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# Norovirus in 2016—Emesis Aplenty but Clear Signs of Progress

**Michael G. Head**[1,2], **Benjamin A. Lopman**[3]

[1]Farr Institute for Health Informatics, University College London

[2]Faculty of Medicine, University of Southampton, United Kingdom

[3]Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

## Abstract

The key theme emerging from the articles in this supplement is that burden of norovirus in the United Kingdom and elsewhere is substantial and that new tools for prevention, diagnosis, and treatment are required. Basic understanding of norovirus biology continues to accelerate, but parallel increases in capacity and research funding are going to be needed to translate this knowledge into clinical trials and translational research that can result in public health gains.

### Keywords

norovirus; norwalk; calicivirus

Acute gastroenteritis (AGE) causes a substantial global disease burden estimated at 89.5 million disability-adjusted life-years (DALYs) annually [1]. Norovirus is a major contributor to this burden and is associated with around one fifth of AGE episodes worldwide [2]. Reliable estimates for norovirus burden have been difficult to obtain for a number of reasons, including the unavailability of simple clinical diagnostic tests [3], the lack of routine case-based surveillance, the challenges in developing a case definition that adequately captures norovirus within the larger syndrome of AGE, and the challenge of attributing disease causation. Despite these challenges, the totality of evidence is clear: norovirus gastroenteritis is of huge consequence in the community in high-income and low-income regions alike and within healthcare settings of industrialized nations.

The introduction of rotavirus vaccines has led to tremendous reductions in the AGE burden in the United Kingdom [4], a number of other European states [5], and other countries with



Correspondence: M. Head, University College London, Farr Institute for Health Informatics, 222 Euston Road, London, NW1 2DA, UK (m.head@ucl.ac.uk).

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national programs, which has, in turn, left norovirus standing as the primary cause of AGE across all age groups. We hope this transition will bring greater attention to noroviruses, as developments in better diagnostic tests, therapeutics, and vaccines are urgently required. This supplement, born out of a United Kingdom research workshop that took place in October 2014 (available at: http://www.idrn.org/events/previous/norovirus.php), focuses on the current state of norovirus-related research and public health efforts, mainly in England. Specific articles address many topics, including historic trends in research funding and published outputs [6], the epidemiology of norovirus surveillance in this high-income setting [7], outbreaks in hospital settings [8], disease in the community [9], the economics of outbreak control [10], and challenges associated with antiviral development [11].

The Research Investments in Global Health study has systematically described funding patterns for infectious disease research in the United Kingdom across 1997–2010, and there was very little funding for norovirus research, compared with that for research of other enteric pathogens and other high-burden infectious diseases [12]. The authors have updated their analyses to include United Kingdom data from 2011–2013 and also a similar comparison of US research funding [6]. There are promising trends toward an increase in research investment in both countries, but total investment remains low. The steady increase in published outputs related to norovirus show that there is a rapidly expanding research interest in the pathogen and its influence, which is yet to be matched by the research investment. The fragmented infrastructure of norovirus research is an issue, and capacity-strengthening initiatives may be able to facilitate cross-disciplinary collaborations and boost the number of new studies related to norovirus.

In 2009, surveillance systems operated by Public Health England incorporated a new web-based tool for reporting suspected and laboratory-confirmed norovirus outbreaks in hospitals. In the first 3 years of operation, surveillance teams received reports on 4000 outbreaks, and these have affected >40 000 patients and 10 000 staff and led to 15 000 lost bed-days [7]. The number of cases consistently peaks during the winter months but also exhibits considerable variation in terms of timing and size from year to year.

Cummins and Ready highlight the example of how an outbreak in one hospital in England in 2010 is estimated to have cost over $10.2 million; another single outbreak in the United States was transmitted among several hospitals over a period of several months and was initially assumed to be separate outbreaks [8]. They also discuss the differences between older and new hospitals and the proportions of beds that are located in side rooms or in open so-called Nightingale-style wards that have greater beds closer together and fewer washing facilities; the older hospital designs potentially provide greater opportunity for transmission of healthcare-associated infections.

However, most cases of norovirus disease occur in the community and never present to health services. O’Brien et al provide some of the few empirical age-specific norovirus incidence estimates ever reported from the Second Infectious Intestinal Disease Study. They found that the incidence among children aged <5 years is about 4 times higher than for those aged ≥5 years and that children <5 years old are 10 times as likely to present for primary care [9]. These data highlight that cases presenting for primary care are only a fraction of the

overall burden and that both community disease and disease requiring medical care are concentrated in young children.

Healthcare-associated norovirus outbreaks have been estimated to result in economic losses to the health service of up to £115 million ($184 million) in a high-incidence season in the United Kingdom [13]. Much of this economic impact is from bed-days lost owing to ward closure, a controversial and impactful intervention. Sadique et al present a mathematical transmission modeling study aiming to examine the cost-effectiveness of closing wards to new admissions [10]. They show that ward closure is likely to reduce the number of other wards affected and clinical cases in a facility, particularity when the index ward is a high-throughput unit. However, the overall impact and cost-effectiveness of the intervention are highly contingent on how well ward closure mediates further interward spread. This parameter is not well-established, pointing to the value of clinical trials to establish what works in controlling healthcare-associated outbreaks of norovirus infection.

Development of therapeutics for norovirus-attributable AGE has been slow and beset by difficulties and complexity at the preclinical stages. There are no licensed antiviral drugs for prophylactic use in outbreak settings or for treatment of immunocompromised individuals, and, to our knowledge, there are no human clinical trials currently underway that are testing anti-norovirus therapeutics [14]. Here, Thorne et al highlight some notable preclinical advances [11], including breakthrough demonstrations of norovirus replication lines in vitro and in vivo, the applications of interferons in targeting viral proteins, and further novel approaches in targeting host cell proteins that are essential for viral replication and lethal mutagenesis of noroviruses. These are signs of real progress in norovirus basic science and the potential for therapeutic development, but increases in infrastructure, capacity, and investment are required to shift these findings along the research pipeline and into clinical trials.

The key theme emerging from the articles in this supplement is that the burden of norovirus in the United Kingdom and elsewhere is substantial and that new tools for prevention, diagnosis, and treatment are required. Basic understanding of norovirus biology continues to accelerate, but parallel increases in capacity and research funding are going to be needed to translate this knowledge into clinical trials and translational research that can result in public health gains.

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