COMMENTARY

Epidemiologic challenges in norovirus vaccine development

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ABSTRACT

Norovirus is the leading cause of acute gastroenteritis (AGE) worldwide. In the United States norovirus is estimated to cause 19–21 million illnesses, 1.7–1.9 million outpatient visits, 56,000–71,000 hospitalizations, and 570–800 deaths annually. Through direct costs and loss of productivity, norovirus disease cost the US economy more than \$5.5 billion annually. Due to the lack of available therapies to treat norovirus infections and their highly infectious nature, preventing norovirus illness through vaccination is an appealing strategy. Currently, several norovirus vaccines are in development, including five vaccines in preclinical trials, an oral monovalent vaccine (Vaxart, Inc.) that recently completed a phase IB clinical trial, and a bivalent intramuscular vaccine (Takeda Pharmaceutical Company Limited) in a phase IIB clinical trial. However, no norovirus vaccines are currently available on the market. In this commentary we aim to describe some of the barriers faced in norovirus vaccine development, particularly focusing on vaccine effectiveness and defining the target population.

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Introduction

Norovirus is the leading cause of acute gastroenteritis (AGE) worldwide,^{1,2} and in the United States norovirus is estimated to cause 19–21 million illnesses, 1.7–1.9 million outpatient visits, 56,000–71,000 hospitalizations, and 570–800 deaths annually.³

Norovirus illness is characterized by a sudden onset of diarrhea and/or vomiting, nausea, and abdominal cramps that generally last for 1–3 days with a subsequent resolution to baseline health.^{2,4,5} However, symptom duration, expression, and severity may change based on age group, immune system status, and previous exposure history.^{2,4,5} Norovirus is transmitted directly from person to person via the fecal-oral route or aerosolized vomit, or through indirect transmission by contaminated food, water, or environmental surfaces.⁴ Once infected, individuals begin viral shedding in stool and vomitus as soon as 8 hours after exposure, with viral shedding peaking 4 days after exposure and, in some instances, continuing for up to 56 days.^{4,6} Given the high titers produced during viral shedding and the low number of viruses that are needed to establish infection, it is possible that one individual could potentially infect thousands.⁴

Currently there are no therapies available to treat an active norovirus infection.² Due to norovirus' highly infectious nature, stability in the environment, and the ability for pre-, post-, and asymptomatic viral shedding, norovirus is challenging to control and frequently causes outbreaks.^{4,7–9} Although the symptom duration is short, norovirus infections cost the US more than \$5.5 billion annually through direct medical costs and loss of

productivity, and this likely underestimates the full economic burden.^{10–12}

Given its public health importance, the challenges posed in controlling infection, and the lack of available therapies, preventing norovirus disease through vaccination is an appealing strategy. Currently, several norovirus vaccines are in development, including five vaccines in preclinical trials, an oral monovalent vaccine (Vaxart, Inc.) that recently completed a phase IB clinical trial, and a bivalent intramuscular vaccine (Takeda Pharmaceutical Company Limited) in a phase IIB clinical trial.^{2,13}

In this commentary we describe some of the barriers faced in norovirus vaccine development, with specific focus on issues pertaining to vaccine effectiveness and defining the target population (Table 1).

Vaccine effectiveness

For norovirus vaccines to achieve high vaccine effectiveness, potential challenges must be overcome with respect to strain selection, defining norovirus illness, and duration of protection.

Strain selection

There are at least seven genogroups (G) of norovirus, of which three – GI, GII, GIV – infect humans.¹⁴ GI norovirus genotypes are a relatively easy target for norovirus vaccines as their genetic profile has remained relatively constant for the last 30 years.^{15,16} GI genotypes, however, only cause 10% of the norovirus disease burden in the US, while GII strains

Table 1. Key barriers faced in norovirus vaccine development.

	Topic	Challenge	Potential Solution
Vaccine Effectiveness	<i>Strain Selection</i>	Multiple norovirus genotypes cause acute gastroenteritis in the United States	Multivalent vaccines will likely be needed to protect against a range of epidemiologically important genotypes
	<i>Defining and Assessing Norovirus Illness</i>	Strains evolve over time. In the past two decades, new genotypes (e.g., GII.4, GII.17, GII.2) have frequently emerged	Vaccines may have to be modified periodically to provide protection against emerging genotypes
		Seroresponse and viral shedding following norovirus infections vary by age group, immune status, and previous exposure history	Further characterization of norovirus seroresponse following infection and the etiologic implications of post-symptomatic and asymptomatic viral shedding
		Studies vary on how norovirus severity or illness is defined, making comparisons difficult	A standardized definition for norovirus illness and a clinical scoring system for disease severity will need to be developed
	<i>Duration of Protection</i>	The duration of long-term immunity conferred by norovirus infection or vaccination is unknown	Challenge and vaccination studies will need to evaluate long-term immunity to norovirus infections
Defining the Target Population	<i>High Income Countries</i>	There is no universally accepted correlate of protection against norovirus	The recently established in vitro culture system can be leveraged to validate previously proposed correlates of protection and potentially identify more definitive markers of immunity
		Vaccine efficacy in children and elderly individuals is unknown	Efficacy studies need to be performed in potential vaccine target groups to see if/how previous exposures or immune system health impact vaccine-conferred protection
	<i>Low and Middle Income Countries</i>	Limited work has explored the cost effectiveness of vaccinating travelers, military members, healthcare workers, and food handlers	Outbreak surveillance data and modeling studies can better identify the transmission dynamics of norovirus so cost effectiveness estimates for these groups can be developed
		In high transmission settings, the impact of norovirus on the overall AGE burden remains unclear	In particular, by implementing longitudinal cohort studies the incidence and etiologic role of norovirus can be better understood, and provide insight on the true burden of norovirus in AGE
		Limited data is available on the genotype distribution of norovirus in LMICs	Establish a global norovirus strain surveillance network to standardized practices and exchange data on circulating genotypes

cause approximately 90%.¹⁷ More specifically, GII.4 has caused approximately 70% of all norovirus illnesses in the US since the 1990s, and is associated with more severe health outcomes.^{4,17–19} Likely driven by the evasion of population immunity, new GII.4 variants have emerged every 2–4 years suggesting that cross-protection within the GII.4 genotype may be incomplete.^{4,20,21} Additionally, other genotypes, such as GII.2 and GII.17, have emerged to prominence in recent years in some regions of the world.^{22,23} To be optimally effective, norovirus vaccines will likely need to protect against a range of epidemiologically important genotypes, including any new genotypes that emerge and become prevalent over time.^{5,11,18}

Defining and assessing norovirus illness

The ability to accurately quantify the effectiveness of a norovirus vaccine revolves around researchers' ability to accurately define and assess norovirus illness. As symptom expression, duration, and viral shedding can vary by age group, immune status, and previous exposure history, defining norovirus-associated illness is surprisingly complex.^{2,4,5} To further complicate matters,

norovirus is frequently detected in healthy asymptomatic individuals, or individuals hospitalized for other conditions without AGE symptoms.^{4,24} To help address this issue, vaccine clinical trials have defined norovirus illness using a combination of symptoms, viral shedding, and/or seroresponse^{15,25} However, investigators have noted that while some subjects met symptomatic criteria, they failed to express viral shedding in feces or exhibit a seroresponse.²⁵ Additionally, current monovalent and bivalent vaccine trials have used different definitions to define norovirus disease, making comparisons of vaccine efficacy difficult.^{15,25} To address this issue, efforts should be directed at better understanding symptom expression, seroresponse, and symptomatic and asymptomatic viral shedding among patients experiencing norovirus-associated illness in order to develop a standardized definition for norovirus illness and a clinical scoring system of disease severity that could be used in future vaccine trials.

Duration of protection

The success of norovirus vaccines depend largely on the duration of immunity they can confer. While modeling

studies have suggested that naturally-induced norovirus immunity could last 4–9 years, challenge studies have found that immunity only lasts from 2 months to 2 years after norovirus inoculation, although norovirus inoculums were significantly higher than would be observed in naturally acquired infections.^{18,26–29} Currently, no clinical data from challenge studies have been published to verify longer immunity durations.^{2,18} Norovirus vaccine clinical trials have shown moderate vaccine efficacy, but participants were challenged with vaccine specific norovirus strains only 4 weeks after receiving the second dose of the vaccine.^{15,25} Results from longer-term immunity studies are unavailable.

Nonetheless, even with a 12-month duration of immunity and 50% vaccine efficacy, norovirus vaccination can remain cost effective for children aged 0–4 years and adults aged ≥ 65 years, depending on vaccine cost.^{5,12,18} Until the duration of immunity is known, however, firm cost effectiveness estimates cannot be established. While short-term immunity may be acceptable for some population groups (e.g., travelers or military), longer duration of immunity would be desirable for those at highest risk of endemic disease (i.e., children and elderly) for the vaccine to have maximal public health impact.¹¹

At the present, there is no universally accepted correlate of protection against norovirus, although many have been explored.³⁰ With the recent development of a viable *in vitro* culture system for norovirus, the identification of markers of norovirus immunity are likely on the horizon.³¹ Future studies should work to explore the duration of immunity that can be established from norovirus infection or vaccination, and further evaluate and define correlates of protection against norovirus illness.

Defining the target population for vaccination

When a norovirus vaccine is licensed, recommendations on who should be vaccinated will be based at least in part on disease burden, the potential to infect others, or both.

High income countries

In the United States, the highest norovirus disease burden occurs among young children and elderly individuals.³ When compared to other age groups, the highest norovirus incidence rates are observed among young children, the highest norovirus-associated hospitalization rates are observed among young children and the elderly, and the highest risk of norovirus-associated deaths are observed among elderly individuals.^{1,3,11,32–36} In addition to a high disease burden, children also have the highest estimated R_0 (4.3) when compared to other age groups (R_0 range 0.4–1.2), and it may be possible that vaccinating children would protect older adults through indirect population effects (i.e., herd immunity).³⁷

Healthcare workers and food handlers represent unique groups in that they have a high risk of transmitting norovirus to others once infected. Due to the nature of their work, healthcare workers have the potential to infect very vulnerable populations, whom if infected, would likely have more severe outcomes than other population groups.^{11,19} Independent of healthcare workers risk of transmission, norovirus outbreaks in healthcare settings are a well-recognized problem, and in

the United States, approximately 60% of all norovirus outbreaks occur in elderly long-term care facilities.^{9,17} While not necessarily interacting with vulnerable populations, infected food workers have the potential to expose and infect large populations.³⁸ In fact, norovirus is the most common food-borne illness in the US, and is frequently caused by infected food workers exercising inadequate hand hygiene.⁹

Current vaccine trials have been conducted primarily among healthy adults with pre-existing norovirus antibodies. While vaccine effectiveness in this group could readily be applied to travelers, military members, healthcare workers, and food handlers, these results do not readily apply to children, elderly, and the immunocompromised.¹¹ Future work will need to be completed to determine vaccine efficacy in these groups, and discover if previous exposures are needed to trigger the vaccine specific immune response among children and if older adults have the immunologic capacity to mount an effective immune response.¹¹ In addition, while cost-effectiveness has been estimated for children and elderly populations, limited work has explored the cost-effectiveness or impact of vaccinating other groups.^{12,37} By better identifying the transmission dynamics of norovirus at the household, community, and population level through modeling studies and outbreak surveillance data, clearer guidance could be issued for recommended vaccination groups.

Low and Middle Income Countries (LMICs)

While norovirus is a leading cause of AGE in the US, the vast majority of norovirus associated illnesses and deaths occur in LMICs.^{39,40} Of the estimated 685 million illnesses and 212,489 deaths that occur globally every year due to norovirus, 85% of the illnesses and 99% of deaths occur in LMICs.^{39,40} However, compared to the availability of data from high income countries, relatively few studies document the burden of norovirus and distribution of circulating strains in LMICs.¹ To ensure norovirus vaccination has the greatest impact where it is needed most, a global norovirus strain surveillance network should be established in LMICs to ensure that any potential norovirus vaccine meets the strain specific needs of that country.

In addition, cohort studies are needed to better understand the course of natural infection, particularly in LMICs.⁴¹ Case-control studies have sometimes found a similar proportion of norovirus in cases and controls, complicating interpretation of the role that norovirus plays in AGE.⁴² Modeling studies have suggested that this may be due to high R_0 in these settings, with healthy controls exhibiting post-symptomatic or asymptomatic viral shedding from frequent previously acquired natural infections.⁴³ With the implementation of longitudinal cohort studies in these settings we can more accurately document the incidence and etiologic role of norovirus, and provide better insight into the true burden of norovirus AGE in LMICs.⁴¹

Conclusion

With multiple norovirus vaccines in development, continued research is required to further accelerate vaccine development and maximize the potential public health impact of these vaccines. Establishing the degree of cross-protection afforded by various norovirus strains while monitoring emerging strains can

help establish which norovirus antigens should be present in vaccines. Through better understanding of symptom expression, viral shedding, and seroresponse among patients experiencing norovirus illness, standardized definitions and severity scales can be developed that could be utilized in future research and vaccine trials. By identifying correlates of protection against norovirus illness, the duration of protection conferred by natural infection and vaccination can be better established and evaluated. Finally, by identifying the role that previous norovirus exposures, immune system status, and transmission dynamics play in norovirus illness, clearer guidance can be developed for recommended vaccination target groups. Progress in each of these areas will help ensure rapid introduction of norovirus vaccines to the market and maximize their public health impacts upon licensure.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

References

- Ahmed SM, Hall AJ, Robinson AE, Verhoef L, Premkumar P, Parashar UD, Koopmans M, Lopman BA. Global prevalence of norovirus in cases of gastroenteritis: a systematic review and meta-analysis. *Lancet Infect Dis*. 2014;14(8):725–730. doi:10.1016/S1473-3099(14)70767-4.
- Mattison CP, Cardemil CV, Hall AJ. Progress on norovirus vaccine research: Public health considerations and future directions. Expert review of vaccines. 2018 Sep 2;17(9):773–784. doi: 10.1080/14760584.2018.1510327
- Hall AJ, Diab S, McGraw S, Barr B, Traslavina R, Higgins R, Talbot T, Blanchard P, Rimoldi G, Fahs Bender E, et al. Norovirus disease in the United States. *Emerging Infect Dis*. 2013;19(8):1198. doi:10.3201/eid1909.130682.
- Pringle K, Lopman B, Vega E, Vinje J, Parashar UD, Hall AJ. Noroviruses: epidemiology, immunity and prospects for prevention. *Future Microbiol*. 2015;10(1):53–67. doi:10.2217/fmb.14.102.
- Debbink K, Lindesmith LC, Baric RS. The state of norovirus vaccines. *Clin Infect Dis*. 2014;58(12):1746–1752. doi:10.1093/cid/ciu120.
- Atmar RL, Opekun AR, Gilger MA, Estes MK, Crawford SE, Neill FH, Graham DY. Norwalk virus shedding after experimental human infection. *Emerging Infect Dis*. 2008;14(10):1553–1557. doi:10.3201/eid1410.080117.
- Lopman B, Gastañaduy P, Park GW, Hall AJ, Parashar UD, Vinje J. Environmental transmission of norovirus gastroenteritis. *Curr Opin Virol*. 2012;2(1):96–102. doi:10.1016/j.coviro.2011.11.005.
- Ramani S, Atmar RL, Estes MK. Epidemiology of human noroviruses and updates on vaccine development. *Curr Opin Gastroenterol*. 2014;30(1):25–33. doi:10.1097/MOG.0000000000000022.
- Hall AJ, Wikswo ME, Pringle K, Gould LH, Parashar UD. Vital signs: foodborne norovirus outbreaks—United States, 2009–2012. *MMWR Morb Mortal Wkly Rep*. 2014;63(22):491–495.
- Lopman BA, Hall AJ, Curns AT, Parashar UD. Increasing rates of gastroenteritis hospital discharges in US adults and the contribution of norovirus, 1996–2007. *Clin Infect Dis*. 2011;52(4):466–474. doi:10.1093/cid/ciq163.
- Aliabadi N, Lopman BA, Parashar UD, Hall AJ. Progress toward norovirus vaccines: considerations for further development and implementation in potential target populations. *Expert Rev Vaccines*. 2015;14(9):1241–1253. doi:10.1586/14760584.2015.1073110.
- Bartsch SM, Lopman BA, Hall AJ, Parashar UD, Lee BY. The potential economic value of a human norovirus vaccine for the United States. *Vaccine*. 2012;30(49):7097–7104. doi:10.1016/j.vaccine.2012.09.040.
- Kim L, Jacobsen KM, Henry CJ, Huey MG, Parker RE, Page LS, Hill AA, Wang X, Frye SV, Earp HS, et al. Safety and immunogenicity of an oral tablet norovirus vaccine, a phase I randomized, placebo-controlled trial. *JCI Insight*. 2018;3(13). doi:10.1172/jci.insight.97941.
- Vinje J. Advances in laboratory methods for detection and typing of norovirus. *J Clin Microbiol*. 2015;53(2):373–381. doi:10.1128/JCM.01535-14.
- Atmar RL, Bernstein DI, Harro CD, Al-Ibrahim MS, Chen WH, Ferreira J, Estes MK, Graham DY, Opekun AR, Richardson C, et al. Norovirus vaccine against experimental human Norwalk Virus illness. *New England J Med*. 2011;365(23):2178–2187. doi:10.1056/NEJMoa1101245.
- Swanstrom J, Lindesmith LC, Donaldson EF, Yount B, Baric RS. Characterization of blockade antibody responses in GII. 2.1976 Snow Mountain virus-infected subjects. *J Virol*. 2014;88(2):829–837. doi:10.1128/JVI.02793-13.
- Vega E, Barclay L, Gregoricus N, Shirley SH, Lee D, Vinje J. Genotypic and epidemiologic trends of norovirus outbreaks in the United States, 2009 to 2013. *J Clin Microbiol*. 2014;52(1):147–155. doi:10.1128/JCM.02680-13.
- Cortes-Penfield NW, Ramani S, Estes MK, Atmar RL. Prospects and challenges in the development of a norovirus vaccine. *Clin Ther*. 2017;39(8):1537–1549. doi:10.1016/j.clinthera.2017.07.002.
- Burke RM, Shah MP, Wikswo ME, Barclay L, Kisselburgh H, Kambhampati A, Marsh Z, Cannon JL, Parashar UD, Vinje J, Hall AJ. The norovirus epidemiologic triad: Predictors of severe outcomes in US Norovirus Outbreaks, 2009–2016. *The Journal of Infectious Diseases*. 2018 Nov 15.
- Lindesmith LC, Donaldson EF, Baric RS. Norovirus GII. 4 strain antigenic variation. *J Virol*. 2011;85(1):231–242. doi:10.1128/JVI.01364-10.
- Debbink K, Lindesmith LC, Donaldson EF, Costantini V, Beltramello M, Corti D, Swanstrom J, Lanzavecchia A, Vinje J, Baric RS. Emergence of new pandemic GII. 4 Sydney norovirus strain correlates with escape from herd immunity. *J Infect Dis*. 2013;208(11):1877–1887. doi:10.1093/infdis/jit370.
- Chan MC, Wang N, Wilksch JJ, Page AJ, Cao H, Gujran S, Keane JA, Lithgow T, Ul-Haq I, Dougan G, et al. Global spread of norovirus GII. 17 Kawasaki 308, 2014–2016. *Emerging Infect Dis*. 2017;23(8):1350. doi:10.3201/eid2311.170833.
- Ao Y, Cong X, Jin M, Sun X, Wei X, Wang J, Zhang Q, Song J, Yu J, Cui J, et al. Genetic analysis of reemerging GII. P16–GII. 2 Noroviruses in 2016–2017 in China. *J Infect Dis*. 2018;218(1):133–143. doi:10.1093/infdis/jiy182.
- Saito M, Goel-Apaza S, Espetia S, Velasquez D, Cabrera L, Loli S, Crabtree JE, Black RE, Kosek M, Checkley W, et al. Multiple norovirus infections in a birth cohort in a Peruvian periurban community. *Clin Infect Dis*. 2013;58(4):483–491. doi:10.1093/cid/cit763.
- Bernstein DI, Atmar RL, Lyon GM, Treanor JJ, Chen WH, Jiang X, Vinje J, Gregoricus N, Frenck RW, Moe CL, et al. Norovirus vaccine against experimental human GII. 4 virus illness: a challenge study in healthy adults. *J Infect Dis*. 2014;211(6):870–878. doi:10.1093/infdis/jiu497.
- Johnson PC, Mathewson JJ, DuPont HL, Greenberg HB. Multiple-challenge study of host susceptibility to Norwalk gastroenteritis in US adults. *J Infect Dis*. 1990;161(1):18–21.
- Parrino TA, Schreiber DS, Trier JS, Kapikian AZ, Blacklow NR. Clinical immunity in acute gastroenteritis caused by Norwalk agent. *New England J Med*. 1977;297(2):86–89. doi:10.1056/NEJM197707142970204.
- Wyatt RG, Dolin R, Blacklow NR, DuPont HL, Buscho RF, Thornhill TS, Kapikian AZ, Chanock RM. Comparison of three agents of acute infectious nonbacterial gastroenteritis by cross-challenge in volunteers. *J Infect Dis*. 1974;129(6):709–714.

29. Simmons K, Diab S, McGraw S, Barr B, Traslavina R, Higgins R, Talbot T, Blanchard P, Rimoldi G, Fahsbender E, et al. Duration of immunity to norovirus gastroenteritis. *Emerging Infect Dis.* 2013;19(8):1260. doi:10.3201/eid1909.130682.
30. Ramani S, Estes MK, Atmar RL. Correlates of protection against norovirus infection and disease—where are we now, where do we go? *PLoS Pathog.* 2016;12(4):e1005334. doi:10.1371/journal.ppat.1005334.
31. Ettayebi K, Crawford SE, Murakami K, Broughman JR, Karandikar U, Tenge VR, Neill FH, Blutt SE, Zeng XL, Qu L, Kou B. Replication of human noroviruses in stem cell–derived human enteroids. *Science.* 2016 Aug 25;aaf5211. doi: 10.1126/science.aaf5211
32. Phillips G, Tam CC, Conti S, Rodrigues LC, Brown D, Iturriza-Gomara M, Gray J, Lopman B. Community incidence of norovirus-associated infectious intestinal disease in England: improved estimates using viral load for norovirus diagnosis. *Am J Epidemiol.* 2010;171(9):1014–1022. doi:10.1093/aje/kwq021.
33. Lindsay L, Wolter J, De Coster I, Van Damme P, Verstraeten T. A decade of norovirus disease risk among older adults in upper-middle and high income countries: a systematic review. *BMC Infect Dis.* 2015;15(1):425. doi:10.1186/s12879-015-1168-5.
34. Hall AJ, Curns AT, McDonald LC, Parashar UD, Lopman BA. The roles of *Clostridium difficile* and norovirus among gastroenteritis-associated deaths in the United States, 1999–2007. *Clin Infect Dis.* 2012;55(2):216–223. doi:10.1093/cid/cis386.
35. Trivedi TK, Desai R, Hall AJ, Patel M, Parashar UD, Lopman BA. Clinical characteristics of norovirus-associated deaths: a systematic literature review. *Am J Infect Control.* 2013;41(7):654–657. doi:10.1016/j.ajic.2012.08.002.
36. Harris JP, Edmunds WJ, Pebody R, Brown DW, Lopman BA. Deaths from norovirus among the elderly, England and Wales. *Emerging Infect Dis.* 2008;14(10):1546–1552. doi:10.3201/eid1410.080188.
37. Steele MK, Remais JV, Gambhir M, Glasser JW, Handel A, Parashar UD, Lopman BA. Targeting pediatric versus elderly populations for norovirus vaccines: a model-based analysis of mass vaccination options. *Epidemics.* 2016;17:42–49. doi:10.1016/j.epidem.2016.10.006.
38. Yang W, Steele M, Lopman B, Leon JS, Hall AJ. The population-level impacts of excluding norovirus-infected food workers from the workplace: A mathematical modeling study. *American Journal of Epidemiology.* 2018 Sep 7. doi:10.1093/aje/kwy198
39. Kirk MD, Lundgren JD, Ross M, Law M, Reiss P, Kirk O, Smith C, Wentworth D, Neuhaus J, Fux CA, 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.* 2015;12(12):e1001921. doi:10.1371/journal.pmed.1001809.
40. Pires SM, Fischer-Walker CL, Lanata CF, Devleeschauwer B, Hall AJ, Kirk MD, Duarte ASR, Black RE, Angulo FJ, Selvey LA. Aetiology-specific estimates of the global and regional incidence and mortality of diarrhoeal diseases commonly transmitted through food. *PLoS ONE.* 2015;10(12):e0142927. doi:10.1371/journal.pone.0142927.
41. Lopman B, Kang G. Editorial commentary: in praise of birth cohorts: norovirus infection, disease, and immunity. Oxford University Press; 2013. doi: 10.1093/cid/cit785
42. Kotloff KL, Nataro JP, Blackwelder WC, Nasrin D, Farag TH, Panchalingam S, Wu Y, Sow SO, Sur D, Breiman RF, et al. Burden and aetiology of diarrhoeal disease in infants and young children in developing countries (the Global Enteric Multicenter Study, GEMS): a prospective, case-control study. *Lancet.* 2013;382(9888):209–222. doi:10.1016/S0140-6736(13)60844-2.
43. Lopman B, Simmons K, Gambhir M, Vinjé J, Parashar U. Epidemiologic implications of asymptomatic reinfection: a mathematical modeling study of norovirus. *Am J Epidemiol.* 2013;179(4):507–512. doi:10.1093/aje/kwt287.