SUPPLEMENT ARTICLE

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Age-Specific Incidence Rates for Norovirus in the Community and Presenting to Primary Healthcare Facilities in the United Kingdom

Sarah J. O'Brien,[1,2,4] Anna L. Donaldson,[1,2] Miren Iturriza-Gomara,[1,3] and Clarence C. Tam[5]

[1]NIHR Health Protection Research Unit in Gastrointestinal Infections, University of Liverpool, [2]Epidemiology and Population Health, [3]Clinical Infection, Microbiology, and Immunology, University of Liverpool Institute of Infection and Global Health, and [4]The Farr Institute@HeRC, Liverpool, United Kingdom; and [5]Saw Swee Hock School of Public Health, National University of Singapore, Singapore

In a prospective, population-based cohort study and a study of primary-healthcare consultations, we had a rare opportunity to estimate age-specific rates of norovirus-associated infectious intestinal disease in the United Kingdom. Rates in children aged <5 years were significantly higher than those for other age groups in the community (142.6 cases per 1000 person-years [95% confidence interval {CI}, 99.8–203.9] vs 37.6 [95% CI, 31.5–44.7]) and those for individuals presenting to primary healthcare (14.4 cases per 1000 person-years [95% CI, 8.5–24.5] vs 1.4 [95% CI, .9–2.0]). Robust incidence estimates are crucial for vaccination policy makers. This study emphasises the impact of norovirus-associated infectious intestinal disease, especially in children aged <5 years.

Keywords. norovirus; acute gastroenteritis; incidence; vaccination; policy; prevention; pediatric; community; primary healthcare; real-time/quantitative RT-PCR.

Approximately 17 million cases of infectious intestinal disease (IID) in the United Kingdom per annum [1] account for at least 11 million people taking time off work and 8 million children being absent from school because of illness. Norovirus is by far the most commonly diagnosed cause of IID, resulting in approximately 3 million cases annually [1, 2] and causing particular problems in closed and semiclosed communities like schools, hospitals and nursing homes where the impact on children and the elderly can be considerable [3]. Currently the main means of controlling the spread of norovirus are good hand hygiene, good environmental cleaning, and exclusion from work or school until cases are symptom free for 48 hours [4]. As the prospect of an effective vaccine against norovirus becomes a reality [5], there is a need for country-specific illness burden estimates to inform potential national vaccination programs [6]. However, there is a paucity of incidence estimates from high-income countries in the peer-reviewed literature, and those that are available are based on data from the 1990s [7, 8]. Furthermore, significant underreporting of norovirus in national surveillance systems can lead to inaccurate estimates of impact [1]. Therefore, we performed a secondary analysis of data from the Second Study of Infectious Intestinal Disease in the Community (hereafter, the IID2 study) in the United Kingdom, which comprised a population-based cohort study and a prospective study of presentation to primary healthcare [1, 2], to generate age-specific incidence estimates for norovirus-associated IID burden in the population.

METHODS

The IID2 study methods have been described in full elsewhere [1, 2, 9]. Briefly, the study comprised 2 main components: (1) a prospective population-based cohort study in which healthy people of all ages were randomly selected from a representative sample of general practices across the United Kingdom and followed up for symptoms of IID on a weekly basis for 12 months (cohort study) and (2) a 12-month prospective study of people consulting a primary healthcare professional with symptoms of IID who were enrolled on clinical presentation (GP presentation study).

Participants who developed symptoms that fulfilled the case definition for IID in either the cohort or the GP presentation studies were requested to complete a symptom questionnaire and submit a stool sample for microbiological examination. Cases were defined as "people with loose stools or clinically significant vomiting lasting less than two weeks, in the absence of a known noninfectious cause, preceded by a symptom-free period of three weeks. Vomiting was clinically significant if it occurred more than once in a 24-hour period and if it incapacitated the case or was accompanied by other symptoms such as cramps or fever [9, p. 3]." The definition of vomiting excluded noninfectious causes such as morning sickness, posseting in infants, and vomiting due to pyloric stenosis. All the study data were collected during 2008 and 2009.

Microbiologic Methods

Two nucleic acid extracts were prepared from each stool sample [2]. Each extract was examined for a comprehensive range of

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Correspondence: S. J. O'Brien, NIHR Health Protection Research Unit in Gastrointestinal Infections, 2nd Floor, Block F, Waterhouse Buildings, 1-5 Brownlow St, Liverpool L69 3GL, UK (s.j.obrien@liverpool.ac.uk).

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gastrointestinal pathogens, including norovirus, using real-time/quantitative reverse transcription–polymerase chain reaction (RT-PCR). A cycle threshold (CT) value of <30 was used to define clinically significant norovirus. This cut-off was based on evidence that a considerable proportion of asymptomatic people have low viral loads detected using real-time/quantitative RT-PCR and so it is assumed that, in these circumstances, norovirus is unlikely to be the cause of the patient's symptoms [10, 11].

Statistical Methods

Methods for estimating incidence in the IID2 study are described in detail elsewhere [1]. Briefly, we estimated age-specific rates in the community from the cohort study by dividing the number of PCR-confirmed norovirus IID cases in each age group by the total number of person-years at risk in that age group. Because not all IID cases submitted stool specimens for analysis, the total number of PCR-confirmed norovirus IID cases was derived from an imputation model that inferred pathogen positivity as a function of age, sex, and symptom profile. Incidence estimates were computed as an average from 20 imputed data sets, accounting for within- and between-imputation variances in the calculation of 95% confidence intervals (CIs).

We estimated age-specific rates of primary healthcare consultation from the GP presentation study by dividing the number of consultations due to norovirus in each age group by the person-years of observation in that age group. This was estimated by multiplying the age-stratified patient population of each practice by the time contributed to the study. As above, we computed norovirus-specific consultation rates as an average from >20 imputed data sets.

We present incidence rates as cases or consultations per 1000 person-years for the community and for the following age groups: <1 year, 1–5 years, 5–15 years, 15–64 years, and ≥65 years. For the GP presentation study, the size of the infant population in each practice was not available, so we present combined rates for children aged <5 years.

Analysis was performed in Stata 11.0 software (Stata, College Station, Texas).

Table 1. Age-Specific Incidence Rates for Norovirus-Associated Infectious Intestinal Disease in the IID2 Cohort Study

Age Group	Cases, No.[a]	Person-Years	Cases/1000 Person-Years, No. (95% CI)
<1 y	5	26.9	178.2 (70.5–450.0)
1–5 y	26	190.8	137.3 (92.6–203.4)
5–15 y	26	424.1	59.6 (36.8–96.5)
15–64 y	103	2647.8	39.0 (31.3–48.7)
≥65 y	38	1369.1	27.7 (19.6–39.1)
<5 y	31	217.6	142.6 (99.8–203.9)
≥5 y	167	4441.0	37.6 (31.5–44.7)

Abbreviation: CI, confidence interval.

[a] Cases represent the mean value from 20 imputations.

Table 2. Age-Specific Incidence Rates for Norovirus-Associated Infectious Intestinal Disease in the IID2 General Practice Presentation Study

Age Group	Cases, No.[a]	Person-Years[b]	Cases/1000 Person-Years, No. (95% CI)
<5 y	242	16 720.4	14.4 (8.5–24.5)
5–15 y	56	35 211.3	1.5 (.6–4.2)
15–64 y	236	205 597.8	1.1 (.7–1.8)
≥65 y	114	54 702.1	2.1 (1.1–4.0)
<5 y	242	16 720.4	14.4 (8.5–24.5)
≥5 y	406	295 511.2	1.4 (.9–2.0)

Abbreviation: CI, confidence interval.

[a] Cases represent the mean value from 20 imputations.

[b] Data for individuals aged <1 year were not available.

Ethics and Consent

A favorable ethical opinion to perform the IID2 study was granted by the NHS North West Research Ethics Committee (07/MRE08/5), and all participants gave informed written consent prior to being enrolled in the study.

RESULTS

The overall incidence of norovirus-associated IID in the community was 47.0 cases per 1000 person-years (95% CI, 39.1–56.5), and 2.1 norovirus-associated IID cases per 1000 person-years (95% CI, 1.4–3) presented to primary healthcare. Age-specific norovirus-associated IID incidence rates in the community were significantly higher in children aged <5 years, compared with rates in other age groups (Table 1). Similarly norovirus-associated IID consultation rates were much higher in children aged <5 years presenting to primary healthcare (Table 2). For children aged <5 years, the rate of norovirus-associated IID in the community was 10 times the rate associated with primary healthcare consultations. By contrast, among older children and adults, there were >30 cases in the community per primary healthcare consultation; among those aged ≥65 years, this ratio was 13 cases per primary healthcare consultation.

These results indicate that, among children aged <5 years, approximately 15% experience norovirus IID each year, and 1.5% present to primary healthcare for this illness. Uncertainty around these estimates was high, particularly for the community rates, because of the relatively modest number of cases in each age group.

DISCUSSION

The IID2 study is one of only a handful of population-based prospective studies globally designed to measure disease incidence by pathogen [1, 7, 8, 13–15], which gives a rare opportunity to estimate age-specific incidence for norovirus-associated IID. The incidence estimates of norovirus-associated IID in the

United Kingdom population and presenting to primary healthcare were highest in children aged <5 years.

In a similar study (the IID1 study), in which data were collected between 1993 and 1996, the incidence of norovirus-associated IID in children aged <5 years in the community was 214 cases per 1000 person-years (95% CI, 159–277), and so there had not been a significant change over time, as witnessed by a large overlap in CIs [12]. However, the incidence of norovirus-associated IID in children <5 years of age presenting to primary healthcare had halved between 1993–1996 (32 cases per 1000 person years; 95% CI, 26–38) and 2008–2009, and this change was statistically significant [12]. In the IID2 study, 15% of children aged <5 years experienced norovirus-associated IID in a year. The corresponding percentage in the IID1 study was 20% [12].

Given the lack of a population-level intervention, such as vaccination, it is not surprising that incidence rates in the 2 population-based cohort studies conducted over a decade apart were similar. What was more surprising was the significant decrease in children with norovirus-associated IID presenting to primary healthcare. This is unlikely to have been because of a diminution in the severity of illness. The proportion of people taking time off work or school because of IID was similar in the 2 studies, and our hypothesis is that changes to the appointment system in primary healthcare services in the United Kingdom in intervening years, coupled with advice on the NHS Choices website (available at: http://www.nhs.uk/conditions/norovirus/pages/treatment.aspx) advising against seeking general practitioner appointments for suspected norovirus, are more likely explanations for the decrease in consultations.

This study had several strengths. The proportion of people agreeing to take part in the IID2 cohort study was lower than that in the IID1 study, but this was compensated for by much better compliance with weekly follow-up [1]. Furthermore, the number of people lost to follow-up was much lower than that in the IID1 study [1].

Using molecular methods for pathogen detection meant that we could investigate low-volume samples, and this decreased the diagnostic gap among community cases [2]. We used the same real-time/quantitative RT-PCR assays and the same CT cutoffs for analyzing the IID1 and IID2 study data, so the change in the incidence of norovirus-associated IID presenting to primary healthcare is likely to be real and not an artifact caused by using different assays.

The study was limited by the lack of a control group in the IID2 study, and so, based on previous work, we used a CT value of <30 as a marker of norovirus-associated IID [12]. Had we used a more sensitive cutoff of <40, which is the standard in most clinical microbiology laboratories, it is likely that the age-specific incidence rates would have been higher. However, using a more sensitive cutoff would almost certainly have involved misclassifying asymptomatic excretors as clinical cases of norovirus-associated IID.

In conclusion, as rotavirus-associated diarrhea comes under control through vaccination, norovirus-associated IID will assume greater importance. Robust incidence estimates are crucial for guiding vaccination policy, and this study emphasizes the impact of norovirus-associated IID across age groups, but especially in children aged <5 years.

Notes

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S. J. O. and M. I.-G. conceived the study. C. C. T. undertook the statistical analyses. S. J. O., A. D., M. I.-G., and C. C. T. drafted the manuscript. All authors have read and approved the final manuscript. All authors had full access to the whole study data set (including statistical reports and tables) and can take responsibility for the integrity of the data and the accuracy of the data analysis. S. J. O. is the guarantor of the study.

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