh JJP, Ting P, Yeo WX, Gao CQH, Lee VJM, et al. Outbreak of caliciviruses in the Singapore military, 2015. *BMC Infect Dis* [Internet]. 2017;17:719. <https://doi.org/10.1186/s12879-017-2821-y>.
- [35] de Graaf M, Villabruna N, Koopmans MP. Capturing norovirus transmission. *Curr Opin Virol* [Internet]. 2017;22:64–70. <https://doi.org/10.1016/j.coviro.2016.11.008>.
- [36] Johnson PC, Mathewson JJ, DuPont HL, Greenberg HB. Multiple-challenge study of host susceptibility to Norwalk gastroenteritis in US adults. *J Infect Dis* [Internet]. 1990;161:18–21. <https://doi.org/10.1093/infdis/161.1.18>.
- [37] Rogawski McQuade ET, Liu J, Kang G, Kosek MN, Lima AAM, Bessong PO, et al. Protection from natural immunity against enteric infections and etiology-specific diarrhea in a longitudinal birth cohort. *J Infect Dis* [Internet]. 2020;222:1858–68. Available from: [Doi: 10.1093/infdis/jiaa031](https://doi.org/10.1093/infdis/jiaa031).
- [38] Wyatt RG, Dolin R, Blacklow NR, DuPont HL, Buscho RF, Thornhill TS, et al. Comparison of three agents of acute infectious nonbacterial gastroenteritis by cross-challenge in volunteers. *J Infect Dis* [Internet]. 1974;129:709–14. <https://doi.org/10.1093/infdis/129.6.709>.
- [39] Mirelman AJ, Ballard SB, Saito M, Kosek MN, Gilman RH. Cost-effectiveness of norovirus vaccination in children in Peru. *Vaccine* [Internet]. 2015;33:3084–91. <https://doi.org/10.1016/j.vaccine.2015.05.004>.
- [40] Gao Z, Liu B, Yan H, Li W, Jia L, Tian Y, et al. Norovirus outbreaks in Beijing, China, from 2014 to 2017. *J Infect* [Internet]. 2019;79:159–66. Available from: [Doi: 10.1016/j.jinf.2019.05.019](https://doi.org/10.1016/j.jinf.2019.05.019).
- [41] Sakon N, Yamazaki K, Nakata K, Kanbayashi D, Yoda T, Mantani M, et al. Impact of genotype-specific herd immunity on the circulatory dynamism of norovirus: a 10-year longitudinal study of viral acute gastroenteritis. *J Infect Dis* [Internet]. 2015;211:879–88. <https://doi.org/10.1093/infdis/jiu496>.
- [42] Arowolo KO, Ayolabi CI, Lapinski B, Santos JS, Raboni SM. Epidemiology of enteric viruses in children with gastroenteritis in Ogun State, Nigeria. *J Med Virol* [Internet]. 2019;91:1022–9. <https://doi.org/10.1002/jmv.25399>.
- [43] Guarines KM, Mendes RPG, de Magalhães JFF, Pena L. Norovirus-associated gastroenteritis, Pernambuco, Northeast Brazil, 2014–2017. *J Med Virol* [Internet]. 2020;92:1093–101. Available from: [Doi: 10.1002/jmv.25631](https://doi.org/10.1002/jmv.25631).
- [44] Degiuseppe JI, Barclay L, Gomes KA, Costantini V, Vinjé J, Stupka JA. Molecular epidemiology of norovirus outbreaks in Argentina, 2013–2018. *J Med Virol* [Internet]. 2020;92:1330–3. <https://doi.org/10.1002/jmv.25684>.
- [45] Stewart S, Robertson C, Pan J, Kennedy S, Dancer S, Haahr L, et al. Epidemiology of healthcare-associated infection reported from a hospital-wide incidence study: considerations for infection prevention and control planning. *J Hosp Infect* [Internet]. 2021;114:10–22. Available from: [Doi: 10.1016/j.jhin.2021.03.031](https://doi.org/10.1016/j.jhin.2021.03.031).
- [46] Burch T. Validation of quantitative microbial risk assessment using epidemiological data from outbreaks of waterborne gastrointestinal disease. *Risk Anal* [Internet]. 2019;39:599–615. <https://doi.org/10.1111/risa.13189>.
- [47] Rockx B, De Wit M, Vennema H, Vinjé J, De Bruin E, Van Duynhoven Y, et al. Natural history of human calicivirus infection: a prospective cohort study. *Clin Infect Dis* [Internet]. 2002;35:246–53. <https://doi.org/10.1086/341408>.
- [48] Bartsch SM, Lopman BA, Hall AJ, Parashar UD, Lee BY. The potential economic value of a human norovirus vaccine for the United States. *Vaccine* [Internet]. 2012;30:7097–104. <https://doi.org/10.1016/j.vaccine.2012.09.040>.
- [49] Sauer M, Vasudevan P, Meghani A, Luthra K, Garcia C, Knoll MD, et al. Situational assessment of adult vaccine preventable disease and the potential for immunization advocacy and policy in low- and middle-income countries.

- Vaccine [Internet]. 2021;39:1556–64. Available from: [Doi: 10.1016/j.vaccine.2021.01.066](https://doi.org/10.1016/j.vaccine.2021.01.066).
- [50] Jin M, Wu S, Kong X, Xie H, Fu J, He Y, et al. Norovirus outbreak surveillance, China, 2016–2018. *Emerging Infect Dis* [Internet]. 2020;26:437–45. Available from: [Doi: 10.3201/eid2603.191183](https://doi.org/10.3201/eid2603.191183).
 - [51] Sherwood J, Mendelman PM, Lloyd E, Liu M, Boslego J, Borkowski A, et al. Efficacy of an intramuscular bivalent norovirus GL1/GII.4 virus-like particle vaccine candidate in healthy US adults. *Vaccine* [Internet]. 2020;38:6442–9. <https://doi.org/10.1016/j.vaccine.2020.07.069>.
 - [52] Tallant A, Porter CK, Putnam SD, Tribble DR, Hooper TI, Riddle MS. Relative cost-effectiveness of a norovirus vaccine in the deployed military setting compared to a vaccine against campylobacter sp., ETEC, and shigella sp. *Vaccine* [Internet]. 2014;32:5156–62. Available from: [Doi: 10.1016/j.vaccine.2014.07.070](https://doi.org/10.1016/j.vaccine.2014.07.070).
 - [53] Arnold BF, Martin DL, Juma J, Mkocha H, Ochieng JB, Cooley GM, et al. Enteropathogen antibody dynamics and force of infection among children in low-resource settings. *ELife* [Internet]. 2019;8. Available from: <https://doi.org/10.7554/eLife.45594>.
 - [54] Kulkarni R, Lole K, Chitambar SD. Seroprevalence of antibodies against GII.4 norovirus among children in Pune, India. *J Med Virol* [Internet]. 2016;88:1636–40. <https://doi.org/10.1002/jmv.24495>.
 - [55] Evaluation of infectivity and illness of Norwalk GI.1 virus Lot 001-09NV in the human challenge model. 2018 Oct 26 [last updated 2020 Jan 22; cited 2022 May 11]. In: *ClinicalTrials.gov* [Internet]. Bethesda (MD): U.S. National Library of Medicine. 2018-. Available from: <https://clinicaltrials.gov/ct2/show/NCT03721549>.
 - [56] Phase I norovirus challenge model. 2019 Nov 22 [last updated 2021 Apr 9; cited 2022 May 11]. In: *ClinicalTrials.gov* [Internet]. Bethesda (MD): U.S. National Library of Medicine. 2019-. Available from: <https://clinicaltrials.gov/ct2/show/NCT04174560>.
 - [57] Atmar RL, Bernstein DI, Harro CD, Al-Ibrahim MS, Chen WH, Ferreira J, et al. Norovirus vaccine against experimental human Norwalk Virus illness. *N Engl J Med* [Internet]. 2011;365:2178–87. <https://doi.org/10.1056/NEJMoa1101245>.
 - [58] Bernstein DI, Atmar RL, Lyon GM, Treanor JJ, Chen WH, Jiang X, et al. Norovirus vaccine against experimental human GII.4 virus illness: a challenge study in healthy adults. *J Infect Dis* [Internet]. 2015;211:870–8. Available from: [Doi: 10.1093/infdis/jiu497](https://doi.org/10.1093/infdis/jiu497).
 - [59] Tan M. Norovirus vaccines: current clinical development and challenges. *Pathogens* [Internet]. 2021;10. Available from: <https://doi.org/10.3390/pathogens10121641>.
 - [60] Cates JE, Vinjé J, Parashar U, Hall AJ. Recent advances in human norovirus research and implications for candidate vaccines. *Expert Rev Vaccines* [Internet]. 2020;19:539–48. <https://doi.org/10.1080/14760584.2020.1777860>.
 - [61] Ettayebi K, Tenge VR, Cortes-Penfield NW, Crawford SE, Neill FH, Zeng X-L, et al. New insights and enhanced human norovirus cultivation in human intestinal enteroids. *MSphere* [Internet]. 2021;6. Available from: [Doi: 10.1128/mSphere.01136-20](https://doi.org/10.1128/mSphere.01136-20).
 - [62] Gaensbauer JT, Lamb M, Calvimontes DM, Asturias EJ, Kamidani S, Contreras-Roldan IL, et al. Identification of enteropathogens by multiplex pcr among rural and urban Guatemalan children with acute diarrhea. *Am J Trop Med Hyg* [Internet]. 2019;101:534–40. Available from: [Doi: 10.4269/ajtmh.18-0962](https://doi.org/10.4269/ajtmh.18-0962).
 - [63] Mathew S, Smatti MK, Al Ansari K, Nasrallah GK, Al Thani AA, Yassine HM. Mixed viral-bacterial infections and their effects on gut microbiota and clinical illnesses in children. *Sci Rep* [Internet]. 2019;9:865. <https://doi.org/10.1038/s41598-018-37162-w>.
 - [64] Pouletty M, De Pontual L, Lopez M, Morin L, Poilane I, Pham LL, et al. Multiplex pcr reveals a high prevalence of multiple pathogens in traveller's diarrhoea in children. *Arch Dis Child* [Internet]. 2019;104:141–6. <https://doi.org/10.1136/archdischild-2017-314327>.
 - [65] Andersson M, Kabayiza J-C, Elfving K, Nilsson S, Msellem MI, Mårtensson A, et al. Coinfection with enteric pathogens in East African children with acute gastroenteritis—associations and interpretations. *Am J Trop Med Hyg* [Internet]. 2018;98:1566–70. Available from: [Doi: 10.4269/ajtmh.17-0473](https://doi.org/10.4269/ajtmh.17-0473).
 - [66] Ramani S, Estes MK, Atmar RL. Correlates of protection against norovirus infection and disease—where are we now, where do we go? *PLoS Pathog* [Internet]. 2016;12:e1005334.
 - [67] Tenge VR, Hu L, Prasad BVV, Larson G, Atmar RL, Estes MK, et al. Glycan recognition in human norovirus infections. *Viruses* [Internet]. 2021;13. Available from: <https://doi.org/10.3390/v13102066>.
 - [68] Optimal human dose for GII.2 norovirus (snow mountain) challenge studies. 2015 Jun 16 [last updated 2018 Dec 7; cited 2021 Dec 20]. In: *ClinicalTrials.gov* [Internet]. Bethesda (MD): U.S. National Library of Medicine. 2015-. Available from: <https://clinicaltrials.gov/ct2/show/NCT02473224>.
 - [69] New challenge pool of Norwalk virus inoculum. 2005 Aug 30 [last updated 2014 May 9; cited 2022 May 11]. In: *ClinicalTrials.gov* [Internet]. Bethesda (MD): U.S. National Library of Medicine. 2005-. Available from: <https://clinicaltrials.gov/ct2/show/NCT00138476>.
 - [70] Efficacy and safety of two doses of HIL-214 in children. 2022 Mar 16 [last updated 2022 Jun 10; cited 2022 May 11]. In: *ClinicalTrials.gov* [Internet]. Bethesda (MD): U.S. National Library of Medicine. 2022-. Available from: <https://clinicaltrials.gov/ct2/show/NCT05281094>.
 - [71] A clinical trial to evaluate the safety and immunogenicity of norovirus bivalent vaccine. 2019 Dec 6 [last updated 2021 Apr 22; cited 2022 May 3]. In: *ClinicalTrials.gov* [Internet]. Bethesda (MD): U.S. National Library of Medicine. 2019-. Available from: <https://clinicaltrials.gov/ct2/show/NCT04188691>.
 - [72] Clinical trial to evaluate the recombinant norovirus bivalent (GI.1/GII.4) vaccine (hansenula polymorpha). 2021 Jun 28 [last updated 2022 May 6; cited 2022 Apr 17]. In: *ClinicalTrials.gov* [Internet]. Bethesda (MD): U.S. National Library of Medicine. 2021-. Available from: <https://clinicaltrials.gov/ct2/show/NCT04941261>.
 - [73] Clinical trial of quadrivalent recombinant norovirus vaccine (pichia pastoris). 2020 Sep 24 [last updated 2020 Sep 25; cited 2022 Apr 18]. In: *ClinicalTrials.gov* [Internet]. Bethesda (MD): U.S. National Library of Medicine. 2020-. Available from: <https://clinicaltrials.gov/ct2/show/NCT04563533>.
 - [74] Kim L, Liebowitz D, Lin K, Kasperek K, Pasetti MF, Garg SJ, et al. Safety and immunogenicity of an oral tablet norovirus vaccine, a phase I randomized, placebo-controlled trial. *JCI Insight* [Internet]. 2018;3. Available from: <https://doi.org/10.1172/jci.insight.121077>.
 - [75] Gaythorpe KAM, Trotter CL, Conlan AJK. Modelling norovirus transmission and vaccination. *Vaccine* [Internet]. 2018;36:5565–71. <https://doi.org/10.1016/j.vaccine.2018.07.053>.
 - [76] Steele MK, Remais JV, Gambhir M, Glasser JW, Handel A, Parashar UD, et al. Targeting pediatric versus elderly populations for norovirus vaccines: a model-based analysis of mass vaccination options. *Epidemics* [Internet]. 2016;17:42–9. <https://doi.org/10.1016/j.epidem.2016.10.006>.
 - [77] Steimle LN, Havumaki J, Eisenberg MC, Eisenberg JNS, Prosser LA, Pike J, et al. Cost-effectiveness of pediatric norovirus vaccination in daycare settings. *Vaccine* [Internet]. 2021;39:2133–45. <https://doi.org/10.1016/j.vaccine.2021.02.066>.
 - [78] Bartsch SM, O'Shea KJ, Wedlock PT, Ferguson MC, Siegmund SS, Lee BY. Potential clinical and economic value of norovirus vaccination in the community setting. *Am J Prev Med* [Internet]. 2021;60:360–8. <https://doi.org/10.1016/j.amepre.2020.10.022>.
 - [79] Ballard S-B, Tallant A, Guerra RG, Quigley D, Stiegmann R, Mirelman AJ, et al. Application of a cost-effectiveness analysis of pathogen-specific vaccines against gastroenteritis to a military population in a developing country setting. *Vaccine* [Internet]. 2020;38:2292–7. <https://doi.org/10.1016/j.vaccine.2020.01.075>.
 - [80] PATH. Injectable rotavirus vaccines – what value could they bring? *Vaccines Work* [Internet]. 2021 Oct 28 [cited 2022 May 12]; [about 6 screens]. Available from: <https://www.gavi.org/vaccineswork/injectable-rotavirus-vaccines-what-value-could-they-bring>.
 - [81] World Health Organization. From vaccine development to policy: a brief review of WHO vaccine-related activities and advisory processes (2017) 2017:11 p.
 - [82] Neuzil KM, Bresee JS, de la Hoz F, Johansen K, Karron RA, Krishnan A, et al. WHO Preferred Product Characteristics for Next-Generation Influenza Vaccines Advisory Group. Data and product needs for influenza immunization programs in low- and middle-income countries: rationale and main conclusions of the WHO preferred product characteristics for next-generation influenza vaccines. *Vaccine* [Internet]. 2017;35. Available from: <https://doi.org/10.1016/j.vaccine.2017.08.088>.
 - [83] World Health Organization. Guidance for the development of evidence-based vaccination-related recommendations. Version 8 2017:55 p.
 - [84] Dellepiane N, Wood D. Twenty-five years of the WHO vaccines prequalification programme (1987–2012): lessons learned and future perspectives. *Vaccine* [Internet]. 2015;33:52–61. <https://doi.org/10.1016/j.vaccine.2013.11.066>.
 - [85] WHO Vaccine Prequalification Program [Internet]. Silver Spring (MD): U.S. Food & Drug Administration; [updated 2018 Mar 23; cited 2022 May 12]. Available from: <https://www.fda.gov/vaccines-blood-biologics/who-engagements/who-vaccine-prequalification-program>.
 - [86] World Health Organization. WHO - Prequalification of Medical Products (IVDs, Medicines, Vaccines and Immunization Devices, Vector Control). [cited 2022 May 12]. Available from: <https://extranet.who.int/pqweb/>.
 - [87] Buttery JP, Kirkwood C. Rotavirus vaccine implementation: evidence to fill the gap? *Lancet Glob Health* [Internet]. 2021;9:e885–6. Available from: [Doi: 10.1016/S2214-109X\(21\)00265-5](https://doi.org/10.1016/S2214-109X(21)00265-5).
 - [88] Vaxart. Oral. [Internet]. Vaxart Inc 2021. San Francisco (CA): Vaxart; [cited 2022 May 10]. Available from: <https://vaxart.com/portfolio-item/oral/>.