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Tropical and travel-associated norovirus: current concepts

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Abstract

Purpose of review—We highlight recent advances relevant to understanding norovirus infections in the tropics, both in populations living in developing settings and travelers to these regions.

Recent findings—Because of the decrease in diarrheal disease associated with the global rollout of vaccines against rotavirus, norovirus is emerging as the predominant cause of diarrhea morbidity among children in the tropics, and evidence suggests that it contributes to adult disease in endemic populations and travelers. In addition to identifying potential target populations for preventive measures, we provide an update on norovirus vaccine development and concepts related to their implementation in low-income and middle-income countries.

Summary—These current concepts related to norovirus-attributable disease burden, clinical significance, and economic impact can potentially be applied to tailoring efforts to prevent and mitigate the effects of this important enteropathogen.

Keywords

calicivirus; diarrhea; gastroenteritis; low-income and middle-income country; norovirus; travelers; vaccine

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Conflicts of interest

There are no conflicts of interest.

INTRODUCTION

Globally, norovirus is the most common cause of acute sporadic gastroenteritis in adults and the second leading cause of severe diarrhea in children, after rotavirus. In countries with mature rotavirus immunization programs, norovirus is emerging as the predominant diarrhea-associated pathogen in young children [1]. This review covers the latest scientific insights into norovirus infections in the tropics while addressing the challenges of controlling this disease in low-income and middle-income country (LMIC) populations and travelers to these regions.

ASSESSING NOROVIRUS DISEASE BURDEN IN THE TROPICS

Norovirus detection in symptomatic cases

Ahmed *et al.* [2■] estimated a global norovirus prevalence of 18% among acute gastroenteritis cases in a meta-analysis of 175 studies published between 2008 and 2014. The pooled prevalences among hospitalized and community cases were 17 and 24%, respectively [2■]. When stratified by WHO mortality category [3], norovirus was more prevalent in diarrhea stools from low mortality than high mortality developing settings (19 versus 14%, respectively) [2■]. This likely represents a more diverse enteropathogen landscape in the context of higher overall diarrhea incidence in high-mortality settings [2■]. Prior to rotavirus vaccine implementation, norovirus was the most frequently identified pathogen in ambulatory [4] and community [5■■] diarrhea cases in certain LMIC settings. Rotavirus was usually reported more frequently in hospitalized children [4], although up to 55% of hospital diarrhea cases demonstrated human calicivirus (norovirus and/or sapovirus) infection when evaluated with both immunologic and molecular detection methods [6,7]. Following successful universal rotavirus vaccination in LMICs, norovirus is recognized as the predominant pathogen in hospitalized [8■], outpatient [4], and community [9■] diarrhea cases. Norovirus has also been associated with adult diarrhea in LMIC military service members [10■■].

Norovirus detection in asymptomatic individuals

The detection of norovirus in stools from asymptomatic individuals complicates disease burden estimates. Globally, the pooled asymptomatic prevalence from the 20 controlled studies in Ahmed's meta-analysis was 7% [2■]. Fifteen to 35% of norovirus infections are asymptomatic, but both symptomatically infected and asymptomatically infected individuals shed virus at similar levels for similar amounts of time, although duration may vary by genotype and variant [5■■]. Host genetic factors, such as the absence of the α-1,2-fucosyltransferase enzyme in 'secretor negative' individuals, appear to confer absolute protection to infection to specific variants [11■]. Other host factors, such as histo-blood group antigen polymorphisms, result in heterogeneous susceptibility to norovirus infection [11■]. Following infection, viral shedding lasts approximately 20–30 days in adults [12]. Excretion can be prolonged in children, the elderly, and immunocompromised who serve as reservoirs for transmission [13] and may also contribute to the emergence of novel epidemic variants [1]. In Saito *et al.*'s [5■■] Peruvian birth cohort, norovirus excretion was longer for genogroup (G) II (median 34.5 days; maximum 98) than GI (median 8.5 days; maximum

49). Both symptomatic and asymptomatic infections during the first year of life were associated with lower mean length-for-age z scores (coefficient −0.33) that persisted into the second year of life [5■■].

In the absence of longitudinal data, distinguishing symptomatic from asymptomatic norovirus infections is difficult. Asymptomatic individuals tend to have higher real-time reverse transcriptase polymerase chain reaction cycle threshold values than individuals with acute gastroenteritis, but there is no clear viral load cutoff that corresponds with symptom resolution [14]. To illustrate the marked increase in asymptomatic norovirus prevalence resulting in small increases in basic reproduction number, Lopman *et al.* [15■■] created a dynamic norovirus transmission model of norovirus infection, immunity, and disease. In this model, the case:control prevalence ratio was high in developed settings and decreased dramatically in a high-exposure scenario with the same disease incidence [15■■]. This could explain why the Global Enteric Multi-Center Study (GEMS), a case–control analysis of diarrhea in the tropics, noted similar frequencies of norovirus in case and control stools, ultimately determined that norovirus contributed minimally to moderate-to-severe diarrheal disease [16]. In contrast, longitudinal studies that more clearly distinguish symptomatic and asymptomatic infections demonstrate higher burdens of norovirus-associated diarrhea in similar developing settings [5■■,17■■]. In their Peruvian birth cohort, Saito *et al.* [5■■] calculated a norovirus attributable diarrheal disease fraction of 7.8% in the first and 23.1% in the second year of life.

Defining norovirus disease and severity

The lack of standard norovirus case definitions and clinical severity measures complicate disease burden estimation and comparative intervention evaluations in tropical settings. Historically dubbed ‘winter vomiting disease,’ norovirus often causes emesis in the absence of diarrhea. As a result, diarrhea-based gastroenteritis case definitions likely under-estimate disease burden by excluding vomiting-only disease. Of the 175 studies included in Ahmed *et al.*’s meta-analysis of norovirus gastroenteritis, 143 (82%) either did not provide a case definition for acute gastroenteritis or excluded vomiting-only disease. Clinical severity measures are most commonly based on the 20-point Vesikari scale, which dichotomizes gastroenteritis into ‘mild’ (<11) or ‘severe’ disease [18,19]. Other measures of disease severity include the 24-point Clark scale [20], modified Vesikari scales [5■■], the World Health Organization scale [21], and severity scores based on signs and symptoms [22,23■■, 24–27], reported symptoms [28–31], length of hospitalization [29,32], and impact on daily activities [33■]. Different gastroenteritis case and severity definitions can bias results against specific pathogens. For example, defining ‘moderate-to-severe’ diarrhea as the presence of sunken eyes, loss of skin turgor, intravenous fluid prescription, dysentery, or hospital admission, GEMS reported that norovirus contributed minimally to moderate-to-severe disease [16]. In contrast, O’Ryan *et al.*’s [34] hospital-based study of diarrheal disease in Chile reported that norovirus was a leading cause of moderate-to-severe disease, as defined by a Vesikari score greater than 6 (of 20 possible points) [19]. Using uniform case definitions and severity measures for norovirus vaccine efficacy studies will allow direct comparison of results, avoiding the possibility that different results might be

attributable to the use of different scales, as was the case when Rotateq and Rotarix were evaluated using the Clark and Vesikari scales, respectively [35].

Malnutrition and norovirus infection

Undernutrition affects one in five children in the tropics and has been associated with half of deaths in children younger than 5 years worldwide [36]. Poor nutrition weakens host immune responses and alters the gut microbiota, both of which can worsen the clinical course of diarrheal disease [37■■]. After infecting well-nourished and protein energy deficient mice with murine norovirus, Hickman *et al.* [37■■] found that malnourished mice demonstrated more weight loss, reduced antibody responses, loss of protective immunity, and enhanced viral evolution. Although the well-nourished mice fared better in terms of disease severity, norovirus infection resulted in a gut microbial environment similar to that of malnourished mice [37■■]. Human studies are currently being conducted by the Interactions of Malnutrition & Enteric Infections: Consequences for Child Health and Development (MAL-ED) group, but results are pending [38■■,39■–41■,42–49]. Particularly relevant to assessing tropical norovirus infections are investigations that assess the role of the gut microbiota in nutritional status [50■], immune markers and vaccine failure in undernourished populations [51■,52■], tropical enteropathy and gut function [51■,53■■,54], and the long-term impact of these factors on child development [38■■, 55].

Norovirus coinfections

Individuals living in tropical settings often have intense exposure to enteric pathogens, and detection of more than one pathogen, particularly helminths, in stool samples is common. Helminth coinfections impair viral immunity via an innate immunomodulation pathway. In this pathway, helminth-activated T_H2 cells release interleukin (IL)-4 and IL-13, which ligate IL-4 receptors on M2 macrophages [56■■,57■■]. This inhibits the production of virus-specific T-cells and greatly increases viral replication in macrophages [57■■]. Helminth infections are also associated with changes in the gut microbiota [58,59], although the extent to which these changes affect host responses to viruses and other enteropathogens is not clear. The type 2 immune response stimulated by helminth infection is also associated with enhanced tissue repair and reduced inflammation [60], which could mitigate the severity of disease in coinfected individuals.

The molecular and cellular interactions between enteropathogens are important to consider when evaluating norovirus disease burden and pathogen-specific interventions [61■]. However, currently used qualitative pathogen detection [62,63■] and regression-based coinfection adjustment [16] methods are imperfect in the setting of asymptomatic infection, postinfectious shedding [64], and varying durations of immunity [65]. Probabilistic analytical methods that give weight to first infections and account for pathogen prevalance prior to symptom onset may present a clearer picture of pathogen-specific disease burdens in tropical settings where polymicrobial infections are detected frequently [66■■].

NOROVIRUS IN TRAVELERS TO THE TROPICS

Up to 100 million people from high-income countries travel to the tropics each year, and 40–60% of them develop diarrhea [67,68]. Norovirus is the second leading cause of travelers' diarrhea after enteropathogenic *Escherichia coli* (ETEC) [69■]. A systematic review of 51 published studies of travelers' diarrhea reported a pooled norovirus case stool prevalence of 6.6%, with higher norovirus prevalence in stools from travelers to Latin America (16.9%) and Africa (12.8%) than travelers to Asia (3.2%) [70■]. Norovirus has been associated with diarrhea in both children and adults returning from tropical settings [70■], and norovirus coinfections with other pathogens, particularly ETEC, are common, [71,72]. Travelers' diarrhea is associated with alterations in the gut microbiota that appear similar, regardless of the infecting enteropathogen [69■].

Norovirus afloat

Norovirus has a very low infectious dose [73,74,75■,76■] and is extremely hard to eliminate from the environment [6], making contamination of ships common. The US Centers for Disease Control and Prevention's Vessel Sanitation Program assists to prevent outbreaks on cruise ships with foreign itineraries, where the impact of norovirus has been well documented [77]. During the 1990 s, the implementation of sanitation measures resulted in the reduction of cruise-ship norovirus outbreaks from 6.3 to 3.7 per 1,000 ship-weeks [78]. In US military populations afloat, gastroenteritis out-breaks have been reported at nearly 10 times the rate of cruise ships, with an overall incidence of 33.2 outbreaks per 1,000 ship-weeks among 44 Navy ships deployed to the Middle East during a 12-month analysis period [79]. It is assumed that norovirus contributed significantly to these out-breaks since a concurrent surveillance study identified norovirus in at least one of the 11 outbreaks included in this study, and in four of four Navy ships which submitted outbreak stool specimens for testing as part of a separate surveillance report [79]. Attack rates were similar on large and small military ships (3.3% overall), but larger ships had more frequent outbreaks than smaller ships (66 versus 26 per 1,000 ship weeks, respectively) [79]. Smaller ships had increased outbreak durations, possibly because less intense transmission resulted in slower saturation of the susceptible population relative to the more crowded big ships [79]. Unlike international cruise ships, which demonstrate a winter-spring predominance, US Navy shipboard outbreaks occurred throughout the year [79].

Norovirus in deployed troops ashore

Norovirus outbreaks among ground troops in deployed settings are also common. Among 20,320 deployed US service members presenting with acute gastroenteritis from 2005 to 2012, 60% of cases were associated with viral pathogens, and norovirus detection increased steadily from 2006 to 2012 [80]. Still another 25,938 cases from this period were documented as 'nonspecific diarrhea,' although norovirus likely contributed significantly [80]. During Operations Desert Shield and Desert Storm, numerous norovirus outbreaks occurred in service members [81–83]. Norovirus outbreaks also clustered at the beginning of the conflicts in Iraq and Afghanistan [84–87]. One such outbreak resulted in the evacuation of 11 British troops from Afghanistan, including one individual with disseminated intravascular coagulation and two individuals requiring ventilator support [86]. This

outbreak highlighted the potential for norovirus to cause severe disease in otherwise healthy individuals under extreme environmental stress [86]. In another norovirus outbreak in Iraq, 975 of 1,340 affected British troops were admitted to a field hospital, where significant transmission to medical staff occurred, resulting in hospital closure [85,88,89].

NOROVIRUS VACCINES IN THE TROPICS

Recent reviews by Vesikari and Blazevic [90] and Debbink *et al.* [91] detail current vaccine development strategies. Briefly, LigoCyte used a baculovirus-insect cell system to develop the first virus-like particle (VLP) vaccine against norovirus GI.1 [92]. Their monophosphoryl lipid A (MPL) and chitosan-adjuvanted intranasal vaccine produced a moderate level of protection against the homologous virus in subsequent challenge studies [92,93]. This proof-of-principle vaccine was followed by an MPL-adjuvanted bivalent GI.1/GII.4 VLP vaccine candidate, delivered intramuscularly [94■]. The corresponding challenge study was performed with a heterologous GII.4 virus, a better representation of natural infection than challenge with a virus homologous to the vaccine VLP [95■■]. This vaccine provided 100% protection against severe vomiting and severe diarrhea, but was not protective against infection, and only partially protective against symptoms of any severity. Using a Vesikari scale, the vaccine reduced diarrhea severity significantly, from 7.3 in the placebo group to 4.5 in the vaccine group [95■■]. Other candidate vaccines in development include a ‘trivalent’ vaccine containing a rotavirus VP6 protein and norovirus GI.3 and GII.4 VLPs [96,97■■]; an intranasal dry-powder vaccine [98]; an *E. coli*-produced P particle vaccine [99]; and a combined norovirus P particle–rotavirus VP8 antigen vaccine [100]. Multivalent α-virus replicon particle platforms for VLP formation [101], polyvalent norovirus P domain glutathione S-transferase complexes [102], and edible vaccine delivery mechanisms [103] are also being explored. Significant work remains to enhance the efficacy of norovirus vaccines against genetically diverse norovirus variants, lengthen the duration of vaccine-induced immunity, lower vaccination costs, determine the acceptability of an adjuvant, and optimize dosing and delivery.

Vaccine efficacy considerations in the tropics

To date, norovirus vaccine trials have occurred in well-nourished adults from high-income countries. However, vaccine underperformance is common in developing settings [104–106], where diarrhea frequently occurs, the prevalence of undernutrition is high, and the duration of breast-feeding is suboptimal [107■■]. Recent mouse model studies demonstrated that malnourished mice infected with murine norovirus develop fairly normal serum antiviral immunoglobulin G responses, but have significantly reduced mucosal immunoglobulin A responses that correspond with a lack of protective immunity [37■■]. Parenteral vaccine administration could potentially overcome the apparent intestinal barrier to immunization in undernourished populations. Promoting exclusive breastfeeding and improving nutrition may also improve oral vaccine performance in developing settings [107■■]. Given that 70% of pediatric norovirus infections occur between 6 and 24 months of age worldwide, and 60% occur before 12 months of age in high-mortality developing settings, Shioda *et al.* estimated that a pediatric norovirus vaccine would have to be delivered before 6 months of age to prevent the majority of childhood infections [108■].

Vaccine cost-effectiveness in the tropics

Mirelman *et al.* [109■■] recently developed a model to evaluate norovirus vaccine cost-effectiveness in LMIC populations. When applied to a hypothetical Peruvian birth cohort, this model found that norovirus vaccination could offer economic value under the right conditions by averting poor health outcomes and substantial healthcare utilization costs [109■■]. Assuming a two-dose vaccination cost of $26.44 per individual vaccinated, 85% vaccine coverage, the 47% reported vaccine efficacy in Atmar *et al.*'s vaccine trial, and peri-urban diarrhea incidence rates reported by Saito *et al.*, the vaccine cost-effectiveness was $19.86 per diarrhea case averted, $68.23 per outpatient visit averted, and $21,415.95 per disability adjusted life year (DALY) averted [109■■]. Using higher norovirus incidence rates from a less developed rural setting, vaccine cost-effectiveness improved to $9.20 per diarrhea case averted, $32.29 per outpatient visit averted, and $10,135 per DALY averted [109■■]. This model did not include the indirect costs of norovirus infection or the out-of-pocket direct costs for self-treatment and home care, which are expected to be significant and would further augment the economic value of norovirus vaccination [110■]. Likewise, it did not consider the relationship between diarrhea and malnutrition, the prevention of which would result in additional health, social, and economic benefits. The impact of reduced norovirus transmission to older children and adults was not included in the model, but could also be significant, as young children play a key role in transmitting norovirus to all age groups [65].

Tallant *et al.*'s [111■■] recently published a new model of diarrhea vaccine cost-effectiveness for deploying US military personnel. Using a diarrhea-based definition of norovirus disease, they calculated a norovirus vaccine cost-effectiveness of $1,344 per duty day lost averted. This model assumed a two-dose vaccination cost of $60.14 per individual vaccinated; 75% vaccine coverage; 80% vaccine effectiveness, reflecting the minimally acceptable military vaccine profile, rather than the efficacy of vaccines currently under development [112,113]; and a duration of immunity of 3.5 months, which is twice the average duration of US military deployments [111■■]. The estimated cost per duty day lost averted for military vaccines against *Campylobacter* sp., ETEC, and *Shigella* sp. were $800, $776, and $1,275, respectively [111■■]. When the norovirus disease definition was modified to include vomiting, the norovirus vaccine cost per duty day lost averted decreased to $572, making it the most cost-effective of the four hypothetical diarrhea vaccines evaluated (against *Campylobacter* sp., ETEC, *Shigella* sp., and norovirus) [111■■]. As a reference, deployment operational costs per troop were an estimated $935 per day, so a norovirus vaccine with the described characteristics would be considered cost-effective for deploying US military personnel (or cost-saving, if vomiting disease is considered) [111■■].

Apart from young children and military service members from high-income countries deployed to tropical regions, other tropical and travel-associated populations that might benefit from norovirus vaccination include the elderly [114■], hospitalized patients [114■], individuals with immune compromise, school-aged children, developing country military personnel [10■■], healthcare workers [114■], food handlers, food processing facility workers, farm workers, and travel industry workers [1]. The key challenge of evaluating

norovirus vaccine cost-effectiveness in these populations is the lack of norovirus disease burden data, in addition to uncertainty about the price, dosing, and effectiveness of candidate vaccines. To aid economic evaluations of vaccines in LMICs, norovirus-specific models should be incorporated into existing cost-effectiveness analysis tools [115■].

CONCLUSION

In conclusion, noroviruses are well recognized as the most common cause of acute gastroenteritis in all age groups worldwide, and they are becoming the predominant pathogen associated with pediatric diarrhea in the tropics in the wake of the global rotavirus vaccine rollout. In order to appropriately assess disease burden and plan health interventions for populations in developing settings, we will need to refine our case definitions, severity measures, and intervention assessment tools. We will also need to better elucidate the complex relationship between diarrhea, malnutrition, gut microbiota, environmental enteropathy, enteric coinfections, and the immune system. Multivalent diarrhea vaccines will likely be more cost-effective if they are effective against rotavirus, norovirus, and other enteropathogens, such as sapovirus [116], which contribute significantly to diarrheal disease. Further, as climate change increases the incidence of diarrhea disease in the tropics, we will need to develop forecasting methods in order to develop appropriate interventions and plan health services [117].

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KEY POINTS

- Noroviruses are responsible for a significant proportion of acute gastroenteritis in populations living in and traveling to tropical regions, where suboptimal water and sanitation, environmental changes, and the vicious cycle of malnutrition, immune compromise, and infection drive both the incidence and severity of gastrointestinal disease.
- Progress has occurred in the development of candidate norovirus vaccines, and multivalent vaccines against a combination of enteropathogens (e.g., rotavirus, norovirus, and sapovirus) may be the most cost-effective option for future diarrhea vaccination programs in LMICs.
- Estimating the norovirus disease burden requires uniform gastroenteritis case definitions, comparable disease severity scales, and disease models that address asymptomatic infection, coinfections with other pathogens, and heterogeneous host susceptibility patterns.