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Noroviruses: The Perfect Human Pathogens?

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Noroviruses are perhaps the perfect human pathogens. These viruses possess essentially all of the attributes of an ideal infectious agent: highly contagious, rapidly and prolifically shed, constantly evolving, evoking limited immunity, and only moderately virulent, allowing most of those infected to fully recover, thereby maintaining a large susceptible pool of hosts. These characteristics have enabled noroviruses to become the leading cause of endemic diarrheal disease across all age groups [1], the leading cause of foodborne disease [2], and the cause of half of all gastroenteritis outbreaks worldwide [3]. In the United States alone, noroviruses are responsible for an estimated 21 million cases of acute gastroenteritis annually, including >70 000 hospitalizations and nearly 800 deaths [2, 4, 5]. In developing countries, where the greatest burden of diarrheal disease occurs, noroviruses have been estimated to cause up to 200 000 deaths each year in children <5 years of age [6]. Although recognition of this immense disease burden is relatively recent, it is unclear whether it has long been present and failed to be recognized because of lack of sensitive diagnostics or if, in fact, noroviruses represent a truly emergent public health issue [7]. Regardless, attempts to address the overwhelming burden of norovirus disease first require an understanding of the complexity and efficiency with which these viruses spread.

The success of noroviruses should come as no surprise once one considers how well adapted they are for transmission within human populations. First, noroviruses have an extremely low infectious dose (≥18 viral particles), coupled with copious viral shedding (10^5–10^{11} viral copies per gram of feces), even among asymptomatic infections [8–10], suggesting that up to 5 billion infectious doses may be shed by an infected individual in each gram of feces. Second, noroviruses are environmentally stable, able to survive both freezing and heating (although not thorough cooking), are resistant to many common chemical disinfectants, and can persist on surfaces for up to 2 weeks [11]. Third, there are a myriad of ways in which noroviruses may be spread, including direct contact between hosts via fecal-oral transmission, ingestion of contaminated foods or water, handling of contaminated fomites followed by hand-to-mouth contact, and—unique among enteric pathogens—via ingestion of aerosolized particles [12]. Finally, noroviruses are a genetically diverse group of viruses

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that rapidly evolve, leading to an apparent lack of prolonged cross-protective immunity following infection [13, 14]. Clearly, public health efforts to prevent and control the spread of noroviruses face an uphill battle.

The investigation Repp and Keene [15] reported in this issue of the *Journal* provides a fascinating example of how a unique exposure and transmission scenario can result in a norovirus outbreak. In this outbreak, one member of a soccer team traveling to a tournament developed acute gastroenteritis, presumably because of an exposure prior to the trip. There was reportedly no opportunity for direct contact between this index case after her symptoms began and any of her teammates. Instead, some of the aforementioned characteristics that have made noroviruses so successful (eg, environmental stability, copious shedding in stool and vomit, aerosol spread) facilitated indirect spread of the virus. First, virus shed in vomitus, and perhaps even feces, became aerosolized in a bathroom where the index case was actively symptomatic. These aerosolized particles then settled on a reusable shopping bag that contained lunch items to be consumed the following day. The authors note that neither the bag nor its contents were ever actually touched by the index case, who left to return home early the next morning before the lunch items were consumed. After handling the food items in this bag and consuming their contents, 7 of 11 individuals (64%) exposed in this manner became ill. Unfortunately, the authors were unable to differentiate between handling of the food packaging versus consumption of the foods they contained. Additionally, there was no assessment of handling of the grocery bag as a stand-alone risk factor, which would have helped further tease out the specific exposure that caused the outbreak. Nonetheless, further evidence that transmission resulted from this contaminated fomite was provided through detection of norovirus from surface swab samples of the bag. Although this finding could not be confirmed by sequencing and comparison with clinical specimens, it would seem highly unlikely for the epidemiologically implicated bag to be positive for norovirus simply by coincidence. The chain of events in this outbreak demonstrates how this tenacious virus finds a way to move from host to host, even when those hosts have no direct contact with one another.

This phenomenon of virus aerosolization contaminating fomites has been previously documented in a variety of settings, although the importance of this mechanism in causing disease transmission is not always clear. Norovirus contamination of environmental surfaces has been reported during nonoutbreak periods in both healthcare and food-service settings [16, 17]. During an outbreak in a hotel in England, environmental samples from mantels and light fittings 1.5 m above the ground were positive for norovirus, suggesting contamination from aerosolized vomitus, although there were no documented exposures to these surface that were associated with disease [18]. Demonstrating this next step of environmentally mediated norovirus transmission is more challenging, and reports of this are more limited. One of the most compelling examples involved gastroenteritis from a rare norovirus genotype among different crews on successive flight sectors, who had no opportunity for direct contact with one another [19]. As multiple transmission pathways may occur during a single outbreak, particularly in closed settings such as nursing homes and cruise ships, it is often difficult to determine which route of exposure is responsible for which cases. For example, environmental transmission was suggested during outbreaks involving successive

voyages on a cruise ship and exposure to contaminated computer keyboards and mice in an elementary school; however, person-to-person transmission could not be excluded in those instances [20, 21]. The investigation by Repp and Keene [15] nicely demonstrates that not only can noroviruses be aerosolized and dispersed onto fomites without direct contact but also that exposure to those contaminated fomites can then cause disease.

This investigation also provides a good example of how environmental sampling can sometimes be useful when there is epidemiologic evidence suggesting that exposure to a specific fomite was associated with disease. In so doing, it underscores the importance of considering fomites among the potential exposures evaluated during an outbreak investigation to first establish that association. Environmental sampling has been used previously to support associations between norovirus disease and contaminated computer keyboards and mice, bathroom and kitchen surfaces, and high-touch surfaces on cruise ships [21, 22]. However, there are limitations to testing environmental swab samples, including variable recovery efficiency depending on swab material used, surface type sampled, and swab technique. Furthermore, as with testing of clinical samples, molecular diagnostic techniques used for environmental samples detect viral RNA, which does not necessarily indicate presence of infectious virus. Results of environmental testing should therefore be interpreted with caution and in the context of the available epidemiologic evidence. More research is needed to develop standardized, validated techniques and better elucidate the role of environmental contamination in spreading noroviruses.

The complex and varied transmission webs through which noroviruses are spread make development of effective prevention and control measures a daunting task. The current pillars of norovirus control rely on relatively generic measures, such as hand hygiene, environmental disinfection, and isolation of infected individuals [12]. However, because of the challenges in modifying human behaviors and the knowledge gaps resulting from our inability to cultivate human noroviruses in vitro, these steps are all too often inadequate. As the investigation by Repp and Keene highlights [15], unique vehicles of transmission and exposure scenarios will continually arise that may circumvent our standard control efforts. Ultimately, a targeted vaccine intervention may be necessary to achieve a significant reduction in norovirus disease and prevent outbreaks. Recent evidence from a candidate norovirus vaccine trial demonstrated a proof of concept that this may indeed be an effective prevention strategy [23]. However, several key questions remain, such as the duration of immunity, the degree of cross-reactivity, the performance in high-risk groups (eg, elderly and young children), and whether protection is afforded against the full range of norovirus infections, including those that are asymptomatic. Although a vaccine may one day serve as another critical tool, thorough epidemiologic investigations and sound infection control practices will undoubtedly continue to be necessary in curtailing the spread of these well-adapted pathogens.

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