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The burden of norovirus gastroenteritis: an important foodborne and healthcare-related infection

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Abstract

Human norovirus (NoV) is now recognized as one of the most important causative agents of gastroenteritis in all age groups worldwide. During the course of NoV infection, symptoms are usually mild and disappear within 48 h after onset. The incidence of NoV infection is high, with hundreds of cases per 10 000 of the population, although the number of infections is still underestimated. Epidemiological surveys conducted in Europe and North America have shown that NoV infections constitute a major disease burden, especially for young children and the elderly, in whom NoV infection leads to high rates of hospitalization and mortality. NoV infections are also of concern in hospitals, where viral infections can be persistent in immunocompromised patients. Although the cost of NoV infection in the hospital community has not yet been clearly established, it appears that NoV infections could cost hundreds of thousands of euros in terms of unit closure, and NoV-related sickness in patients and health workers. Besides their clinical burden, NoVs, as foodborne pathogens, also cause to millions of dollars of losses for the healthcare system and the food industry. Recent estimates in the USA showed that, annually, NoV illness cost $2 billion and led to a loss of approximately 5000 quality-adjusted life-years, making NoV one of the top five pathogens causing enteric illnesses. The highest cost among 14 foodborne pathogens is also attributed to human NoV in The Netherlands. This accumulation of evidence underlines the enormous impact of NoV on populations.

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In the past, studies on norovirus (NoV) were limited by the lack of sensitive detection tools. The development of molecular methods has markedly improved NoV detection [1]. Over the last decade, laboratory networks were set up throughout the world, and have led to a better understanding of the role of NoV as a cause of acute gastroenteritis (AGE). The increasing use of real-time RT-PCR for diagnostic purposes has improved both the sensitivity and specificity of NoV detection. Fast and accurate detection methods enable the follow-up of NoV infection and estimation of the viral load in patients. These new molecular tools have greatly improved the value of epidemiological studies. Population-based studies are now feasible, and have greatly improved the precision of estimates of the NoV health and economic burden.

Symptoms

The time between exposure and the onset of gastroenteritis symptoms (i.e. the incubation period) for NoV is brief, being estimated as 1.2 days on average [2]. Diarrhoea is the predominant symptom, being present in *c.* 90% of cases, with vomiting being present in *c.* 75% of cases [3]. The onset can occur with no prodrome, sometimes resulting in public vomiting incidents, which may be a particularly effective mechanism of transmission [4,5]. Vomiting may also occur in the absence of diarrhoea. Other symptoms may include abdominal cramps, fever, headache, chills, and myalgia. Symptoms generally persist for 2–3 days, but may last longer in

young children and the elderly infected in outbreaks in healthcare facilities [3,6]. The shedding of virus in stools begins before the onset of symptoms, typically peaks (at *c.* 10^{10} viral particles per gram of stool) on day 4 following exposure, and may persist for many weeks in the general population, or for months in immunocompromised individuals [3,7,8]. There are few quantitative data regarding severity (i.e. number of episodes of diarrhoea and vomiting, and dehydration) in adults, but, in children, NoV gastroenteritis tends to be less severe than rotavirus gastroenteritis [9–11].

Incidence of the Disease

Although NoVs are well recognized as constituting the most common cause of outbreaks of AGE, data concerning the incidence and disease burden of sporadic illness in the wider community are sparse, for a number of reasons. NoV AGE is usually mild and lasts for <72 h, so relatively few individuals seek medical care and, for those who do, specimens are frequently not taken or tested for NoV. The lack of a highly sensitive and specific diagnostic test presents challenges on a number of levels. Medical records (such as hospital discharge datasets) rarely include specific codes for NoV (ICD9 008.63 and ICD10 A08.11), owing to the absence of a confirmed diagnosis. Also, and more fundamentally, NoV is also frequently detected in stools of healthy individuals, which complicates the interpretation of individual test results. For these reasons, estimates of disease incidence and burden are compiled from a number of sources and with various methodological approaches.

Indeed, we are aware of only two countries, The Netherlands and the UK, where population-based cohorts have been followed with gastroenteritis cases being systematically tested for NoV in stools, and where the data obtained have been subsequently used to generate disease incidence estimates. These studies have generated fairly consistent estimates of NoV disease incidence of 380 per 10 000 population (95% CI 264–544) for The Netherlands [12,13] and 450 per 10 000 population (95% CI 380–520) and 470 per 10 000 population (95% CI 391–565) for the UK [14,15]. Other studies that either attributed a fraction of all AGE cases to NoV, or extrapolated data based on healthcare-seeking cases, have led to somewhat higher estimates, ranging from 650 to 1040 per 10 000 population for the USA [16,17] and Canada [18].

Estimates of outpatient incidence (i.e. cases presenting to a general practitioner) range internationally from 21 to 92 per 10 000 population [13–16,19,20], suggesting that approximately one in 10 community cases seek care. Hospitalization rates are an order of magnitude lower, and range from 1.2 to 2.4 per 10 000 population (the USA, the UK, and The Netherlands) [13,17,21,22]. NoV-associated deaths are rare, with an incidence of 0.19–0.40 deaths per 10 000 population (the USA and The Netherlands) [13,23].

Notably, none of these disease incidence estimates are for populations in developing countries, where the disease burden is probably greater, for a number of reasons, potentially including poorer water, sanitation and hygiene conditions, and a weaker immune response to infection. Globally, diarrhoeal disease is estimated to result in 1.45 million deaths and 89.5 million disability-adjusted life-years lost annually [24,25]. In a large systematic literature review of 137 studies, NoV was estimated to be associated with 18% (95% CI 17–20%) of gastroenteritis cases globally [26]. The figure is surprisingly lower, at 12% (95% CI 9–15%), in high-mortality developing countries. This discrepancy is probably attributable to a greater burden of other bacterial and parasitic causes of disease in such countries, rather than a lower disease burden in these settings.

Young children

Young children (aged <5 years) have the highest incidence of NoV AGE. The disease incidence in this age group is estimated to be 21 400 (15 900–27 700) per 100 000 population, which is approximately 6.5 times the incidence for the population aged ≥5 years [15]. Rates of NoV-associated outpatient visits, emergency department visits and hospitalizations are also highest for this age group. In the USA, where rotavirus vaccines are in widespread use, NoV is now the leading cause of medically attended AGE for children aged <5 years [27].

Again, data from developing countries are lacking. Although NoV is associated with 18% (95% CI 15–21%) of diarrhoeal disease globally in children aged <5 years [26], NoV is also frequently detected in stools of diarrhoea-free children, making it difficult to definitely attribute a proportion of the diarrhoeal disease burden to NoV for children in low-income settings [28,29]. Defining the disease burden for children in low-income countries with the most robust methodology is an important area of future research.

The elderly

The elderly (usually defined as being aged ≥65 years) suffer disproportionately from severe outcomes of NoV infection. In the USA, 90% of the *c.* 800 deaths/year occur among the elderly [23]. The estimated case-fatality ratio in this age group (estimated at approximately six per 10 000 cases) is approximately 20 times that in the population aged 18–64 years [13,30]. Although the elderly in the community do not appear to have an overall higher risk for infection, those living in