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EDITORIAL COMMENTARY

Waxing Understanding of Waning Immunity

Benjamin A. Lopman[1] and Virginia E. Pitzer[2]

[1]Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, Georgia; and [2]Department of Epidemiology of Microbial Diseases, Yale School of Public Health, Yale University, New Haven, Connecticut

(See the major article by Rogawski et al, on pages 861-8.)

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Of the approximately 150 000 deaths due to rotavirus infection that occur globally every year, >90% are among children in settings of low and low/middle incomes [1, 2]. To counter this burden, the World Health Organization recommends that rotavirus vaccination be included in the immunization program of all countries. Despite the clear signs of progress in reducing the rotavirus disease burden globally [3], there are 2 related challenges specific to lower-income settings that hamper rotavirus vaccines from preventing more deaths and severe diarrheal disease [4]. First, rotavirus vaccines are less effective in low-income as compared to high-income settings. This is, at least in part, an immunological phenomenon. Vaccine responses are considerably more robust among children in high-income settings as compared to low-income settings [5]. Second, vaccine protection appears to wane. Again, this issue appears to be restricted to low-income settings, where vaccine efficacy (VE) has been observed to drop 30%–40% from the first to second year of life in clinical trials in Kenya, Mali, Malawi, Ghana, South Africa, and Bangladesh [6–10]. Contrast this finding to that in Finland, for example, where a VE of >90% persists through the first 5 years of life [11].

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Correspondence: B. A. Lopman, Ben Lopman, PhD, Department of Epidemiology Rollins School of Public Health | Emory University 1518 Clifton Rd NE, Atlanta, GA 30322 (blopman@emory.edu)

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Of course, it is not a country's economic standing per se that compromises vaccine performance. Instead, low income is a proxy for other factors that may either reduce the titer of vaccine reaching the infant's gut, such as maternal antibodies, or inhibit the child's immune response, such as chronic inflammation or coinfection [4]. Similar factors are hypothesized to explain the decline in vaccine protection as children age. Lower antibody titers mounted in response to vaccination more quickly fall below protective levels, although for rotavirus it is not entirely clear what constitutes a protective threshold [12]. These factors may seem a logical explanation for the variable and waning VE measured in rotavirus clinical trials and waning vaccine effectiveness measured in observational studies.

Rogawski et al, in the current issue of *The Journal of Infectious Diseases*, offer another explanation [13]. Perhaps lower and declining VE in low-income settings is not due to an ebbing of antibodies or other correlate of protection, but rather can be explained, at least in part, by a fundamental flaw in how we conceptualize and measure VE. In clinical trials and observational cohort studies, VE and vaccine effectiveness are measured by comparing the differential risks, rates, or hazards of disease in vaccinated groups to those in unvaccinated groups. If the groups are similarly exposed to infection (a safe assumption under randomization), rates of disease are lower among those receiving an efficacious vaccine. However, for so-called leaky vaccines that only provide partial protection to vaccinated individuals, unvaccinated individuals are infected at a higher rate and thus disproportionately acquire immunity naturally over time. In this sense, the unvaccinated individuals become more like the vaccinated individuals as they age and are exposed to infection. Therefore, if we calculate VE on the basis of the risks (ie, number of cases in the vaccinated and unvaccinated groups), it will be biased downward and appear to decline over time. Importantly, there is no waning of immunity in the immunological sense assumed in this scenario, but a biased estimate results. This biased estimator is readily overcome by analyzing instantaneous incidence or hazards. In other words, one must only analyze the rates among those who have not yet had an episode prior to a given time point. This phenomenon was pointed out >30 years ago by Smith et al [14], but it has been applied primarily to infections that confer sterilizing immunity (eg, measles), such that individuals once vaccinated or infected become immune to future infections, as well as disease. However, rotavirus infection, as with many enteric, respiratory, and genitourinary infections of mucosal surfaces, does not confer sterilizing immunity. This means that previously infected individuals get reinfected, just at lower rates and/or with milder disease.

Rogawski et al extend Smith et al's insights to rotavirus infection, an imperfectly immunizing infection, using data from the PROVIDE study [13]. PROVIDE was a randomized controlled trial conducted in Dhaka, Bangladesh, in which 700 children were assigned to receive either monovalent rotavirus vaccine (RV1) at 10 and 17 weeks of age or no RV1

(clinical trials identifier: NCT01375647). The primary outcome—similar to that in other trials—was severe rotavirus gastroenteritis. But, uniquely, PROVIDE also conducted active surveillance for rotavirus diarrhea episodes of any severity, through twice-weekly visits. This way, in their reanalysis, Rogawski et al identified when all rotavirus diarrhea episodes—even mild ones—occurred and could censor observations on that basis. And, as would be predicted from the rationale outlined above, VE against severe rotavirus infection increased from the original estimate of 63% (95% confidence interval, 33%–80%) to 70% (95% confidence interval, 45%–84%) when the comparison group was restricted to those who were rotavirus naive. The VE differential was greater in the second year of life, increasing from 32% (in the original analysis) to 46% (in the reanalysis), which is to be expected, since fewer unvaccinated children than vaccinated children were rotavirus naive at 12 months of age. Using these insights and empirical estimates, the authors then constructed simulations of cohorts from published VE studies that were performed in a range of epidemiological settings. In these simulations, they were able to isolate the rotavirus-naive population and use this as the comparison group. They found that [1] VE in the first 2 years of life could be underestimated by as much as 11% in the original RV1 clinical trial publications and that the degree of underestimation [2], scaled linearly with background incidence [3], was most pronounced with a lower VE and [4] was more biased in the second year of life than in the first.

These are important findings, with the empirical observations elegantly generalized in the simulation study. Importantly, though, neither the reanalyzed VE estimates nor the modeled VE estimates are different enough to explain the observed variation (up to 50%) in VE between high- and low-income settings. Nor are they large enough to explain the differences (up to 40%) between the first and second years of life in low-income settings. Rogawski et al may be on the right track, but despite the active diarrheal surveillance, they still missed many rotavirus infections. The PROVIDE trial did not test for subclinical or asymptomatic infections, so these could not be accounted for in the analysis. In a prevaccination birth cohort study conducted in South India [15], 43% of children experienced at least 1 episode of diarrhea due to rotavirus by 2 years of age, which is very similar to the proportion observed among unvaccinated infants in the Bangladesh PROVIDE trial. However, in the Indian cohort, routine stool specimens and blood samples were also collected and tested for asymptomatic infections. Nearly all children were infected by 2 years of age, and rates of rotavirus infection exceeded 1 rotavirus infection per child-year in India [15]. This is nearly twice as high as the maximum incidence of rotavirus disease modeled in Rogawski et al's simulation study. Put another way, many subjects in the rotavirus-naive groups in the PROVIDE reanalysis and the simulated cohort may have been previously exposed but had asymptomatic infection. It is possible that these higher rates of unobserved rotavirus infections can explain some of the remaining discrepancies in VE between high- and low-income settings and between the first and second years of life. Critically, though, no clinical trials or cohort studies have tested for asymptomatic rotavirus infections in a vaccinated population, and, thus, the protection conferred by vaccination against rotavirus infection remains unknown.

Still, there is little doubt that there is also a biological basis for variable efficacy and declining protection of rotavirus vaccination in low-income settings. These observations cannot exclusively be artifacts of epidemiological measurement. Rotavirus vaccination is markedly more immunogenic among children in high-income settings as compared to low-income settings [5]. However, efforts to unravel the factors underlying the poor immunogenicity of rotavirus vaccines in low-income settings have, thus far, proven largely inconclusive. Assaying antibody titers over time or probing for loss of mucosal immunity by challenging with a live-virus vaccine could provide solid evidence for waning. Such investigations are possible for rare or eliminated infections, such as polio [16]. However, rotavirus is highly endemic, and exposure is common. And since it is not possible to discriminate between naturally acquired and vaccine-induced immunity, such studies may not provide insights into the waning of protection exclusively from vaccination.

These issues are not confined to rotavirus vaccine. Concerns about waning vaccine immunity abound these days. After decades of declining pertussis and mumps incidence, for example, recent years have seen resurgence of each disease despite maintenance of high vaccine coverage. Cases have mainly been among young-adult age groups. In the case of pertussis, acellular vaccine confers a lower level and shorter duration of protection than whole-cell vaccine, which it replaced in the 1990s, resulting in immunity gaps [17]. For mumps, protection appears to wane over decades, prompting the use of additional doses of vaccine for outbreak control [18]. Transmission models have been used to study long-term age-specific time trends of pertussis and mumps. The best-fitting models require waning immunity, leading to the inference that vaccine protection does indeed wane, as well as providing an estimate of the rate of waning [19, 20]. Modeling analyses can help to define the potential range of effect estimates and to identify important data that need to be collected in future observational studies or subjected to experimental scrutiny. Unsatisfyingly, though, these approaches do not directly offer the mechanistic explanations for the loss of immunity that experimental or observational studies could.

Rogawski et al's approach marks an important advance in better-quantifying rotavirus vaccine protection and how it may vary over time. However, sound statistical analysis and mathematical modeling are not sufficient for addressing our relatively limited understanding of the waning of vaccine-induced immunity. In addition

to Rogawski et al's sound advice that the "rotavirus incidence should be considered as one of many potential reasons why rotavirus vaccine efficacy is observed to be low in low-resource settings" [13], their study also highlights the need for even more rigorous fieldwork, plausibly achieved in observational studies, with sampling and testing of specimens from asymptomatic individuals. This would allow for a more definitive analysis of VE and waning of the protection conferred by rotavirus vaccines.

Notes

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