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In Praise of Birth Cohorts: Norovirus Infection, Disease, and Immunity

Ben Lopman¹, Gagandeep Kang²

¹National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

²The Wellcome Trust Research Laboratory, Division of Gastrointestinal Sciences, Christian Medical College, Vellore, India

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Noroviruses are the most common cause of diarrheal disease in the community for all ages [1] and the most common cause of foodborne disease outbreaks in the United States [2]. Despite this ubiquity and high disease burden, there remains substantial uncertainty about some basic features of norovirus infection, epidemiology, and immunity. This knowledge gap partly results from a lack of studies with appropriate designs to examine this rather complicated virus.

Birth cohort studies can be vital for understanding the acquisition of protective immunity against a pathogen. Such studies have led to fundamental improvements in understanding rotavirus, for example, and, in turn, have supported the development of vaccination strategies. In a classic study of a birth cohort in Mexico, Velazquez and colleagues showed that severe disease is restricted to the first 2 infections, that each infection reduces future disease risk, and that homotypic protection comes earlier than protection against other genogroups [3]. The implications for vaccines were clear. Fifteen years after the publication of the Velazquez et al study, rotavirus vaccines are in widespread use and have led to remarkable declines in diarrheal disease in the United States and elsewhere. This is not to say that the Velazquez study single-handedly brought about this chain of events, but rather that it provided insights that were indispensable for the course of subsequent developments.

With the publication of this study by Saito et al in the current issue of *Clinical Infectious Diseases*, in which a birth cohort in a Lima, Peru, shantytown was followed for 2 years, we finally have an analogous study on norovirus. The study is packed full of insights for

Correspondence: Ben Lopman, PhD, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, 1600 Clifton Rd, MS-G04, Atlanta, GA 30333 (blopman@cdc.gov).

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understanding norovirus disease and immunity, with clear implications for vaccines, but, as always seems to be the case with these viruses, the picture is more complex than with other agents of viral gastroenteritis and requires careful interpretation.

First and foremost among the findings is the quantification of the tremendous incidence of norovirus-associated diarrhea, with a per capita rate of >0.5 per year (our recalculations), over the first 2 years of life. Basic incidence estimates are fundamental for assessing the burden of a disease, and this is one of the precious few for norovirus in a developing country, or indeed, any setting. Cohort studies are resource-intensive to conduct, but for a virus that commonly infects and reinfects, sometime subclinically, longitudinal data may be the only way to understand the relationship between primary, secondary, and subsequent infections and development of disease. Even the most meticulously conducted case-control studies that compare norovirus prevalence in cases to that in healthy controls can generate data that are hard to interpret. For example, the seminal Global Enterics Multi-Center Study found norovirus to be generally as common among cases of moderate to severe diarrhea as in healthy controls, and concluded that norovirus is largely not a cause of moderate to severe diarrhea [4]. Saito et al's longitudinal study demonstrates a more complicated and nuanced pattern. Among these children in a Peruvian shantytown, detection of norovirus in nondiarrhea specimens was exceedingly common, and indeed, at similar levels in diarrhea specimens in the first 6 months of life, suggesting that maternal antibody confers some degree of protection against disease early in life. From age 6 months to 2 years, however, the association of norovirus infection with diarrhea became clear.

Why were Saito and colleagues able to find a clear association of norovirus with diarrhea where some others have failed (eg, [4–6])? Part of the reason may lie in the ability to correctly classify infections as symptomatic or asymptomatic, a capacity that comes with the intensive follow-up and sampling of a birth cohort. Duration of shedding, in both symptomatic and asymptomatic infections, was long, at around a mean of 1 month. So, when cross-sectional studies define healthy controls based on absence of diarrhea symptoms for 1, 2, or even 4 weeks in the past, they may incorrectly classify substantial numbers of postsymptomatic infections as asymptomatic infections. Perhaps for the same reason, Saito et al found a difference in viral load (based on real-time polymerase chain reaction cycle threshold value) between symptomatic cases and asymptomatic infections where some other studies have not detected a difference using a case-control design (eg, [7]). Notably, the quantitative difference was small (at approximately 1 log), and likely without a clear cutoff between symptomatic and asymptomatic infections.

Of the numerous novel results in the study, the most crucial for vaccine development is that previous genogroup II (GII) infections protect against subsequent infection, and, more importantly, protect against disease. Notably, substantial declines in disease incidence did not come until after 2 previous GII infections, suggesting that multiple doses of vaccine may be required to generate a protective immunity, at least among naive children. Phase 1 and 2 trials with norovirus virus-like particle vaccines have been encouraging, demonstrating that, in principle, immunization against norovirus is possible [8]. But to date, all human vaccine studies have been conducted among healthy adults. The lion's share of severe norovirus disease burden is in young children and the elderly, so development of vaccine formulations,

and subsequently trials, in these age groups will be needed. Clearly, for a vaccine to have clinical impact, it will have to protect against GII and specifically GII.4 noroviruses. Future studies will need to determine the extent to which infection with a particular virus induces protection against the whole genogroup, or if immunity is specific to a genotype.

Another thought-provoking finding is the association of norovirus infection with reduced weight and length at 1 year of age. The direction of causation is not entirely clear: Does norovirus infection inhibit growth, or are children with compromised growth more susceptible to norovirus? Regardless, these results should provoke us to think about norovirus not just as a cause of diarrhea, but also in the context of overall gut health and the role of this virus and other enteric infections on development. Perhaps the growth and possibly even cognitive effects are, in the life course, more important than the acute diarrhea resulting from infection [9].

Is this the definitive study on the natural history of norovirus infection and disease? Probably not. First, testing was limited to only 2 specimens in the second year of life, so infections are likely to have been considerably underestimated. Second, and more fundamentally, one lesson learned from the experience with rotavirus, polio, and other enteric infections is that immunity induced by either natural infection or vaccine is reduced for children in low-socioeconomic settings in developing countries [10]. In contrast to the Mexico birth cohort study, severe gastroenteritis persists into third and subsequent rotavirus infections in Indian children [11], giving insight that a less protective response to natural infection is analogous to the reduced vaccine efficacy for children in the lower-income parts of the world [12]. To complement Saito's study in urban Peru, others of similar design will be needed in children in both low- and high-resource settings to gain a comprehensive understanding of the natural history and immunity to norovirus, and they should also examine the role of human host genetics, specifically histoblood group antigen secretor status, with norovirus susceptibility. But norovirus affects the entire age range, so these observational studies should also be conducted for the adult and, especially, elderly populations.

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