REVIEW 10.1111/1469-0691.12722

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

G. Belliot[1], B. A. Lopman[2], K. Ambert-Balay[1] and P. Pothier[1]

1) *Laboratory of Virology, National Reference Centre for Enteric Viruses, Public Hospital of Dijon, Dijon, France and* 2) *Division of Viral Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA*

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.

Keywords: Disease burden, economic impact, foodborne, hospital, norovirus
Article published online: 18 June 2014
Clin Microbiol Infect 2014; **20**: 724–730

Corresponding author: G. Belliot, Laboratory of Virology, National Reference Centre for Enteric Viruses, Public Hospital of Dijon, 2 rue Angelique Ducoudray, BP37013, 21070 Dijon, France
E-mail: gael.belliot@u-bougogne.fr

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

healthcare facilities may have a greater risk of being affected during outbreaks [31,32]. These outbreaks are disproportionately caused by genogroup II.4 viruses, which, independently of other factors, appear to result in more severe disease outcomes, including hospitalizations and deaths [30]. There is mounting evidence that NoV is a cause of excess mortality during outbreaks in nursing homes [33].

NoV infections in the context of other severe pathologies

In immunocompetent individuals, NoV gastroenteritis is generally self-limiting and of short duration, although asymptomatic excretion of the virus in faeces has been observed to last for up to 3 weeks in adults [3] or even for more than 47 days in young children [34] and for up to 32 days in elderly patients [35]. However, in immunocompromised patients, including those with congenital conditions and acquired immunodeficiencies, NoV can cause severe diarrhoea, often with prolonged symptoms and excretion.

Numerous studies have reported the excretion of NoV for months and persistent diarrhoea in patients during iatrogenic immunosuppression following transplantation of various organs, including the intestine, kidney, liver, pancreas, and heart [36–38], as well as in patients who have undergone allogeneic haematopoietic stem cell transplantation [39–42]. Chronic diarrhoea lasting for >2 years has been described in a heart transplant patient [36]. Patients suffering from immunosuppressive disease or with oncological disorders can also be subject to persistent NoV infection. Capizzi *et al.* reported two patients suffering from chronic lymphocytic leukaemia [43] who developed chronic diarrhoea, lasting for up to a year, caused by NoV. A previous study also described paediatric oncology patients who suffered from prolonged gastroenteritis and shedding of NoV for up to 420 days [44]. One human immunodeficiency virus-positive patient with chronic NoV infection and persistent diarrhoea has been reported [45].

Prolonged NoV shedding has also been observed in patients with inherited immune deficiencies. Chronic NoV shedding for >1 year has been described in a 2-month-old child with severe combined immunodeficiency syndrome [46]. More recently, Frange *et al.* reported the detection of NoV in children suffering from different types of genetic immunodeficiency with prolonged shedding for >9 months [47].

Apart from being a significant cause of prolonged morbidity, chronic NoV infection in high-risk patients may lead to severe outcomes, necessitating extended hospitalization, with a median of 73 days, as reported in one study [41]. Severe weight loss requiring enteral or parenteral nutrition, malnutrition and severe dehydration, growth retardation and even death have been observed in immunocompromised hosts as a consequence of NoV infection [41–44,48]. Mattner *et al.* reported cardiac complications in a patient with cardiovascular disease after NoV infection [49]. Furthermore, in transplant recipients, who commonly develop gastroenteritis as a result of conditioning therapy, graft-versus-host disease, or drugs, it is crucial to distinguish these clinical complications from NoV diarrhoea, to avoid inappropriate and harmful treatment.

Economic Impact of NoV

As a result of the health burden of NoV, there is a considerable financial impact. Among public health officials, cost of illness and health-adjusted life-years are increasingly popular tools with which to evaluate the burden of an illness, despite the fact that there is some uncertainty in determining the real impact of infectious pathogens, given the influence of comorbidity (chronic NoV infection in transplantees), genetic resistance of the population (e.g. non-secretor status and fast IgA responders), or awareness of the population regarding NoV infection [50]. Although estimating the burden of NoV is still very challenging, over the past few years the financial impact of NoV as a foodborne and nosocomial pathogen has been increasingly studied.

NoV and foodborne diseases

Soon after its discovery, human NoV was implicated as a causative agent in foodborne and waterborne outbreaks of gastroenteritis [51]. To date, there have been numerous reports of NoV outbreaks in the literature, linked to waterborne and foodborne transmission [52]. In Europe, 10% of reported NoV outbreaks are reported by investigators to be spread primarily by foodborne transmission, as compared with 26% in the USA [53,54]. However, if mode of transmission is assigned to the outbreak on the basis of genotype profiles and other outbreak characteristics, the foodborne percentage rises to 20% [55]. These and similar surveillance data have helped researchers to generate better estimates of the foodborne disease burden. In 1999, one of the first large-scale estimates regarding foodborne pathogens showed, surprisingly, that, every year, NoV was responsible for 23 million cases of gastroenteritis, 9.2 million of which were food-related, representing 66.6% of all foodborne illnesses, 20 000 hospitalizations and 124 food-related deaths [56]. Despite the fact that only 18–41% of reported foodborne cases have a known aetiology, and the estimate is based on extrapolations of data, human NoV is one of the main causative agents of foodborne illnesses in the USA, being responsible for *c.* 60% of all cases [17]. In contrast, studies in the UK and The Netherlands showed that NoV was responsible for only 3.6% and 15.6% of foodborne illnesses,

respectively [57,58]. The numbers of hospitalizations and deaths resulting from foodborne disease were usually very high in reports from the USA, with NoV being associated with 15–20% of hospitalizations and 2–10% of deaths. In the UK and Australia, NoV was responsible for <1.5% of the hospitalizations and deaths [57,59]. In the USA, NoV is estimated to cause the majority of mild and moderate cases of foodborne illness, bacterial pathogens being responsible for most of the hospitalizations and deaths. However, NoV still ranks second and fourth in these categories, respectively [60]. These foodborne illnesses are estimated to result in direct and indirect costs of $2 billion, and result in a loss of 5000 quality-adjusted life-years every year [60]. The most recent analogous figures for The Netherlands indicate that NoV infections cost up to $130 million each year, representing the highest cost of illness among food-related pathogens, $22.1 million of which could be directly attributed to contaminated food, corresponding to $1.31 per inhabitant [61]. An older study in the same country estimated that the mean cost was *c.* $90 per case for the year 1999 [62]. In New Zealand, a cost of $3 million, representing $0.67 per inhabitant, could be directly attributed to NoV in foodborne diseases. Food-related NoV infection accounted for approximately 4.66 and 8.63 disability-adjusted life-years per 100 000 inhabitants in New Zealand and The Netherlands, respectively, with a higher proportion of years being lost because of premature deaths in the Dutch study [58,63].

NoV in medical institutions

NoV infection is increasingly being recognized as a major threat for the hospital community. NoV infections affect both patients and healthcare workers. The direct cost for the healthcare system is far greater than the indirect non-healthcare costs, which include absenteeism and loss of productivity. There are reports of a large number of hospitalizations following NoV infection. Between 2002 and 2008, 710 725 cases of NoV gastroenteritis were reported in Germany, 26% of which led to hospitalization. In the same study, the authors observed that 49% of the NoV-related hospitalizations were nosocomially acquired, mainly in elderly patients [64]. Estimates in England showed that NoV was responsible for 8.7% of gastroenteritis-related hospitalizations, increasing to 19% among the elderly; these admission also pose a risk of nosocomial infection [22]. A survey conducted in England in 1999 estimated that nosocomial gastroenteritis outbreaks resulted in an annual loss to the National Health Service of $184 million, a large part of which was attributable to NoV infection [65]. The elderly are most at risk, and it has been estimated that NoV is responsible for one excess hospitalization and one death every four and nine outbreaks, respectively, in nursing homes [33]. Models have suggested that deaths associated with NoV infection might reach 20% among people aged ≥65 years in England and Wales [66]. In the USA, it has been estimated that NoV infection might be responsible for 71 000 hospital admissions per year, representing an average cost of $493 million each year [21]. For young children in the USA in 2009 and 2010, it was estimated that NoV was responsible for 14 000 hospitalizations, 281 000 emergency visits, and 627 000 outpatient visits, representing $273 million of direct health costs for each of the 2 years, nationwide, for children aged <5 years [27].

Analysis of data from the literature showed that NoV was the most common pathogen leading to ward closure (in 44% of 194 outbreaks) [67]. NoV infection can lead to costly ward closure, as exemplified by a nosocomial NoV outbreak that occurred in a tertiary hospital in the USA. The outbreak affected 90 patients and 265 healthcare workers; it required the closure of several units and thorough disinfection of the facilities. Additionally, the authors observed a set-back in the treatment programme and a decrease in medical activities while new admissions were stopped and absentees from the staff were replaced, resulting in a total cost of $657 644 [68]. More recently, the follow-up of 16 patients suffering from NoV infection in an internal medicine unit in a tertiary hospital showed that NoV infection led to an additional cost of $40 675: $37 968 of revenue loss for bed closure, and $2707 for additional laboratory analyses. Differences in NoV-related hospitalization costs might be explained by several factors, such as the number of people affected (patients and healthcare workers), the duration of the outbreak, and the types and volume of medical activity that have been directly affected by the occurrence of NoV infection.

Conclusion

NoV has a major clinical and financial impact on the populations of industrialized countries. All age groups are affected by NoV, but young children and the elderly are subject to higher incidence rates and more severe outcomes of the disease. The symptoms associated with NoV infection are somewhat similar to those observed for rotavirus infection in otherwise healthy patients. However, NoVs are increasingly being found in immunocompromised patients, such as transplantees, in whom chronic infection is a frequently reported problem. In the elderly, complications resulting from dehydration and a weak immune system also provide a favourable situation for NoV infection. Besides the clinical aspects of NoV infection, there is also a considerable financial impact. Large-scale studies have all shown that NoV

infection is responsible for the majority of mild and moderate cases of gastroenteritis in the community. However, studies have shown that nosocomial NoV infections can also be costly for the hospital community. For foodborne diseases, the latest estimate showed that approximately half of all cases of AGE were NoV-related, and that these represented a loss of several million dollars in terms of direct and indirect health costs. Although NoV is a major cause of foodborne disease, most NoV infections result from person-to-person transmission, and the NoV burden might be far greater than estimated. For the food industry, the mandatory decontamination of the production line after accidental NoV contamination could lead to substantial additional costs. NoV is thus a major health issue for the food industry, but can be dealt with by implementing good standards and practices [69].

Early detection and the containment of outbreaks in hospitals, the education of professionals through the establishment of virus-specific hazard analysis and critical control points procedures in the food and catering industries and the protection of vulnerable populations with affordable vaccines are avenues that can be explored to reduce the burden of NoV [70–73].

Acknowledgements

We would like to thank A. Havelaar for his helpful comments. We extend our thanks to the members of the NRC in Dijon for their technical support, and P. Bastable for editorial assistance.

Transparency Declaration

The study was partly funded by the Public Hospital of Dijon, and the National Reference Centre (NRC) for Enteric Viruses (Dijon, France). The findings and conclusions in this report are those of the authors, and do not necessarily represent the official position of the Centers for Disease Control and Prevention, or the position of the French Institute for Public Health Surveillance.

References

1. Bresee JS, Widdowson MA, Monroe SS, Glass RI. Foodborne viral gastroenteritis: challenges and opportunities. *Clin Infect Dis* 2002; 35: 748–753.
2. Lee RM, Lessler J, Lee RA *et al.* Incubation periods of viral gastroenteritis: a systematic review. *BMC Infect Dis* 2013; 13: 446.
3. Rockx B, De Wit M, Vennema H *et al.* Natural history of human calicivirus infection: a prospective cohort study. *Clin Infect Dis* 2002; 35: 246–253.
4. Thornley CN, Emslie NA, Sprott TW, Greening GE, Rapana JP. Recurring norovirus transmission on an airplane. *Clin Infect Dis* 2011; 53: 515–520.
5. Evans MR, Meldrum R, Lane W *et al.* An outbreak of viral gastroenteritis following environmental contamination at a concert hall. *Epidemiol Infect* 2002; 129: 355–360.
6. Lopman BA, Reacher MH, Vipond IB, Sarangi J, Brown DW. Clinical manifestation of norovirus gastroenteritis in health care settings. *Clin Infect Dis* 2004; 39: 318–324.
7. Atmar RL, Opekun AR, Gilger MA *et al.* Norwalk virus shedding after experimental human infection. *Emerg Infect Dis* 2008; 14: 1553–1557.
8. Henke-Gendo C, Harste G, Juergens-Saathoff B, Mattner F, Deppe H, Heim A. New real-time PCR detects prolonged norovirus excretion in highly immunosuppressed patients and children. *J Clin Microbiol* 2009; 47: 2855–2862.
9. Wikswo ME, Desai R, Edwards KM *et al.* Clinical profile of children with norovirus disease in rotavirus vaccine era. *Emerg Infect Dis* 2013; 19: 1691–1693.
10. Pang XL, Honma S, Nakata S, Vesikari T. Human caliciviruses in acute gastroenteritis of young children in the community. *J Infect Dis* 2000; 181(suppl 2): S288–S294.
11. O'Ryan ML, Pena A, Vergara R *et al.* Prospective characterization of norovirus compared with rotavirus acute diarrhea episodes in Chilean children. *Pediatr Infect Dis J* 2010; 29: 855–859.
12. de Wit MA, Koopmans MP, Kortbeek LM *et al.* Sensor, a population-based cohort study on gastroenteritis in the Netherlands: incidence and etiology. *Am J Epidemiol* 2001; 154: 666–674.
13. Verhoef L, Koopmans M, van Pelt W *et al.* The estimated disease burden of norovirus in the Netherlands. *Epidemiol Infect* 2013; 141: 496–506.
14. Tam CC, Rodrigues LC, Viviani L *et al.* Longitudinal study of infectious intestinal disease in the UK (IID2 study): incidence in the community and presenting to general practice. *Gut* 2012; 61: 69–77.
15. Phillips G, Tam CC, Conti S *et al.* Community incidence of norovirus-associated infectious intestinal disease in England: improved estimates using viral load for norovirus diagnosis. *Am J Epidemiol* 2010; 171: 1014–1022.
16. Hall AJ, Rosenthal M, Gregoricus N *et al.* Incidence of acute gastroenteritis and role of norovirus, Georgia, USA, 2004–2005. *Emerg Infect Dis* 2011; 17: 1381–1388.
17. Scallan E, Hoekstra RM, Angulo FJ *et al.* Foodborne illness acquired in the United States—major pathogens. *Emerg Infect Dis* 2011; 17: 7–15.
18. Thomas MK, Murray R, Flockhart L *et al.* Estimates of the burden of foodborne illness in Canada for 30 specified pathogens and unspecified agents, circa 2006. *Foodborne Pathog Dis* 2013; 10: 639–648.
19. Karsten C, Baumgarte S, Friedrich AW *et al.* Incidence and risk factors for community-acquired acute gastroenteritis in north-west Germany in 2004. *Eur J Clin Microbiol Infect Dis* 2009; 28: 935–943.
20. Gastanaduy PA, Hall AJ, Curns AT, Parashar UD, Lopman BA. Burden of norovirus gastroenteritis in the ambulatory setting—United States, 2001–2009. *J Infect Dis* 2013; 207: 1058–1065.
21. Lopman BA, Hall AJ, Curns AT, Parashar UD. Increasing rates of gastroenteritis hospital discharges in US adults and the contribution of norovirus, 1996–2007. *Clin Infect Dis* 2011; 52: 466–474.
22. Haustein T, Harris JP, Pebody R, Lopman BA. Hospital admissions due to norovirus in adult and elderly patients in England. *Clin Infect Dis* 2009; 49: 1890–1892.
23. Hall AJ, Curns AT, McDonald LC, Parashar UD, Lopman BA. The roles of *Clostridium difficile* and norovirus among gastroenteritis-associated deaths in the United States, 1999–2007. *Clin Infect Dis* 2012; 55: 216–223.

24. Murray CJ, Vos T, Lozano R *et al.* Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; 380: 2197–2223.
25. Lozano R, Naghavi M, Foreman K *et al.* Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; 380: 2095–2128.
26. Lopman B, Ahmed SM, Robinson A, Verhoef L, Koopmans M, Hall AJ. *The global prevalence of norovirus among cases of gastroenteritis*. Bangkok, Thailand: Vaccines for Enteritis Diseases, 2013.
27. Payne DC, Vinje J, Szilagyi PG *et al.* Norovirus and medically attended gastroenteritis in US children. *N Engl J Med* 2013; 368: 1121–1130.
28. Kotloff KL, Nataro JP, Blackwelder WC *et al.* Burden and aetiology of diarrhoeal disease in infants and young children in developing countries (the Global Enteric Multicenter Study, GEMS): a prospective, case-control study. *Lancet* 2013; 382: 209–222.
29. Lopman B, Simmons K, Gambhir M, Vinje J, Parashar U. Epidemiologic implications of asymptomatic reinfection: a mathematical modeling study of norovirus. *Am J Epidemiol* 2014; 179: 507–512.
30. Desai R, Hembree CD, Handel A *et al.* Severe outcomes are associated with genogroup 2 genotype 4 norovirus outbreaks: a systematic literature review. *Clin Infect Dis* 2012; 55: 189–193.
31. Wikswo ME, Hall AJ. Outbreaks of acute gastroenteritis transmitted by person-to-person contact—United States, 2009–2010. *MMWR Surveill Summ* 2012; 61: 1–12.
32. Kroneman A, Harris J, Vennema H *et al.* Data quality of 5 years of central norovirus outbreak reporting in the European Network for food-borne viruses. *J Public Health (Oxf)* 2008; 30: 82–90.
33. Trivedi TK, DeSalvo T, Lee L *et al.* Hospitalizations and mortality associated with norovirus outbreaks in nursing homes, 2009–2010. *JAMA* 2012; 308: 1668–1675.
34. Murata T, Katsushima N, Mizuta K, Muraki Y, Hongo S, Matsuzaki Y. Prolonged norovirus shedding in infants <or=6 months of age with gastroenteritis. *Pediatr Infect Dis J* 2007; 26: 46–49.
35. Aoki Y, Suto A, Mizuta K, Ahiko T, Osaka K, Matsuzaki Y. Duration of norovirus excretion and the longitudinal course of viral load in norovirus-infected elderly patients. *J Hosp Infect* 2010; 75: 42–46.
36. Nilsson M, Hedlund KO, Thorhagen M *et al.* Evolution of human calicivirus RNA in vivo: accumulation of mutations in the protruding P2 domain of the capsid leads to structural changes and possibly a new phenotype. *J Virol* 2003; 77: 13117–13124.
37. Lee BE, Pang XL, Robinson JL, Bigam D, Monroe SS, Preiksaitis JK. Chronic norovirus and adenovirus infection in a solid organ transplant recipient. *Pediatr Infect Dis J* 2008; 27: 360–362.
38. Roos-Weil D, Ambert-Balay K, Lanternier F *et al.* Impact of norovirus/sapovirus-related diarrhea in renal transplant recipients hospitalized for diarrhea. *Transplantation* 2011; 92: 61–69.
39. Chakrabarti S, Collingham KE, Stevens RH, Pillay D, Fegan CD, Milligan DW. Isolation of viruses from stools in stem cell transplant recipients: a prospective surveillance study. *Bone Marrow Transplant* 2000; 25: 277–282.
40. Gallimore CI, Lewis D, Taylor C, Cant A, Gennery A, Gray JJ. Chronic excretion of a norovirus in a child with cartilage hair hypoplasia (CHH). *J Clin Virol* 2004; 30: 196–204.
41. Roddie C, Paul JP, Benjamin R *et al.* Allogeneic hematopoietic stem cell transplantation and norovirus gastroenteritis: a previously unrecognized cause of morbidity. *Clin Infect Dis* 2009; 49: 1061–1068.
42. Saif MA, Bonney DK, Bigger B *et al.* Chronic norovirus infection in pediatric hematopoietic stem cell transplant recipients: a cause of prolonged intestinal failure requiring intensive nutritional support. *Pediatr Transplant* 2011; 15: 505–509.
43. Capizzi T, Makari-Judson G, Steingart R, Mertens WC. Chronic diarrhea associated with persistent norovirus excretion in patients with chronic lymphocytic leukemia: report of two cases. *BMC Infect Dis* 2011; 11: 131.
44. Ludwig A, Adams O, Laws HJ, Schroten H, Tenenbaum T. Quantitative detection of norovirus excretion in pediatric patients with cancer and prolonged gastroenteritis and shedding of norovirus. *J Med Virol* 2008; 80: 1461–1467.
45. Wingfield T, Gallimore CI, Xerry J *et al.* Chronic norovirus infection in an HIV-positive patient with persistent diarrhoea: a novel cause. *J Clin Virol* 2010; 49: 219–222.
46. Chrystie IL, Booth IW, Kidd AH, Marshall WC, Banatvala JE. Multiple faecal virus excretion in immunodeficiency. *Lancet* 1982; 1: 282.
47. Frange P, Touzot F, Debre M *et al.* Prevalence and clinical impact of norovirus fecal shedding in children with inherited immune deficiencies. *J Infect Dis* 2012; 206: 1269–1274.
48. Schwartz S, Vergoulidou M, Schreier E *et al.* Norovirus gastroenteritis causes severe and lethal complications after chemotherapy and hematopoietic stem cell transplantation. *Blood* 2011; 117: 5850–5856.
49. Mattner F, Sohr D, Heim A, Gastmeier P, Vennema H, Koopmans M. Risk groups for clinical complications of norovirus infections: an outbreak investigation. *Clin Microbiol Infect* 2006; 12: 69–74.
50. Mangen MJ, Batz MB, Kasbohrer A *et al.* Integrated approaches for the public health prioritization of foodborne and zoonotic pathogens. *Risk Anal* 2010; 30: 782–797.
51. Griffin MR, Surowiec JJ, McCloskey DI *et al.* Foodborne Norwalk virus. *Am J Epidemiol* 1982; 115: 178–184.
52. Bitler EJ, Matthews JE, Dickey BW, Eisenberg JN, Leon JS. Norovirus outbreaks: a systematic review of commonly implicated transmission routes and vehicles. *Epidemiol Infect* 2013; 141: 1563–1571.
53. Kroneman A, Verhoef L, Harris J *et al.* Analysis of integrated virological and epidemiological reports of norovirus outbreaks collected within the Foodborne Viruses in Europe network from 1 July 2001 to 30 June 2006. *J Clin Microbiol* 2008; 46: 2959–2965.
54. Hall AJ, Wikswo ME, Manikonda K, Roberts VA, Yoder JS, Gould LH. Acute gastroenteritis surveillance through the National Outbreak Reporting System, United States. *Emerg Infect Dis* 2013; 19: 1305–1309.
55. Verhoef L, Vennema H, van Pelt W *et al.* Use of norovirus genotype profiles to differentiate origins of foodborne outbreaks. *Emerg Infect Dis* 2010; 16: 617–624.
56. Mead PS, Slutsker L, Dietz V *et al.* Food-related illness and death in the United States. *Emerg Infect Dis* 1999; 5: 607–625.
57. Adak GK, Meakins SM, Yip H, Lopman BA, O'Brien SJ. Disease risks from foods, England and Wales, 1996–2000. *Emerg Infect Dis* 2005; 11: 365–372.
58. Havelaar AH, Haagsma JA, Mangen MJ *et al.* Disease burden of foodborne pathogens in the Netherlands, 2009. *Int J Food Microbiol* 2012; 156: 231–238.
59. Hall G, Kirk MD, Becker N *et al.* Estimating foodborne gastroenteritis, Australia. *Emerg Infect Dis* 2005; 11: 1257–1264.
60. Hoffmann S, Batz MB, Morris JG Jr. Annual cost of illness and quality-adjusted life year losses in the United States due to 14 foodborne pathogens. *J Food Prot* 2012; 75: 1292–1302.
61. Mangen MJ, Bouwknegt M, Friesema IH, Kortbeek LM, Van Pelt W, Havelaar A. Disease burden and cost-of-illness of food-related pathogens in the Netherlands. RIVM, 2013. Contract No.: 330331007/2013.
62. van den Brandhof WE, De Wit GA, de Wit MA, van Duynhoven YT. Costs of gastroenteritis in the Netherlands. *Epidemiol Infect* 2004; 132: 211–221.

63. Lake RJ, Cressey PJ, Campbell DM, Oakley E. Risk ranking for foodborne microbial hazards in New Zealand: burden of disease estimates. *Risk Anal* 2010; 30: 743–752.
64. Spackova M, Altmann D, Eckmanns T, Koch J, Krause G. High level of gastrointestinal nosocomial infections in the German surveillance system, 2002–2008. *Infect Control Hosp Epidemiol* 2010; 31: 1273–1278.
65. Lopman BA, Reacher MH, Vipond IB *et al.* Epidemiology and cost of nosocomial gastroenteritis, Avon, England, 2002–2003. *Emerg Infect Dis* 2004; 10: 1827–1834.
66. Harris JP, Edmunds WJ, Pebody R, Brown DW, Lopman BA. Deaths from norovirus among the elderly, England and Wales. *Emerg Infect Dis* 2008; 14: 1546–1552.
67. Hansen S, Stamm-Balderjahn S, Zuschneid I *et al.* Closure of medical departments during nosocomial outbreaks: data from a systematic analysis of the literature. *J Hosp Infect* 2007; 65: 348–353.
68. Johnston CP, Qiu H, Ticehurst JR *et al.* Outbreak management and implications of a nosocomial norovirus outbreak. *Clin Infect Dis* 2007; 45: 534–540.
69. FAO/WHO. Guidelines on the application of general principles of food hygiene to the control of viruses in food. Codex alimentarius, 2012. CAC/GL 79-2012.
70. Koopmans M, Duizer E. Foodborne viruses: an emerging problem. *Int J Food Microbiol* 2004; 90: 23–41.
71. Moe CL. Preventing norovirus transmission: how should we handle food handlers? *Clin Infect Dis* 2009; 48: 38–40.
72. Lee BY, McGlone SM, Bailey RR, Wettstein ZS, Umscheid CA, Muder RR. Economic impact of outbreaks of norovirus infection in hospitals. *Infect Control Hosp Epidemiol* 2011; 32: 191–193.
73. Bartsch SM, Lopman BA, Hall AJ, Parashar UD, Lee BY. The potential economic value of a human norovirus vaccine for the United States. *Vaccine* 2012; 30: 7097–7104.