HHS Public Access

Author manuscript

J Pediatric Infect Dis Soc. Author manuscript; available in PMC 2017 December 03.

Published in final edited form as:

J Pediatric Infect Dis Soc. 2013 March ; 2(1): 61–62. doi:10.1093/jpids/pis134.

Challenges to Estimating Norovirus Disease Burden

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In the United States, acute gastroenteritis (AGE) is a significant cause of morbidity, accounting for approximately 179 million illnesses annually [1]. Noroviruses are recognized as the leading cause of AGE across all ages and are responsible for approximately 21 million annual illnesses. However, before 2006, rotaviruses accounted for the majority of severe AGE cases among children under 5 years of age [2]. The introduction of rotavirus vaccines into the recommended infant immunization schedule in 2006 has resulted in a substantial overall decline in pediatric rotavirus disease (and thus AGE) in the United States, with evidence of indirect benefits among some older age groups [3, 4]. Given these declines in the post-rotavirus vaccine era, it is thought that noroviruses are now likely the leading cause of AGE among children, although substantiating this assumption with robust data on the burden of norovirus disease is not a straightforward endeavor.

There are several challenges to estimating norovirus disease burden, many of which relate to the lack of a rapid and sensitive clinical assay for diagnosis of norovirus infections. Because norovirus disease is a relatively nonspecific syndrome that can manifest similar symptoms as other agents of AGE, laboratory confirmation is necessary to identify sporadic cases. However, current diagnostics rely on molecular methods that are largely restricted to public health and research laboratories, and no commercial assay has been approved for use in the United States to diagnose individual norovirus cases. As a result, there is no case or clinical laboratory-based reporting system for sporadic norovirus disease. Likewise, norovirus-specific codes in administrative data, such as insurance claims, are typically used only when there is laboratory confirmation and thus are highly insensitive. Moreover, only approximately 15% of patients with AGE in the community seek medical attention, and of those who seek medical attention, diagnostic testing is requested from only 13% [5]. These healthcare use indicators can vary significantly based on patient factors (eg, age, socioeconomic status, insurance coverage) and healthcare provider practices, which further complicate attempts to extrapolate findings from inpatients and outpatients to the community. Given these challenges, national surveillance for norovirus disease in the United States is limited to outbreaks, which are reported passively and therefore are subject to tremendous variability, and vastly underestimate the overall burden of disease.

In this month's edition of the *Journal of the Pediatric Infectious Diseases*, Koo et al present an impressive longitudinal epidemiologic study to assess trends in viral etiologies of AGE at

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Potential conflict of interest. Both authors: No reported conflicts.

a large pediatric hospital [6]. The authors tested over 3000 stool specimens for enteric viruses over an 8.5-year period, during which time they report significant reduction in rotavirus prevalence after introduction of rotavirus vaccine and subsequent emergence of norovirus as the leading viral enteropathogen. Although there likely was a real shift in the etiologic distribution of pediatric AGE over the study period, interpretation of the reported disease trends is complicated by the surveillance limitations mentioned above. For example, the authors tested stool specimens that were submitted for viral testing, presumably for rotavirus antigen detection primarily. This selection and screening process may have yielded a biased sample of all patients with AGE (eg, inclusion criterion of physician request may result in overrepresentation of the pathogen being ordered for testing and thereby underrepresent other etiologies), thus making it more difficult to generalize the study findings. In addition, the absence of an approved commercial diagnostic assay for norovirus necessitated reliance on nonstandard diagnostic techniques, which changed over the course of the study from conventional reverse transcription-polymerase chain reaction (RT-PCR) to a more sensitive real-time RT-PCR assay. This change in testing practices makes it more difficult to determine whether the described trends are a true reflection of changes in norovirus disease burden, although the authors reassuringly note high concordance between the 2 assays in a subset of specimens tested by both methods. Finally, the use of laboratory testing data without a well-defined catchment population did not allow for the calculation of disease incidence rates, which provide a more comprehensive estimation of disease burden than simply etiologic prevalence. Nonetheless, the study by Koo et al demonstrates an important change in the leading causes of severe pediatric AGE, which may reflect a similar pattern in the overall disease burden [6].

Until simple, sensitive, and rapid testing methods for norovirus are widely available in clinical settings, there are a few methodologic approaches that can be taken to improve our understanding of norovirus disease burden and, in turn, better guide diarrheal disease prevention efforts and clinical management practices. The ideal strategy is active population-based surveillance, which involves systematic sampling of all AGE cases within a known catchment area and allows for the calculation of incidence rates of disease. Examples of this approach include the Sensor Study, conducted in the Netherlands, and the studies of Infectious Intestinal Disease, conducted in the United Kingdom [7, 8]. Because this approach is expensive and labor-intensive, less costly approaches can be taken that overcome at least some of the challenges noted above. Passive testing of specimens submitted for routine clinical purposes, as exemplified by Koo et al, can be a viable approach if sample selection and diagnostics are performed consistently and if the catchment population can be defined. This approach has been used previously to estimate outpatient norovirus incidence among members of a health maintenance organization in Georgia [7]. Alternatively, indirect modeling methods can be used to estimate the fraction of unspecified AGE that are likely due to norovirus, using population-based administrative data on healthcare encounters or mortality [9, 10]. Consistent use of these surveillance platforms and analytical strategies over time can help elucidate trends in norovirus disease burden, which appear to be quite dynamic given the rapid evolution and frequent emergence of new strains.

Although it is challenging to obtain precise estimates, noroviruses clearly cause a substantial disease burden, and their relative importance is increasing due to declines in rotavirus

disease. As norovirus vaccine development continues to progress [11], it is crucial that accurate, long-term disease norovirus burden estimates be developed in a variety of settings to help establish a baseline of the global burden and to identify priority target populations. This in turn will allow for accurate measurement of the impact of interventions, such as vaccines, and will help guide future policy decisions regarding the prevention and control of AGE.

Acknowledgments

Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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