The estimated disease burden of norovirus in The Netherlands

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Received 31 August 2011; Final revision 23 March 2012; Accepted 4 April 2012; first published online 17 May 2012

SUMMARY

Noroviruses are an important cause of acute gastroenteritis in humans. We incorporated new insights gained over the past decade in an updated estimate of the disease burden of (foodborne) norovirus illness in The Netherlands in 2009. The disease outcomes – non-consulting cases, visiting a general practitioner, hospitalization and mortality – and the foodborne proportion were derived from cohort studies, surveillance data and literature. Age-specific incidence estimates were applied to the population age distribution in The Netherlands in 2009. The general population incidence was 3800/100 000 (95% CI 2670–5460), including 0.4 fatal cases/100 000, resulting in 1622/100 000 (95% CI 966–2650) disability-adjusted life-years in a population of 16.5 million. The updated burden of norovirus is over twofold higher than previously estimated, due in particular to the new insights in case-fatality ratios. Results suggest that the burden of norovirus institutional outbreaks is relatively small compared to the burden of community-acquired norovirus infections.

Key words: Foodborne infections, gastroenteritis, incidence, Norwalk agent and related viruses, surveillance.

INTRODUCTION

Noroviruses are responsible for a large number of infections worldwide each year. Noroviruses are highly infectious [1], environmentally stable [2], and able to utilize different transmission routes. Transmission can occur from person to person, after ingestion of contaminated food or water, or through contact with contaminated surfaces or aerosols [3]. Several prospective population-based studies were performed, e.g. in the UK and The Netherlands, resulting in estimates of norovirus gastroenteritis incidence of 1/80 to 1/64 of the population per annum in the UK between 1993 and 1996 [4] and 1/18 to 1/26 in 2008–2009 [5], and 1/31 inhabitants in The Netherlands in 1999 (Sensor) [6]. The annual burden of norovirus in The Netherlands was estimated to be 450 disability-adjusted life-years (DALYs) with an
incidence of 2900/100 000 (470 000 cases/year), costing Dutch society 25 million euros in 2004 [7]. Estimating the incidence or burden due to solely foodborne norovirus transmission is difficult due to the entanglement of transmission modes; after foodborne introduction, person-to-person transmission quickly takes over.

The initial burden estimates did not include institutional norovirus outbreaks for which epidemiological and health impacts may be different [8]. Moreover, at the time of the Sensor study, norovirus infection was considered a mild and self-limiting disease with a low case-fatality ratio (CFR) [9]. Over the past decade, significant progress has been made in the field of norovirus research, yielding new knowledge about the virus and its health outcomes. For example, recent studies revealed that significant mortality may be associated with norovirus infections, particularly in the elderly [10, 11]. Newly emerging variants have been recognized every 2 years since 2002, causing epidemics across Europe and worldwide [12] corresponding with an increase in the number of norovirus outbreaks [13] and increased mortality [10].

Given the changes and new insights obtained over the last decade, there is a need for an updated burden estimate for norovirus infections. Our objective is to determine the disease burden of norovirus illness in The Netherlands in 2009 and its estimated foodborne proportion, while including the newly derived knowledge of the past decade.

**METHODS**

Our starting point was the burden estimate for The Netherlands 2004 [7], using methods and updates described elsewhere [14, 15].

**Disease outcomes**

The disease outcomes following infection were defined by designing an outcome tree, in which each block represents a health outcome, while between blocks transition probabilities must be established (Fig. 1).

**Input parameters**

The studies described in literature that provided data for our input parameters are listed in Table 1. Details of the data used are given in annex 2 of Havelaar et al. [15].

**Burden estimate**

The different outcomes of (infectious) disease can be combined in one single metric, the DALY, following the methodology described previously [14], with a DALY being the sum of years of life lost (YLL) and the number of years lived with disability (YLD).

**Community-acquired acute gastroenteritis**

Age-specific incidence rates of community-acquired gastroenteritis attributed to norovirus as well as the fraction of patients visiting a general practitioner...
Table 1. Overview of studies providing data for the calculation of norovirus burden in The Netherlands

<table>
<thead>
<tr>
<th>Factor</th>
<th>Population</th>
<th>Measure</th>
<th>Period</th>
<th>Study design</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality from unexplained GE</td>
<td>Deceased Dutch elderly (≥65 yr)</td>
<td>Attribution of mortality to norovirus</td>
<td>1999–2006</td>
<td>Syndromic surveillance</td>
<td>[10]</td>
</tr>
<tr>
<td>Mandatory reporting norovirus</td>
<td>General German population</td>
<td>Case-based data including mortality</td>
<td>Since 2001</td>
<td>Mandatory reporting</td>
<td>[19]</td>
</tr>
<tr>
<td>Hospitalization due to community-acquired norovirus</td>
<td>Dutch hospitalized children aged</td>
<td>Overall incidence hospitalization due to norovirus</td>
<td>1 year between May 2008 and Nov. 2009</td>
<td>Prospective in six hospitals</td>
<td>[18]</td>
</tr>
<tr>
<td>Outbreaks of GE in The Netherlands</td>
<td>General Dutch population</td>
<td>Number of GE outbreaks</td>
<td>Jan.–Dec. 2002</td>
<td>Intensified surveillance</td>
<td>[23]</td>
</tr>
<tr>
<td>Gastroenteritis surveillance systems</td>
<td>General Dutch population</td>
<td>Hospital diagnosis of GE</td>
<td>Since 2002</td>
<td>Surveillance</td>
<td>[17]</td>
</tr>
<tr>
<td>Outbreaks of viral GE in The Netherlands</td>
<td>General Dutch population</td>
<td>Numbers of Dutch healthcare seekers and laboratory-confirmed outbreaks</td>
<td>Since 1995</td>
<td>Routine laboratory surveillance</td>
<td>[22]</td>
</tr>
<tr>
<td>Risk factors of norovirus infection</td>
<td>General Dutch population that tested positive in population-based study</td>
<td>Population attributable risk</td>
<td>1999</td>
<td>Community-based prospective cohort including nested case-control</td>
<td>[40]</td>
</tr>
<tr>
<td>Life expectancy of the elderly in long-term care facilities</td>
<td>Long-term care patients in Dublin hospital</td>
<td>Mean and median survival, risk factors, death</td>
<td>1997–2003</td>
<td>Cohort study</td>
<td>[24]</td>
</tr>
<tr>
<td>Foodborne proportion of community-acquired norovirus</td>
<td>Norovirus cases internationally</td>
<td>Expert opinion</td>
<td></td>
<td>Qualitative research among experts</td>
<td>[26]</td>
</tr>
<tr>
<td>Foodborne proportion of norovirus outbreaks</td>
<td>Norovirus outbreaks in 13 European countries</td>
<td>Estimates of foodborne proportion</td>
<td>1999–2008</td>
<td>Outbreak surveillance</td>
<td>[27]</td>
</tr>
</tbody>
</table>

GE, Gastroenteritis.
(GP) were estimated using methodology described elsewhere [14, 15], using data from a nested case-control study within the 1999 population-based study Sensor [16]. Information on the percentage of patients visiting their GP for a norovirus infection was derived from a nested case-control study within the Sensor study [16]. These estimates were applied to the population age distribution in The Netherlands in 2009, as derived from Statistics Netherlands (www.cbs.nl). Incidence estimates were updated from 1999 to 2009 with a trend correction of 125%, as derived from trends in hospitalizations for viral gastroenteritis by all causes collected in the Dutch National Disease Registry for hospitalization (Prismant) with a national coverage of 88% [17]. According to this registry, 21,932 persons were admitted to hospital for gastroenteritis in 2009, 38% of them were children (aged <18 years). Data on aetiology were obtained from the GastroEnteritis Admission Study (Dutch acronym: GEops) [18]. Briefly, patients admitted to six hospitals for gastroenteritis during the period May 2008–November 2009 were included in the study. Ninety-six faecal samples from children and 41 samples from adults (aged ≥18 years) were analysed for pathogens by multiplex PCR (eight bacteria and five viruses) or microscopy (six parasites). At least one pathogen was detected in 98% of samples from children and 59% of samples from adults. Co-infections (two or more pathogens in one sample) were detected in 40% and 22% of samples from children and adults, respectively. The fraction of hospitalized cases due to acute gastroenteritis attributable to norovirus \( fG \), was modelled as a beta distribution also accounting for mixed infections (e.g. attributing the infection for half to norovirus if one additional pathogen was detected):

\[
fG = \frac{w_1}{w_1 + w_2 + w_3} \sum_{j=1}^{3} \left\{ \text{beta}(\text{posG}(j) + a, G - \text{posG}(j) + b) \right\} w(j),
\]

where \( G \) = number of samples tested for presence or absence of norovirus in GEops; \( \text{posG}(j) \) = number of samples from which norovirus was isolated as \( j = 1 \) the only pathogen; \( j = 2 \) with one other pathogen; \( j = 3 \) with two other pathogens; \( w(j) = \text{weight} \) \( w(1) = 1; w(2) = 1/2; w(3) = 1/3 \); \( \text{beta}(a, b) \) = prior distribution for \( fG \); in this case an informed prior distribution beta(0.15, 4) was used.

Mortality due to norovirus was derived from Germany’s electronic surveillance system of infectious diseases, in which norovirus infection is statutorily notifiable [19] and thereby one of the few systems, if not the only, in Europe providing case-fatality ratios for all age groups. Local health departments follow-up each notification and complete a case-report that is transmitted, via state health departments, to the Robert Koch-Institute. Each case-form has a field for ‘death’, which should be marked if the death of the notified person is ‘causally related’ to the infection or where this, according to the information of the local health department, cannot be excluded. Age group-specific CFRs were derived from this surveillance system using the age categorization of the Sensor study, and applied to the age-specific estimates of community-acquired gastroenteritis attributed to norovirus in The Netherlands in 2009. An informed prior distribution beta(0.15, 4) was used. We adopted the life expectancy derived from the standard model life table (West model 25 and 26 for males and females), as recommended by WHO [20]. Disability weights were derived from a Dutch population panel, using elicitation protocols as described by Haagsma et al. [21], and presented in Table 2.

### Institutional outbreaks

The numbers of outbreaks in nursing homes, hospitals and other institutional settings were derived from passive laboratory-based surveillance on outbreaks reported to the RIVM in 2009 [22]. The mean number of cases involved in outbreaks in these settings was derived from a 1-year intensified outbreak surveillance study in The Netherlands in 2002 [23], while assuming that the proportion of patients visiting a GP is comparable to that in community-acquired cases. The incidence of fatal cases in institutional outbreaks (i.e. in nursing homes, hospitals and other institutional settings) was based on the case-fatality ratio for people aged ≥65 years as derived from Germany’s electronic surveillance system. For fatal cases living in institutions, a life-expectancy of 30 months was used, as described by Cunningham et al. [24], to account for comorbidity. Disability weights representative of persons living in nursing homes were not available, and may differ from the elderly living in the community due to underlying illness and quality of life. Therefore, the disability weight of living in an institution was assumed to be in the middle between the disability weight of hospital admission and visiting a GP.

### Discounting

Disease burden is presented both undiscounted and discounted at a rate of 1.5% as currently recommended in The Netherlands [25].
The proportion of norovirus cases attributed to food was based on expert elicitation [26], i.e. food safety experts were asked to provide their estimates of the most likely range for each of the parameters, and joint probability distributions were created by probabilistic inversion.

Outbreaks

The proportion of outbreaks attributed to food was derived from previous analyses of the Foodborne Viruses in Europe (FBVE) network’s database [27].

Statistical analysis

A stochastic Monte Carlo simulation model was built to quantify the uncertainty in the disease burden of norovirus-associated illness, using @RISK 5.0 (Palisade Decision Tools, USA), a Monte Carlo simulation add-in for Excel 2002 (Microsoft, USA). The model was run for 10,000 iterations. The distribution functions of parameters that were used to estimate the disease burden of infection with norovirus are described elsewhere [15], and estimates based on new data are shown in Tables 3–5. The sensitivity of model outcomes in relation to uncertain input parameters were analysed using regression analyses using the Tornado Plot function in @RISK. Other sources of uncertainty were analysed by scenario analysis.

RESULTS

Community acquired

The estimates for age-specific CFRs are presented in Table 3, clearly showing the highest CFR for people aged ≥65 years. The data of hospital admissions due to norovirus in children and adults are presented in Table 4.

### Table 2. Disability weights and duration

<table>
<thead>
<tr>
<th>Source</th>
<th>Disability weight</th>
<th>Duration (years)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community-acquired</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>Variable</td>
<td></td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not visiting GP</td>
<td>0.000</td>
<td>–</td>
<td>[21]</td>
</tr>
<tr>
<td>Visiting GP</td>
<td>0.015</td>
<td>1</td>
<td>[21]</td>
</tr>
<tr>
<td>Hospitalized</td>
<td>0.041</td>
<td>1</td>
<td>[21]</td>
</tr>
<tr>
<td>Institutional outbreaks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>2.5 (2–3.3)</td>
<td>[24]</td>
</tr>
<tr>
<td>Nursing homes</td>
<td>0.028</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hospitals</td>
<td>0.028</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

GP, General practitioner.

### Table 3. Estimates of the case-fatality ratios (CFRs) based on German surveillance data 2004–2008

<table>
<thead>
<tr>
<th>Age group (yr)</th>
<th>CFR median (/1000)*</th>
<th>CFR mean (/1000)*</th>
<th>(95% CI) (/1000)*</th>
<th>Mean beta distribution (/1000)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.09</td>
<td>0.09</td>
<td>(0.0136–0.2728)</td>
<td>0.10%</td>
</tr>
<tr>
<td>1–4</td>
<td>0.00</td>
<td>0.00</td>
<td>(0.0–0.01727)</td>
<td>0.00%</td>
</tr>
<tr>
<td>5–11</td>
<td>0.00</td>
<td>0.00</td>
<td>(0.0–0.04244)</td>
<td>0.01%</td>
</tr>
<tr>
<td>12–17</td>
<td>0.07</td>
<td>0.09</td>
<td>(0.0037–0.3397)</td>
<td>0.10%</td>
</tr>
<tr>
<td>18–64</td>
<td>0.03</td>
<td>0.03</td>
<td>(0.0121–0.0625)</td>
<td>0.03%</td>
</tr>
<tr>
<td>≥65</td>
<td>0.63</td>
<td>0.63</td>
<td>(0.5453–0.7287)</td>
<td>0.63%</td>
</tr>
</tbody>
</table>

CI, Confidence interval.
* CFRs on the basis of the German surveillance system
† CFRs estimated for the Dutch population using an informed prior distribution beta(0.15, 4).
Outbreaks

The data of outbreaks in nursing homes and other settings are presented in Table 5, showing a total of 132 laboratory-reported outbreaks involving 4650 cases in The Netherlands in 2009.

Burden of disease

Community-acquired gastroenteritis

In a population of 16.5 million people the incidence of community-acquired norovirus disease cases in The Netherlands in 2009 was estimated to be 3800/100 000 (95% CI 2670–5460), the number of fatal cases 0.4/100 000 (95% CI 0.2–0.7), the number of undiscounted DALYs 1622 (95% CI 966–2650), and the number of discounted DALYs 1285 (95% CI 801–1910).

Outbreaks

The number of cases involved in outbreaks in institutions was estimated to be 30/100 000, of which 20 (67%) were in nursing homes and 10 (33%) in hospitals. The number of fatal cases due to norovirus outbreaks was estimated to be 0.02/100 000.

Burden

The burden estimate calculations are shown in Tables 5 and 6. The general population incidence of norovirus gastroenteritis in 2009 was estimated to be 3800 cases/100000 (95% CI 2670–5460), the number of fatal cases 0.4/100000 (95% CI 0.2–0.7), the number of undiscounted DALYs 1622 (95% CI 966–2650), and the number of discounted DALYs 1285 (95% CI 801–1910).

Burden of foodborne disease

Community acquired

On the basis of expert opinion [26], 17% (95% CI 13–28) of norovirus illness cases can be attributed to food, which comprises 650/100 000 (95% CI 490–1065) cases and 0.06/100 000 (95% CI 0.05–0.11) deaths in The Netherlands in 2009, resulting in a burden of 275 (95% CI 105–450) undiscounted and 194 (95% CI 125–320) discounted DALYs.
Outbreaks

On the basis of analysis of outbreaks reported to the FBVE network [27] a total of 22% of all outbreaks can be attributed to food, which comprised 6/100 000 cases and 0.01/100 000 deaths in The Netherlands in 2009, resulting in a burden of 30 undiscounted and 30 discounted DALYs.

Overall

In 2009, a total of 662/100 000 (95% CI 496–1071) norovirus cases and 0.07/100 000 (95% CI 0.06–0.12) deaths could be attributed to food, which comprises 305 (95% CI 135–480) undiscounted and 224 (95% CI 155–350) discounted DALYs.

Sensitivity analysis

Community-acquired

The main parameters influencing the uncertainty of the overall DALY estimate, either discounted or undiscounted, were the CFR in the 12–17 years age group and 0-year-olds, and the incidence of community-acquired norovirus gastroenteritis in the 18–64 years age group and people aged ≥65 years (data not shown). The main parameters influencing the uncertainty of deaths in community-acquired cases were incidence of community-acquired norovirus gastroenteritis in people aged ≥65 years and, to a much lesser extent, the incidence of overall gastroenteritis in this age group. In a scenario analysis, we assumed that mortality was limited to persons that had visited a GP, as these may be considered the most severe cases. This resulted in a sharp decrease of mortality to only one fatal case and of the burden to 561 DALYs. In a second scenario, we evaluated the mortality in people aged ≥65 years, as described by van Asten et al. [10] on the basis of syndromic surveillance of unexplained gastroenteritis, i.e. a conservative estimate of 0.14 of deaths in the community for each laboratory-reported outbreak. This resulted in a total of 39 fatal cases in this age group, which is in the same order of magnitude compared to the 45 fatal cases based on the German surveillance system. In a third sensitivity scenario, we evaluated the potential effect of underreporting of mortality due to norovirus in surveillance systems, and assumed 50% of under-reporting [28]. This resulted in a sharp increase of mortality to 119 fatal cases an increase of the burden to 2627 DALYs.

Institutional

The main parameter influencing the uncertainty of the DALY estimate, either discounted or undiscounted, was the disability weight for persons living in nursing homes (regression coefficient 0.93), and can be considered a data gap.

Overall

We compared three scenarios to investigate the contribution of increased incidence and new insights into...
CFRs (Fig. 2) to the observed increase in the estimated burden. First, the burden of norovirus in 2004 was recalculated using our model but without the trend correction and using a CFR of 0.001% as described by Mead et al. [9]. Since Mead et al. did not provide an age stratification, 95% of the mortality was attributed to people aged ≥65 years, and 5% to people aged <65 years. Second, the burden in 2009 was calculated using trend corrections and the CFR of Mead et al. Third, the burden was calculated using a trend correction and CFRs based on the German surveillance system but assuming no child mortality, to evaluate the influence of mortality in young children (i.e. aged <12 years). Results show that the incidence increased from 3100 to 3800/100 000 between 2004 and 2009. The corresponding increase in burden was 110 DALYs. A further increase from 900 to 1600 DALYs resulted from the new insights in mortality, of which 200 DALYs can be attributed to mortality in young children.

**DISCUSSION**

The burden of norovirus illness was estimated to be >1600 DALYs in The Netherlands in 2009, which is comparable to the burden of Salmonella spp. in The Netherlands [29] which, in contrast to norovirus, is well known as an enteric pathogen with a high burden. The population-based age-adjusted estimates of all norovirus cases in The Netherlands slightly increased from almost 3170 cases/100 000 in 1999 on the basis of the Sensor study [6] and 3100/100 000 in 2004 [7] to 3800 cases/100 000 in 2009 using a trend correction of 125%. However, the evidence for correction may be weak due to its indirect link to norovirus infections as a consequence of the absence of a case-based reporting system in The Netherlands. In addition, an increase was observed for one level of the reporting pyramid, i.e. hospitalizations, and there is an implicit assumption that community cases have also increased by the same proportion. Nevertheless, an actual increase is likely as a result of the emergence of new variants, as described by Siebenga et al. [13]. The updated number of 1285 estimated discounted DALYs is higher compared to ~500 in 1999 [6] and 2004 [7]. This difference is mainly attributed to the use of a new estimate of 0.4 fatal cases/100 000 due to norovirus. The old estimate was 5 cases/100 000 in 2004, based on the CFR reported by Mead et al. [9], which is likely to be an underestimation. As Mead et al. explain, the assumptions underlying the Norwalk-like viruses figures were at that time among the most difficult to verify, and sensitive methods for detection were not commonly used at that time [9]. Moreover, different methods used for mortality estimates complicate the inferences of a time trend, as was also concluded by Scallan et al. [28]. Nevertheless, higher mortality due to norovirus was found to correspond with the recent increases in norovirus activity [10], which was associated with rapidly emerging new norovirus types of genogroup II type 4. The increases were either due to changes in pathogenic characteristics or as a consequence of a larger number of cases including deaths, since the population is again available as a pool of susceptible persons for each new variant. The estimated mortality in children contributed considerably to the estimated DALYs: three fatal cases in children aged <5 years contributed 263 YLL (22% of the total YLL) resulting in an overall mean of 20 years of life lost per fatal case. This finding is remarkable and indicates that mortality due to norovirus needs further investigation. For
decades ago, the incidence of norovirus infections may have increased since 1999 due to newly emerging variants. For example, the studies in the UK suggest increased incidence over a 10-year period from 12–16/1000 to 38–55/1000 person-years. This potential increase is incorporated in our estimate by using updated records of hospitalizations and outbreaks. However, if a study like Sensor is performed again it may be advisable to include over-sampling of the elderly and adults, so that the uncertainties in proportions of pathogens can be diminished. The effect of the disability weight of living in nursing homes can work both ways. Either the persons living in these institutions receive better care compared to the elderly living at home, resulting in a lower disability weight, or the persons that need to live in these institutions need more care resulting in a higher disability weight.

Given that several studies were performed in nursing homes in The Netherlands [33, 34], there should be possibilities to investigate quality of life in nursing homes as well as mortality during outbreaks in the near future.

Despite the new insights in sequelae of norovirus infection, only mortality was of influence at the population level and is included in our calculations. For other sequelae, like longer duration of illness for children or hospitalized patients [35], the added burden was estimated to be low, as it would not implicate chronic effects. Benign infantile seizures [36] are severe sequelae but have a very short duration of several minutes and no lingering symptoms. Encephalopathy [37] was not included because this was only described in case reports. Although irritable bowel syndrome was prospectively identified as a lingering symptom of viral gastroenteritis [38], the attribution of this disease outcome to a norovirus infection is not yet established and needs further investigation. Similarly, the potential of chronic norovirus diarrhoea in immunocompromised individuals requires confirmation before it can be included in our estimates.

In conclusion, on the basis of newly gained insights in the potential severe outcome of the disease, the burden of norovirus infections overall and the consequential burden of foodborne norovirus infections are now estimated to be higher than previously assumed, despite the fact that it is still considered a conservative estimate. Several investigations illustrate the previous underestimation of the burden of norovirus illness [39], especially the foodborne proportion of norovirus infections. Still, there are knowledge gaps in the potential sequelae which need to be further investigated.
and which may result in an even higher burden of norovirus illness.

ACKNOWLEDGEMENTS

We are grateful to Helen Bernard and Klaus Stark for kindly sharing the data recorded in the German surveillance system. We thank Ingrid Friesema, Jolanda Bogerman, Kees van den Wijngaard, Remko Enserink, and Yvonne van Duynhoven for their valuable feedback during the analysis. This work was supported by the Dutch Food and Consumer Product Safety Authority.

DECLARATION OF INTEREST

None.

REFERENCES


