Epidemiol. Infect. (2013), **141**, 496–506. © Cambridge University Press 2012
doi:10.1017/S0950268812000799

The estimated disease burden of norovirus in The Netherlands

L. VERHOEF[1]*, M. KOOPMANS[1,2], W. VAN PELT[1], E. DUIZER[1], J. HAAGSMA[3], D. WERBER[4], L. VAN ASTEN[1] AND A. HAVELAAR[1,5]

[1] *National Institute for Public Health and the Environment, Bilthoven, The Netherlands*
[2] *Erasmus Medical Centre, Rotterdam, The Netherlands*
[3] *Department of Public Health, Erasmus Medical Centre, Rotterdam, The Netherlands*
[4] *Robert Koch Institute, Berlin, Germany*
[5] *Institute for Risk Assessment Sciences, Faculty of Veterinary Medicine, Utrecht University, Utrecht, The Netherlands*

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

* Author for correspondence: Dr L. Verhoef, National Institute for Public Health and the Environment (RIVM), Postbak 22, PO Box 1, 3720 BA Bilthoven, The Netherlands.
(Email: linda.verhoef@rivm.nl)

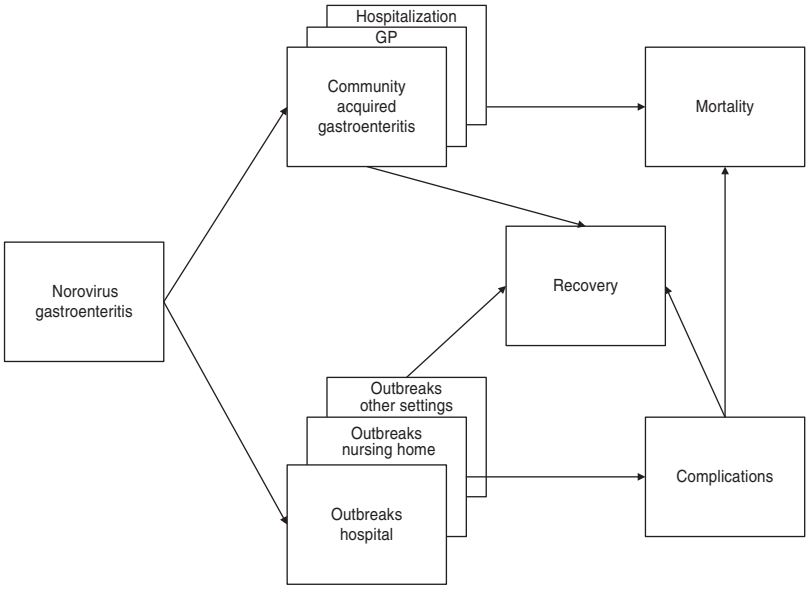

Fig. 1. Outcome tree for norovirus-associated gastroenteritis.

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*

Factor	Population	Measure	Period	Study design	Ref.
Mortality from unexplained GE	Deceased Dutch elderly ($\geqslant$65 yr)	Attribution of mortality to norovirus	1999–2006	Syndromic surveillance	[10]
Mandatory reporting norovirus	General German population	Case-based data including mortality	Since 2001	Mandatory reporting	[19]
Hospitalization due to community-acquired norovirus	Dutch hospitalized children aged 0–17 yr and adults aged $\geqslant$18 yr	Overall incidence hospitalization due to norovirus	1 year between May 2008 and Nov. 2009	Prospective in six hospitals Friesema *et al.* (unpublished data)	[18]
Community-acquired sporadic GE due to norovirus	General Dutch population	Incidence of overall GE and proportion of norovirus	Dec. 1998–Dec. 1999	Community-based prospective cohort including nested case-control	[6]
Outbreaks of GE in The Netherlands	General Dutch population	Number of GE outbreaks	Jan.–Dec. 2002	Intensified surveillance	[23]
Gastroenteritis surveillance systems	General Dutch population	Hospital diagnosis of GE	Since 2002	Surveillance	[17]
Outbreaks of viral GE in The Netherlands	General Dutch population	Numbers of Dutch healthcare seekers and laboratory-confirmed outbreaks	Since 1995	Routine laboratory surveillance	[22]
Risk factors of norovirus infection	General Dutch population that tested positive in population-based study	Population attributable risk	1999	Community-based prospective cohort including nested case-control	[40]
Life expectancy of the elderly in long-term care facilities	Long-term care patients in Dublin hospital	Mean and median survival, risk factors, death	1997–2003	Cohort study	[24]
Foodborne proportion of community-acquired norovirus	Norovirus cases internationally	Expert opinion		Qualitative research among experts	[26]
Foodborne proportion of norovirus outbreaks	Norovirus outbreaks in 13 European countries	Estimates of foodborne proportion	1999–2008	Outbreak surveillance	[27]

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 $\geqslant 18$ 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):

$$fG = \sum_{j=1}^{3} [\text{beta}(\text{pos}G(j) + a, G - \text{pos}G(j) + b)^{*} w(j)],$$

where G = number of samples tested for presence or absence of norovirus in GEops; pos$G(j)$ = 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; $w(j)$ = weight [$w(1)=1$; $w(2)=1/2$; $w(3)=1/3$]; 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 $\geqslant 65$ 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].

Table 2. *Disability weights and duration*

	Disability weight	Duration (years)	Source
Community-acquired			
Death	1	Variable	
Gastroenteritis			
Not visiting GP	0·000	–	[21]
Visiting GP	0·015	1	[21]
Hospitalized	0·041	1	[21]
Institutional outbreaks			
Death	1	2·5 (2–3·3)	[24]
Nursing homes	0·028	1	
Hospitals	0·028	1	

GP, General practitioner.

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

Age group (yr)	CFR median (/1000)*	CFR mean (/1000)*	(95% CI) (/1000)*	Mean beta distribution (/1000)†
0	0·09	0·09	(0·0136–0·2728)	0·10%
1–4	0·00	0·00	(0–0·01727)	0·00%
5–11	0·00	0·00	(0–0·04244)	0·01%
12–17	0·07	0·09	(0·0037–0·3397)	0·10%
18–64	0·03	0·03	(0·0121–0·0625)	0·03%
⩾65	0·63	0·63	(0·5453–0·7287)	0·63%

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).

Burden of foodborne disease

Community acquired

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 4. *Hospitalizations due to community-acquired norovirus based on GEops data (i = 1, 2, 3) [18] as fractions of the total number of hospitalizations due to gastroenteritis in general (Prismant) [17]*

		GEops			Prismant			
		Norovirus infections			Hospitalizations due to norovirus			
Age group (yr)	Samples	Single norovirus infections	Double infections	Triple infections	Hospitalizations due to gastroenteritis	Median	Mean	(95% CI)
<18	96	8	6	1	8334	947	966	(541–1498)
⩾18	41	2	2	0	13 598	905	971	(294–2134)

GEops, GastroEnteritis Admission Study; CI, confidence interval.

Table 5. *Outbreaks reported in The Netherlands, 2009 (National Institute of Public Health, The Netherlands, unpublished data), numbers of cases per outbreak [23] and case-fatality ratios (CFRs) in the elderly in outbreaks [10]*

Setting	Outbreaks	Number of cases per outbreak	Mean CFR per outbreak	(95% CI)	Mean life-expectancy	(95% CI)
Nursing homes	75	43	0·14	(0·11–0·17)	30 months	(24–40)
Hospitals	57	25	0·14	(0·11–0·17)		

CI, Confidence interval.

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 2640–5440) of which 3700/100 000 (97·6%) (95% CI 2550–5340) were estimated as seeking no medical care, while 92/100 000 (2·4%) (95% CI 50–150) were estimated to visit a GP for their complaints, and 12/100 000 (12·5%) (95% CI 5–20) were estimated as hospitalized due to their norovirus infection. The number of fatal community-acquired cases was estimated to be 0·4/100 000 (95% CI 0·2–0·7).

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/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).

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.

Table 6. *Incidence of gastroenteritis due to norovirus in The Netherlands, 2009*

	Community-acquired	Institutional outbreaks	Total
Outcome incidences			
General population (95% CI) (× 1000)	610 (418–878)	5*	
GP visit (95% CI) (× 1000)	15 (9–24)		
Hospitalized (95% CI) (× 1000)	1·9 (1·1–3·2)		
Total incidence (95% CI) (× 1000)	625 (433–893)	5*	630 (438–898)
Fatal cases (95% CI)	59 (25–112)	3	62 (28–115)
Undiscounted burden estimates, *n* (95% CI)			
YLD	306 (202–452)	130 (73–188)	436 (310–594)
YLL	1178 (541–2203)	8 (6–10)	1188 (548–2210)
DALYs	1486 (835–2524)	138 (80–195)	1622 (966–2650)
Discounted burden estimates, *n* (95% CI)			
YLD	305 (200–450)	129 (72–187)	434 (308–592)
YLL	844 (388–14 674)	7 (6–9)	851 (396–1481)
DALYs	1148 (673–1796)	137 (80–194)	1285 (805–1937)

GP, General practitioner; YLD, years lived with disability; YLL, years of life lost; DALYs, disability-adjusted life-years.
* Based on reported outbreaks, i.e. no uncertainty included.

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 $\geqslant$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 $\geqslant$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 more 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 $\geqslant$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 underreporting [28]. This resulted in a sharp increase of mortality to 119 fatal cases an increase of the burden to 2627 DALYs.

Outbreaks

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

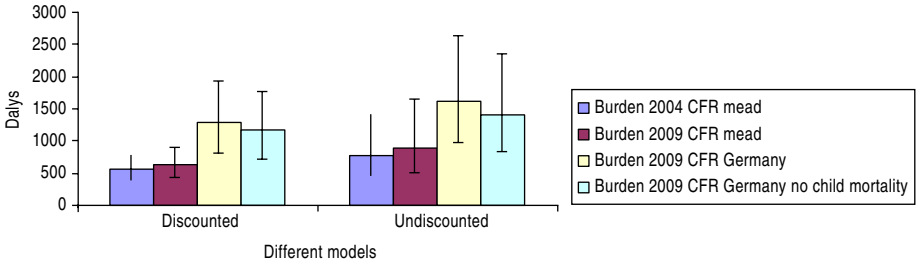

Fig. 2. [*colour online*]. Estimated burden in discounted and undiscounted disability-adjusted life-years (DALYs) while comparing the effects of different assumptions. *Burden 2004*: case-fatality ratio (CFR) Mead (no trend correction, CFRs as described by Mead *et al*. [9]). *Burden 2009*: CFR Mead (trend correction, CFRs as described by Mead *et al*. [9]). *Burden 2009*: CFR Germany (trend correction and CFRs as reported in the German surveillance system [19]). *Burden 2009*: CFR Germany [no child mortality; trend correction and CFRs as reported in the German surveillance system [19] but when setting child mortality in very young children (aged <12 years) to 0].

CFRs (Fig. 2) to the observed increase in the estimated burden. First, the burden of norovirus in 2004 was (re)calculated 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 $\geqslant 65$ 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 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

deceased children laboratory testing may be more frequently performed, and thereby norovirus may be proportionally more often recognized as the causative agent, compared to other age groups. However, this would underestimate CFRs in adults instead of overestimate CFRs in children. Several groups indicated a likely underreporting of mortality rates due to norovirus for specific age groups [10, 30]. We considered the use of a surveillance system of a country where norovirus is notifiable to be the most direct approach for obtaining the CFRs for all age groups. On the basis of previous lower estimates, norovirus infection already outnumbered by far, with respect to incidence, any other foodborne pathogen [7]. Here, we found that over 100 000 symptomatic infections and 11 deaths can be attributed to the foodborne transmission of norovirus.

Since scenario analysis showed comparable results when using mortality data from different surveillance systems, i.e. as described by van Asten *et al*. [10], we consider this as a confirmation of the robustness of our analysis. Moreover, the CFR for outbreaks in nursing homes based on German surveillance data is in the same order of magnitude as the 0·03 % found in Australia [31]. In line with other burden studies, we only partly accounted for comorbidity, which may be considered a limitation of our study and may have resulted in an overestimation of the burden. However, for several reasons, we consider our estimate conservative. First, we consider underreporting of mortality due to norovirus illness likely. Underreporting is a common problem in surveillance systems [32], as was also illustrated during an outbreak investigation where death certificates were analysed [11], and therefore the mortality ratios derived from surveillance systems may be considered conservative. Another reason is that we now assumed that every institutional outbreak was reported, which is not likely to be the case.

Sensitivity analysis also pointed out that the disability weight of disease in those living in a nursing home, the incidence of norovirus gastroenteritis in adults and the elderly, and mortality due to norovirus in young people were the main factors influencing the uncertainty in the burden estimates, and these may be data gaps to be filled by future research that can contribute to improving the burden estimates. The uncertainty in incidences is mainly due to low numbers of persons in these categories in the Sensor study [6]. Given that the Sensor study was performed over a decade 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

1. **Teunis PF, *et al.*** Norwalk virus: how infectious is it? *Journal of Medical Virology* 2008; **80**: 1468–1476.
2. **Cannon JL, *et al.*** Surrogates for the study of norovirus stability and inactivation in the environment: a comparison of murine norovirus and feline calicivirus. *Journal of Food Protection* 2006; **69**: 2761–2765.
3. **WHO, FAO.** Viruses in food: scientific advice to support risk management activities, 2008. Meeting Report. Microbiological Risk Assessment Series, no. 13.
4. **Wheeler JG, *et al.*** Study of infectious intestinal disease in England: rates in the community, presenting to general practice, and reported to national surveillance. The Infectious Intestinal Disease Study Executive. *British Medical Journal* 1999; **318**: 1046–1050.
5. **Tam CC, *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.
6. **de Wit MA, *et al.*** Sensor, a population-based cohort study on gastroenteritis in the Netherlands: incidence and etiology. *American Journal of Epidemiology* 2001; **154**: 666–674.
7. **Kemmeren JM, *et al.*** Priority setting of foodborne pathogens: disease burden and costs of selected enteric pathogens. RIVM, 2006. Report No.: 330080001/2006.
8. **Bruggink L, Sameer R, Marshall J.** Molecular and epidemiological characteristics of norovirus associated with community-based sporadic gastroenteritis incidents and norovirus outbreaks in Victoria, Australia, 2002–2007. *Intervirology* 2010; **53**: 167–172.
9. **Mead PS, *et al.*** Food-related illness and death in the United States. *Emerging Infectious Diseases* 1999; **5**: 607–625.
10. **van Asten L, *et al.*** Unspecified gastroenteritis illness and deaths in the elderly associated with norovirus epidemics. *Epidemiology* 2011; **22**: 336–343.
11. **Rondy M, *et al.*** Norovirus disease associated with excess mortality and use of statins: a retrospective cohort study of an outbreak following a pilgrimage to Lourdes. *Epidemiology and Infection* 2011; **139**: 453–463.
12. **Verhoef L, *et al.*** Emergence of new norovirus variants on spring cruise ships and prediction of winter epidemics. *Emerging Infectious Diseases* 2008; **14**: 238–243.
13. **Siebenga JJ, *et al.*** Phylodynamic reconstruction reveals norovirus GII.4 epidemic expansions and their molecular determinants. *PLoS Pathogens* 2010; **6**: e1000884.
14. **Havelaar AH, *et al.*** Disease burden in The Netherlands due to infections with Shiga toxin-producing *Escherichia coli* O157. *Epidemiology and Infection* 2004; **132**: 467–484.
15. **Havelaar AH, *et al.*** Disease burden of foodborne pathogens in the Netherlands, 2009. *International Journal of Food Microbiology* 2012. Published online: 5 April 2012. doi:http://dx.doi.org/10.1016/j.ijfoodmicro.2012.03.029.
16. **de Wit MA, *et al.*** Gastroenteritis in sentinel general practices. The Netherlands. *Emerging Infectious Diseases* 2001; **7**: 82–91.
17. **Pelt van W, *et al.*** Trends in gastroenteritis in the Netherlands, 2008 and 2009 [in Dutch]. Bilthoven: RIVM, 2010.
18. **Friesema IH, *et al.*** Etiology of acute gastroenteritis in children requiring hospitalization in the Netherlands. *European Journal of Clinical Microbiology and Infectious Diseases* 2012; **31**: 405–415.
19. **Koch J, *et al.*** Norovirus infections in Germany [in German]. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 2006; **49**: 296–309.
20. **Murray CJ.** Quantifying the burden of disease: the technical basis for disability-adjusted life years. *Bulletin of the World Health Organization* 1994; **72**: 429–445.
21. **Haagsma JA, *et al.*** Disability adjusted life years and minimal disease: application of a preference-based relevance criterion to rank enteric pathogens. *Population Health Metrics* 2008; **6**: 7.
22. **Svraka S, *et al.*** Etiological role of viruses in outbreaks of acute gastroenteritis in The Netherlands from 1994 through 2005. *Journal of Clinical Microbiology* 2007; **45**: 1389–1394.
23. **van Duynhoven YT, *et al.*** A one-year intensified study of outbreaks of gastroenteritis in The Netherlands. *Epidemiology and Infection* 2005; **133**: 9–21.
24. **Cunningham CJ, *et al.*** Survival of patients discharged to long term care. *Irish Medical Journal* 2008; **101**: 305–307.
25. **Hakkaart-van Roijen L, Tan SS, Bouwmans CAM.** Guideline for cost research – methods and standardized costs for economic evaluations in health care. Diemen, The Netherlands: Board of Health Insurance, 2010 [in Dutch].
26. **Havelaar AH, *et al.*** Attribution of foodborne pathogens using structured expert elicitation. *Foodborne Pathogens and Disease* 2008; **5**: 649–659.

27. **Verhoef L, *et al.*** Selection tool for foodborne norovirus outbreaks. *Emerging Infectious Diseases* 2009; **15**: 31–38.
28. **Scallan E, *et al.*** Foodborne illness acquired in the United States – major pathogens. *Emerging Infectious Diseases* 2011; **17**: 7–15.
29. **Haagsma JA, *et al.*** Disease burden of post-infectious irritable bowel syndrome in The Netherlands. *Epidemiology and Infection* 2010; **138**: 1650–1656.
30. **Harris JP, *et al.*** Deaths from norovirus among the elderly, England and Wales. *Emerging Infectious Diseases* 2008; **14**: 1546–1552.
31. **Kirk MD, *et al.*** Surveillance for outbreaks of gastroenteritis in long-term care facilities, Australia, 2002–2008. *Clinical Infectious Diseases* 2010; **51**: 907–914.
32. **Doyle TJ, Glynn MK, Groseclose SL.** Completeness of notifiable infectious disease reporting in the United States: an analytical literature review. *American Journal of Epidemiology* 2002; **155**: 866–874.
33. **Friesema IH, *et al.*** Norovirus outbreaks in nursing homes: the evaluation of infection control measures. *Epidemiology and Infection* 2009; **137**: 1722–1733.
34. **Enserink R, *et al.*** Absence of influenza A(H1N1) during seasonal and pandemic seasons in a sentinel nursing home surveillance network in the Netherlands. *Journal of the American Geriatrics Society* 2011; **59**: 2301–2305.
35. **Lopman BA, *et al.*** Clinical manifestation of norovirus gastroenteritis in health care settings. *Clinical Infectious Diseases* 2004; **39**: 318–324.
36. **Chen SY, *et al.*** Norovirus infection as a cause of diarrhea-associated benign infantile seizures. *Clinical Infectious Diseases* 2009; **48**: 849–855.
37. **Ito S, *et al.*** Norovirus-associated encephalopathy. *Pediatric Infectious Disease Journal* 2006; **25**: 651–652.
38. **Marshall JK, *et al.*** Postinfectious irritable bowel syndrome after a food-borne outbreak of acute gastroenteritis attributed to a viral pathogen. *Clinical Gastroenterology and Hepatology* 2007; **5**: 457–460.
39. **O'Brien S.** The challenge of estimating the burden of an underreported disease. In: Koopmans M, Cliver DO, Bosch A, eds. *Food-borne Viruses*. Washington: ASM Press, 2008, pp. 87–116.
40. **de Wit MA, Koopmans MP, van Duynhoven YT.** Risk factors for norovirus, Sapporo-like virus, and group A rotavirus gastroenteritis. *Emerging Infectious Diseases* 2003; **9**: 1563–1570.