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Health burden in the Netherlands due to infection with thermophilic *Campylobacter* spp.

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SUMMARY

Infection with thermophilic *Campylobacter* spp. usually leads to an episode of acute gastroenteritis. Occasionally, more severe diseases may be induced, notably Guillain–Barré syndrome and reactive arthritis. For some, the disease may be fatal. We have integrated available data in one public health measure, the Disability Adjusted Life Year (DALY). DALYs are the sum of Years of Life Lost by premature mortality and Years Lived with Disability, weighted with a factor between 0 and 1 for the severity of illness. The mean health burden of campylobacter-associated illness in the Dutch population in the period 1990–5 is estimated as 1400 (90% CI 900–2000) DALY per year. The main determinants of health burden are acute gastroenteritis (440 DALY), gastroenteritis related mortality (310 DALY) and residual symptoms of Guillain–Barré syndrome (340 DALY). Sensitivity analysis demonstrated that alternative model assumptions produced results in the above-mentioned range.

INTRODUCTION

Infectious intestinal diseases are a major cause of mortality in the developing world, and cause significant morbidity in developed countries. Food and water are important routes of infection, and there is a large amount of national and international legislation to reduce the burden of food- and waterborne disease. Traditionally, emphasis has been on testing of end products for indicator organisms of faecal pollution or for process hygiene. Recent developments have introduced the concepts of process control (e.g. the Hazard Analysis Critical Control Point system in food processing) and the use of quantitative risk assessment to formulate safety objectives for the quality of food [1, 2] and water [3].

In this context, risks are preferably expressed as a function of the probability and severity of an undesirable health effect [4]. The spectrum of disease by intestinal pathogens may vary from a short, self-limiting episode of nausea and vomiting to life-long sequelae or even death. The relative importance of these different outcomes is not usually taken into account [5–9]. To integrate the different health effects of gastrointestinal infection, a common measure is needed. Economic analyses, which identify all costs to society, including a monetary equivalent of life years

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lost, are frequently used for this purpose [10]. However, they do not take into account the effects of disease on the quality of life, which is an important objective of public health policy.

In this article, we present a methodology to integrate the health burden of different outcomes of gastrointestinal disease, illustrated by a case study of the health burden due to infection with thermophilic *Campylobacter* species in the Netherlands. To achieve this, we summarized the available epidemiological and clinical literature, and infer quantitative estimates of the incidence of important disease end-points, their duration and severity. The data were primarily selected to reflect the situation in the Netherlands in the period 1985–95, with an emphasis on the second half of this decade. Where necessary and appropriate, we have also used international data. Infection with campylobacter may result in diseases that range from mild, self-limiting gastroenteritis with limited duration to life-long sequelae of serious, debilitating disease and premature mortality. Many of these outcomes are extremely rare [10–12]. For the purpose of characterizing the health burden, we only consider complications that occur relatively frequently: Guillain–Barré syndrome and reactive arthritis. We integrated the available data in the public health indicator 'Disability Adjusted Life Years' (DALYs), which combines the effects of morbidity and mortality. Similar concepts, such as Quality Adjusted Life years, have been used extensively in medical technology assessment (MTA) and in health economics to optimise decision-making, both from the perspective of individual patients and society. The concept is increasingly being used in public health research, as demonstrated by the hallmark publication of the Global Burden of Disease study [13, 14]. It has also been adopted as a basis for Dutch public health policy, as described in the Public Health Forecast study [15–17]. Both studies provide extensive background information on the scientific and social implications of using deliberately simplifying measures to capture intricately complex phenomena such as health in a single measure. The DALY methodology requires the availability of high quality data for all relevant inputs, which are currently available to only a limited extent. Therefore, not only point estimates are given but also appropriate distribution functions are generated to describe uncertainty and variability in these estimates. The uncertainty in the final estimate is formally evaluated using simulation methods and by sensitivity analysis.

ACUTE, DIARRHOEAL DISEASE

Incidence

The incidence of acute campylobacter enteritis was estimated from different data sources: outbreak reports, laboratory reports, surveillance in general practices and population-based surveys. In the Netherlands, outbreaks of campylobacteriosis are rarely recognized: in the years 1987–94, 8 outbreaks involving 40 cases were identified by Food Inspection Services, i.e. an average annual incidence of 5 cases per year.

Laboratory surveillance data for the Netherlands are available since April 1995. In the 15 participating Regional Public Health Laboratories the annual average rate of campylobacter isolations from submitted faecal specimens was 3–4%. On average, campylobacter was isolated from 3600 patients per year. It is estimated (W. van Pelt, personal communication) that for *Campylobacter* spp. these laboratories cover about 62% of the Dutch population of 15 million, leading to an estimated annual incidence of laboratory-confirmed campylobacter enteritis of approx. 5800 cases per year (4 per 10000 persons per year). Whereas the total number of submitted faecal specimens was relatively constant throughout the year, there was remarkable seasonal variation in the incidence of laboratory confirmed campylobacteriosis. The isolation rates peaked in summer, when 6–7% of all samples were positive for campylobacter.

A sentinel study on the incidence of gastroenteritis in general practices was carried out in the years 1992–3. The study used the established NIVEL (Netherlands Institute for Primary Health Care, Utrecht, the Netherlands) sentinel surveillance system, which is a representative selection of practices throughout the country [18, 19]. The incidence of acute gastroenteritis was 55·3 per 10000 person-years; after correction for non-response it was 89·9 per 10000 person-years [20]. In 1993, the incidence was significantly lower than in 1992: 59·6 *vs.* 46·6 per 10000 person-years. The incidence was not different between men and women, and was highest in the summer months. The incidence peaked in the younger age classes (420 and 182 respectively per 10000 person-years in the 0 and 1–4 year old). Campylobacter were cultured from 14·6% of all faecal samples (4·4% yielded salmonella). The isolation percentage was lowest ($\leqslant 5\%$) in the very young (0 years) and in the old (65+), and peaked in the 15–19 age-class (33%).

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The estimated age- and sex standardized incidence of campylobacter enteritis was 6·9 per 10000 person-years. If a correction for non-response was applied, this estimate was 11·7 per 10000 person years. It is likely, however that the non-response was biased towards less severe cases and the corrected incidence was an overestimation because infection with thermophilic *Campylobacter* spp. usually leads to a relatively severe form of enteritis. In 1991, a population-based surveillance study on the incidence of acute gastroenteritis was performed, leading to an age-standardized estimate of 447 episodes per 1000 person-years [21, 22]. Campylobacter was isolated from 4·5% of faecal samples (1·6% yielded salmonella). The number of positive samples was too small to draw conclusions on the effect of sex, age or region. Thus, the standardized incidence of campylobacter enteritis in the Dutch population is estimated as 20·1 per 1000 person-years.

In summary, in the Netherlands with a population of 15 million, approximately 300000 persons per year experience symptoms of acute campylobacter-related gastroenteritis and 18000 patients visit their general practitioner (excluding consultations by telephone). A faecal sample is sent to a laboratory and tested positive for campylobacter for 5800 patients. Only a small fraction of all cases is involved in recognized foodborne outbreaks.

Duration and severity

We obtained data on symptoms and severity of campylobacter enteritis from outbreak reports and studies based on cases identified by laboratory surveillance. An analysis of the available data showed that the frequency of reported symptoms from both sources is similar. The majority of patients reported diarrhoea (90–100%), abdominal pain (70–90%) and fever (60–80%), whereas 25–30% reported blood in their stool. Patients in outbreaks more frequently reported vomiting than clinical cases (40 *vs.* 25%) which may be related to the time that elapsed between onset of the symptoms and consultation of a doctor. Therefore, it might be concluded that the above data represent the clinical course of all patients with campylobacter enteritis. It is possible however, that outbreak associated strains of bacteria are more virulent than average, and that the majority of cases in the general population have a more benign course.

The median duration of outbreak cases was estimated as 4–6 days, but follows a highly skewed distribution with a maximum up to a month or more. There are no adequate data to fit a statistical distribution. We therefore used a lognormal distribution for the duration of campylobacteriosis in the general population with parameters on the $\log_{10}$ scale: mean $\mu = 1{\cdot}5$, S.D. $\sigma = 0{\cdot}5$ (median 4·5 days, 90% range 2–10 days).

The duration of gastroenteritis of patients who consulted their general practitioner was generally longer than of patients who did not. Again, there are few data and an approximation must be used. We fitted a lognormal distribution (parameters $\mu = 2{\cdot}0$ and $\sigma = 0{\cdot}5$, median 7·5 days, 90% range 3–17 days) to data reported by Rijntjes [23] on the clinical aspects of acute diarrhoea (including campylobacteriosis) in general practice.

Mortality

There is little information on campylobacter associated mortality. Tauxe [24] estimated the case-fatality ratio of campylobacteriosis as 3/10000 outbreak related cases (2 deaths among 6000 cases) and applied this rate to an estimate of all cases of campylobacter enteritis in the USA (incidence 96–108 per 10000 person-years, or 2·2–2·4 million cases per year) to arrive at an estimate of 680–730 campylobacter associated deaths per year in the USA. A similar estimate for the Netherlands would be 90 deaths per year. Smith and Blaser (cited in 24) reported 2 deaths among 600 cases detected by laboratory surveillance in Colorado, USA, leading to an estimated 200 deaths per year for the USA and 23 deaths per year in the Netherlands. The CAST Report on Foodborne pathogens [25] estimates the annual number of campylobacter associated deaths in the USA as based on the work of Bennet and colleagues [26] and Todd [27] as 2100 and 1, respectively. The reported number of diarrhoeal deaths from all causes in the USA is approximately 3200 per year [28]. Hence, if the high estimates of Tauxe [24] and Bennet and colleagues [26] were realistic, it would be concluded that campylobacter accounts for a major part of diarrhoeal deaths in the USA, or that there is considerable underreporting. Alternatively, these data overestimate the actual situation. Thus, there is major uncertainty in the estimated number of deaths related to campylobacter enteritis. We used a conservative estimate of 30 fatal cases per year, with a range between a minimum of 3 and a maximum of 90. Hence, we estimated that the most likely value of the case-fatality ratio was 1/10000 with a range between

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minimum 1/100000 and maximum 2/10000. Having no distributional information, we have formalized the uncertainty in a Beta-Pert distribution [29]. We used data from Statistics Netherlands on the age-distribution of mortality from all infectious intestinal disease (ICD codes 1–9) and assumed these to be representative for mortality associated with campylobacteriosis (median age at death 78 years, interquartile range 35–85 years).

GUILLAIN–BARRÉ SYNDROME

The Guillain–Barré syndrome (GBS) is an acute immune-mediated disease of the peripheral nervous system. Because the pathogenesis is still largely unknown, it is defined by a set of clinical, laboratory and electrodiagnostic criteria [30]. The disease is characterized by areflexia, acute progressive and symmetrical motor weakness of more than one limb, ranging from minimal weakness of the legs to total paralysis of all extremities, and rapid progression (50% of patients reach their nadir in less than 2 weeks and 90% within 4 weeks). Respiratory muscles may also be affected and up to one-third of patients may need artificial ventilation. There is marked patient-to-patient variation in the clinical features of GBS, and it is suggested that the disease is not a single entity, but may result from different pathogenic mechanisms. The functional status of patients with GBS is scored on a seven-point disability scale (*F*-score, see Table 1). Two-thirds of patients with GBS suffer from a preceding gastrointestinal, flu-like or respiratory infectious illness. The muscle weakness usually occurs 1–3 weeks after recovery, suggesting that the immune response rather than the infectious agent is related to the onset of the syndrome. Several studies have shown that particular infective agents are strongly associated with the onset of GBS. Jacobs and colleagues [32] demonstrated a significant relation with antecedent infection by *C. jejuni*, cytomegalovirus and Epstein–Barr virus. Worldwide, the crude incidence of GBS varies between 0·8 and 2·0 per 100000 persons per year [33]. There appears to be no trend over the years, or in relation to factors such as race, standard of living, season or climate. Most studies report an increase of incidence with age, and sometimes also a peak incidence in young adults. Van Koningsveld and colleagues [33] reported a retrospective study on the incidence of GBS in the southwest Netherlands in the years 1986–97 and present an estimate of 1·18 (S.D. 0·05) per 100000 person years. The mean age of patients was 47 years (S.D. 21 years). Thus, in the Netherlands with a population of approximately 15 million, the incidence of GBS is estimated as 177 cases per year. Patients with a severe course of the disease ($F > 2$ at nadir) are frequently included in clinical trials, and detailed information is available on this subgroup. On the contrary, very limited information is available on patients for which the disease takes a mild course ($F \leqslant 2$). In the retrospective study, data were available for 436 patients of which 121 (28%) were mildly affected ($F \leqslant 2$) and 315 (72%) were severely affected ($F > 2$).

Serological evidence for antecedent infection with *C. jejuni* was obtained for 38/114 (33%) of severe cases and 3/14 (21%) of mild cases. No serological data for non-GBS controls are available in this study. However, the patients in the Dutch Guillain–Barré trial [34], in which treatment with plasma exchange (PE) was compared with intravenous immunoglobulins (IVIg), were recruited from the same cohort so that we can use data from the healthy control group reported by Jacobs and colleagues [32]. Based on this information, the attributable proportion of cases induced by *C. jejuni* is estimated to be 15% for mild cases of GBS and 28% for severe cases. When interpreting these data, one must realise that criteria for a positive serological test result are usually chosen to prevent false-positive results, with a concurrent loss in sensitivity. In Table 2, the results from the retrospective study are corrected for published performance characteristics of the serological tests applied in this study [35]. Combining these data, we estimated the incidence of *C. jejuni* associated GBS in the Netherlands as 59 cases per year (10 mild cases of which $7 < 50$ years of age, and 49 severe cases of which $24 < 50$ years of age). Combining with estimates given previously, we estimated the probability of GBS given campylobacter-associated enteritis as $59/300000 = 2{\cdot}0 \times 10^{-4}$ (1 per 5000). Note that a small proportion of campylobacter-associated enteritis is caused by other species, mainly *C. coli*. Because GBS is exclusively associated with *C. jejuni*, the risks are slightly underestimated. Allos [37] estimates that in the USA, one of every 1058 campylobacter infections results in a case of GBS. There is about a fivefold difference between this estimate and that for the Netherlands. This is due partly to a higher estimate of the incidence of GBS in the USA (3 per 100000 *vs.* 1 per 100000 person years) and partly to a lower estimate of the incidence of campylobacteriosis (10 per 1000 *vs.* 20 per 1000 person years). The surveillance data from the USA as well as from the Netherlands are subject to different

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Table 1. *Scoring system for functional status of patients with Guillain–Barré syndrome* [31]

F-score	Functional status
0	Healthy
1	Having minor symptoms and signs, but fully capable of manual work
2	Able to walk $\geqslant$ 10 m without assistance
3	Able to walk $\geqslant$ 10 m with a walker or support
4	Bedridden or chair-bound (unable to walk $\geqslant$ 10 m with a walker or support)
5	Requiring assisted ventilation for at least part of the day
6	Dead

sources of bias, making it difficult to evaluate further this difference. We have used the USA estimate as a high limit of the probability of developing GBS after campylobacteriosis. McCarthy and colleagues [38] estimated the probability of GBS following campylobacteriosis in a follow-up study of three outbreaks in Sweden, involving 8000 patients. No cases of GBS were detected, so that the probability was 0 in 8000 (95% CI 0–3). Hence, the Dutch estimate would fall in this range, whereas the USA estimate would fall outside. It is possible that the campylobacter strains involved in the Swedish outbreaks were not causal agents of GBS, which might result in underestimation of the probability in the general population.

Duration and severity

Visser [39] has shown that the probability of recovering to the stage of independent locomotion after 6 months ($F \leqslant 2$) is smaller for patients over 50 years of age. Other clinical studies also commonly report age as an important determinant of recovery, hence in the following the clinical course is described separately for patients younger or older than 50 years and it is also necessary to distinguish the prognosis of mild and severe cases. Very limited information is available on the recovery of mildly affected patients. Clinical experience at the outpatient department of University Hospital Rotterdam suggests that after 6 months, 50% of the patients are fully recovered ($F = 0$), whereas virtually all patients have reached $F = 1$. From this information, a model for the clinical course of mildly affected patients was constructed, assuming a simple exponential decrease of the number of patients with *F*-scores 2 and 1. According to the model, 79% of patients were fully recovered after 1 year whereas 21% still suffered from minor symptoms ($F = 1$). The initial ratio of patients with *F*-scores 1 and 2 was independent of age. In the absence of further information, we assumed that the time course of recovery of mild cases is also independent of age. Information on the clinical course of severe cases was obtained from original data of the Dutch IVIg trial [34]. Visser [39] describes the clinical heterogeneity of these patients in relation to antecedent infections and treatment choice. *C. jejuni* associated GBS was more severe in nature than other GBS, as was obvious from the difference in functional score at nadir: a very high proportion of *C. jejuni* positive patients required assisted ventilation ($F = 5{:}54\%$ *vs.* 20% for all patients). *C. jejuni* positive patients recovered significantly better when subjected to IVIg as compared with PE. For other patients, including those infected with cytomegalovirus, this difference was only apparent after 8 weeks of treatment, but not after 6 months. Using IVIg treatment, 75% of *C. jejuni* positive patients were able to walk independently after 6 months. This figure is in-between the values of 73 and 82%, which were found for all patients, treated with PE and IVIg, respectively. Hence we assumed that the data on all patients in the Dutch trial are representative for *C. jejuni* positive patients, provided they receive optimal treatment.

Directly after hospitalization, 60% of the randomized patients are in *F*-score 4. At nadir, approximately 20% of the patients are in *F*-score 5. Throughout the hospitalization period, patients tend to recover and this is reflected by a gradual increase of the percentage of patients in *F*-scores 0–2. Virtually all patients recovered from the need of intensive care treatment, but after half year, the end of follow-up in the clinical trial, a sizeable proportion were still severely affected (17% in *F*-scores 3 and 4). Bernsen and colleagues [40] evaluated the residual health status of patients after a period of 31 months to 6 years after onset of GBS and demonstrated that within this time period, there were no significant differences in residual functional health status related to the time since the acute phase. We therefore assumed that the health status at follow-up in this study will persist life-long. This study showed that only 25% of all patients recovered functionally ($F = 0$) but continued to report psychosocial impairment, whereas 44% of patients continued to suffer from minor symptoms ($F = 1$). As much as 31% of the severely affected patients did not recover fully but continued to suffer from functional limitations.

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Table 2. *Estimation of the true attributable proportion of* C. jejuni *associated cases of Guillain–Barré syndrome*

	Mild cases		Severe cases	
	Cases	Controls	Cases	Controls
ELISA (positive/total)	3/14	4/50	38/114	4/50
Apparent odds ratio (95% CI)	3·1/0·6–16		5·8 (1·9–17)	
Apparent attributable proportion	0·15		0·28	
Apparent prevalence	0·214	0·080	0·333	0·080
Sensitivity	74%*		74%*	
Specificity	97%		97%	
True prevalence†	0·260	0·070	0·427	0·070
C. jejuni infection (+ve/total)	4/14	4/50	49/114	4/50
True odds ratio (95% CI)	4·6 (1·0–22)		8·7 (2·9–26)	
True attributable proportion	0·22		0·38	

* 34 positive results of 46 patients with culture confirmed *C. jejuni* gastroenteritis.
† Calculated as $P_{true} = (P_{app} + SP - 1)/(SE + SP - 1)$, with P_{app} = apparent prevalence, SP = specificity, SE = sensitivity [36].

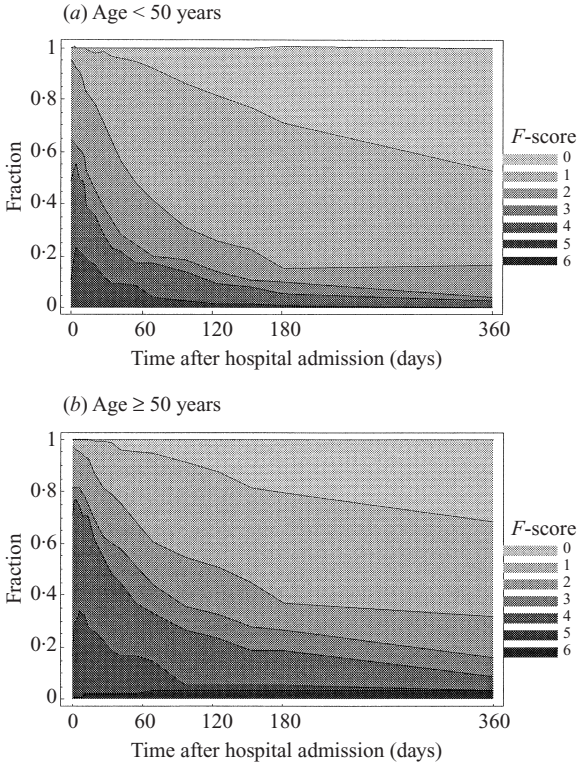

Fig. 1. Functional status of patients with Guillain–Barré syndrome (above age < 50 years, below age ⩾ 50 years).

($F = 2$–4). Figure 1 shows the time-course of the functional status of GBS-patients, combining the information on mild and severe cases.

Mortality

Mortality related to GBS is usually low. In the Dutch IVIg trial, a case-fatality ratio of only 2% was observed [34], but other studies report ratios up to 5%. Van Koningsveld and colleagues [33] reported 16 fatal cases among 476 cases of GBS in the southwest Netherlands (mortality ratio 3·4%). We used a Beta-Pert distribution with most likely value 2%, minimum 1% and maximum 5% to simulate the uncertainty in the case-fatality ratio. The mean age of the fatal cases in the retrospective study was 17 years (range 30–86).

REACTIVE ARTHRITIS

Reactive arthritis is an immune-mediated inflammation of the joints that is associated with recent infection at a distant site, usually the urogenital or gastrointestinal tract. There may or may not be extra-articular features. Rheumatic symptoms develop between 3 and 30 days after infection, and are accompanied by an increase in specific antibodies. The pathogenic mechanism is not clear; there is evidence of genetic predisposition because in the Netherlands, approximately 70% of patients with reactive arthritis are HLA-B27 positive compared with only 7% in the general population [41]. Berden and colleagues [42] and Van de Putte and colleagues [43] in the Netherlands first reported infection with *C. jejuni* as the triggering agent of reactive arthritis.

Incidence

The incidence of reactive arthritis is difficult to estimate. The diagnosis depends on clinical or laboratory evidence of recent infection but subclinical

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precipitating infections are well known. Also, different studies have used different case-definitions, resulting in inclusion of cases with different degrees of severity and duration. Kvien and colleagues [44] reported a general practitioner based survey of the incidence of reactive arthritis in Oslo, Norway in the period March 1988 to March 1990. They found the incidence of reactive arthritis associated with gastroenteritis was 2·9 per 100000 person years for the total population and 5·0 per 100000 person years for the population between 18 and 60 years of age. Of these, 11% (3/27 patients) were associated with *C. jejuni*, or 3·2 per 1000000 person years for the total population. Similar data are not available for the Netherlands. Extrapolation of the Oslo data may give a rough indication of the expected number of patients, but ignores differences in incidence of infection with *C. jejuni* and prevalence of the HLA-B27 gene (83% of all patients in Oslo carried this gene). These data would lead to an estimate of 50 GP consultations in the Netherlands per year because of *C. jejuni* associated reactive arthritis. Eastmond and colleagues [45] carried out a follow-up study of 136 culture-positive individuals, who were infected with *C. jejuni* as a consequence of a power failure at a milk pasteurization plant. Of this cohort, 88 had symptoms of gastroenteritis and one patient developed reactive arthritis (1·1% of clinical, culture-positive cases or 0·74% of all culture-positive individuals). The duration of the symptoms was 2 weeks. Bremell and colleagues [46] also conducted a follow-up study of 86 attendants at a banquet, 35 of whom developed gastroenteritis and 31 of whom were asymptomatically infected. These authors found symptoms in joints, muscles or spine in seven subjects with enteritis (20%), but in none of the asymptomatically infected persons. In six patients, the symptoms were restricted to pain in the muscles, joints or lower back that lasted less than a month. One HLA-B27 patient who was diagnosed as having incomplete reactive arthritis had a familial history of arthritis and again developed classical reactive arthritis in association with a new episode of gastroenteritis after 7 years.

In the outbreak studies, the risk of developing reactive arthritis after *C. jejuni* associated enteritis was 1–3%. On this basis, the estimated number of cases of *C. jejuni* related reactive arthritis in the Netherlands would range between 3000 and 9000 per year. This is considerably higher than the number of 50 estimated above, which may possibly be explained by the fact that GPs or hospitals see only the more severe cases which are of longer duration. To estimate the health burden of *C. jejuni* associated reactive arthritis on a population basis, we used the risk as derived from outbreak studies.

Duration

In a follow-up study of the Oslo cohort of patients reporting to their GP, the outcome of disease was independent of the triggering agent or the presence of the HLA-B27 gene [47]. The medium duration of reactive arthritis, estimated by Kaplan–Meier analysis, was 25 weeks (25 and 75 percentiles were 14 and 53 weeks, respectively). After 2 years, none of the patients had persistent arthritic symptoms with the exception of one patient who had a history of backpain and stiffness. We have assumed that the duration of unselected cases of *C. jejuni* associated reactive arthritis is considerably shorter than that in cases seen by GPs or in hospitals and therefore have adopted a wide range of 2–10 weeks.

DISABILITY ADJUSTED LIFE YEARS

The different outcomes of infectious disease can be combined in one single measure, the Disability Adjusted Life Year (DALY), following the methodology proposed by Murray [48].

$$DALY = YLL + YLD.$$

YLL is the number of years of life lost due to mortality and *YLD* is the number of years lived with a disability, weighted with a factor between 0 and 1 for the severity of the disability. *YLL* is calculated by accumulation over all diseases and age-strata of the product of d, the number of deaths due to a particular disease and $e^*(a)$, the standard life expectancy at the age of death due to that disease. Thus:

$$YLL = \sum_i e^*(a_i) \sum_j d_{ij},$$

Where i is an index for different age-classes, and j is an index for different disease categories. We have assumed that mortality affects the population in a random fashion, and derive the life expectancy from the standard life table as proposed by Murray [48]. This table is based on the highest observed national life expectancy (for Japanese women), but takes into account differences in life expectancy between men and women.

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Table 3. *Severity weights of severe gastroenteritis and of GBS in different functional grades*

Disease	Case-definition	Euroqol 5D score	Severity weight		
			Median	Range	Beta-distribution
Severe gastroenteritis	Patients suffer from watery diarrhoea, with a defecation frequency of a few to more than ten times per day, sometimes preceded by a period of anorexia, nausea, vomiting and abdominal pain. Some patients may suffer from severe abdominal cramps, fever, chills, headache and myalgia, nausea and malaise. Blood or mucus is often present in the faeces. In some cases, diarrhoea leads to dehydration. Symptoms usually last one to a few weeks	113211, 213211, 113111, 213311 (25% each)	0·368	0·05–0·97	1·23, 1·90
GBS, $F = 1$	Completely recovered from an episode of Guillain–Barré syndrome, but having problems of insomnia, fatigue and related emotional and social restraints	11211	0·10	0·00–0·61	0·66, 4·13
GBS, $F = 2$	Muscle weakness in legs and arms, able to walk at least 10 m without a walking aid, but unable to run	21211	0·30	0·04–0·65	2·16, 5·62
GBS, $F = 3$	Muscle weakness in legs and arms, and only able to walk at least 10 m with a walking aid	22321	0·44	0·20–0·80	5·50, 6·70
GBS, $F = 4$	Severe muscle weakness in legs and arms, not able to walk, bedridden of in a wheelchair	33322	0·80	0·25–0·95	5·55, 1·53
GBS, $F = 5$	Severe muscle weakness in legs and arms, not able to walk, bedridden and need artificial ventilation for at least part of the day	33332	0·94	0·75–0·99	18·35, 1·63

YLD is calculated by accumulation over all diseases of the product of the number of cases N, the duration L and the severity weight W:

$$YLD = \sum_j N_j L_j W_j.$$

SEVERITY WEIGHTS

The severity weight is not directly observable but reflects social values. There are different approaches to establish severity weights, which differ with respect to the group whose values are chosen (e.g. general public, patients, medical professionals), the method for evoking value choices (e.g. Standard Gamble (SG), Time Trade-Off (TTO), Person Trade-Off (PTO), Visual Analog Scale (VAS)), and the presentation of the diseases to be valued (e.g. case-definitions or generic descriptions). In this paper, we have followed the methodology developed for the Global Burden of Disease (GBD) study [13, 14] as modified for the purpose of the Dutch Public Health Status and Forecast (VTV) study [15–17]. For the purpose of the VTV study, a two-step procedure was adopted [49]. First, using the PTO protocol, a panel of medical experts evaluated 16 indicator conditions with different severity, selected to cover evenly the total range of disabilities. The diseases to be evaluated were characterized by a short clinical description and a standardized classification using the dimensions from the EuroQol-5D+C questionnaire [50] was applied to harmonize the mental image. Second, the same panels valued other diseases by interpolation on the scale of indicator diseases, i.e. ranking as similar to or in-between indicator conditions. For our study, we have obtained severity weights for various diseases in the framework of a broader study to elicit severity weights for several health states related to environ-

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Table 4. *Distribution functions* of parameters used to estimate the health burden of infection with thermophilic* Campylobacter *spp. in the Netherlands*

Model parameters	Input distribution	Mean	5-percentile	Median	95-percentile
Gastroenteritis					
General Population					
Incidence rate all gastroenteritis (per 1000 person years)	Lognormal (6·1, 0·058)	447	405	446	490
Attr. proportion *Campylobacter* spp.	Beta(12, 235)	0·049	0·028	0·047	0·073
Severity	**Beta(1·5, 21)**	**0·067**	**0·008**	**0·054**	**0·168**
Duration (days)	**Lognormal (1·5, 0·5)**	**5·08**	**1·97**	**4·48**	**10·2**
Case-fatality ratio (per 100 000 cases)	Beta-Pert (1, 10, 20)	10·2	4·33	10·1	16·1
Life expectancy of fatal cases (years)	**Custom**	**13·2**	**2·60**	**8·18**	**47·0**
General Practitioner					
Incidence rate campylobacteriosis (per 10 000 pyr)	Normal (11·7, 0·87)	11·7	10·3	11·7	13·1
Severity	**Beta(1·23, 1·90)**	**0·393**	**0·049**	**0·368**	**0·821**
Duration (days)	**Lognormal (2·0, 0·5)**	**8·37**	**3·24**	**7·39**	**16·8**
Guillain–Barré Syndrome					
Clinical					
Incidence rate (per 100 000 pyr)	Normal (1·18, 0·05)	1·18	1·10	1·18	1·26
Attr. proportion *C. jejuni* mild cases	Bootstrapping†	0·15	0·03	0·15	0·37
Attr. proportion *C. jejuni* severe cases	Bootstrapping†	0·28	0·17	0·27	0·37
Sensitivity serology	Bootstrapping†	0·74	0·63	0·74	0·85
Specificity serology	Fixed	0·97	–	–	–
Proportion of mild cases $<$ 50 year	Bootstrapping	0·69	0·63	0·74	0·85
Proportion of severe cases $<$ 50 year	Bootstrapping	0·48	0·43	0·48	0·54
Severity weights (composite)					
mild	**Beta(1·49, 15·29) + 0·001‡**	**0·080**	**0·012**	**0·073**	**0·223**
severe, $<$ 50 years	**Beta(3·47, 22, 18) + 0·130‡**	**0·244**	**0·175**	**0·256**	**0·389**
severe, $\geqslant$50 years	**Beta(5·83, 32·74) + 0·19‡**	**0·316**	**0·259**	**0·335**	**0·444**
Duration (years)	Fixed	1	–	–	–
Case-fatality ratio	Beta-Pert (0·01, 0·02, 0·05)	0·023	0·013	0·023	0·036
Life expectancy of fatal cases (years)	**Custom**	**18·7**	**5·73**	**11·2**	**81·3**
Residual Symptoms					
Severity weights					
mild	**Beta(0·87, 29·67)‡**	**0·027**	**0·001**	**0·019**	**0·088**
severe, $<$ 50 years	**Beta(2·50, 18·36) + 0·041‡**	**0·161**	**0·074**	**0·147**	**0·294**
severe, $\geqslant$50 years	**Beta(3·54, 22·34) + 0·074‡**	**0·211**	**0·124**	**0·200**	**0·334**
Duration	**Custom, see Fig. 3·6**	**37·1**	**11·3**	**37·2**	**66·7**
Reactive arthritis					
Risk after enteritis by *Campylobacter spp.*	Beta-Pert (0·01, 0·02, 0·03)	0·020	0·008	0·020	0·032
Severity	**Beta-Pert (0·00, 0·21, 0·42)**	**0·210**	**0·079**	**0·210**	**0·340**
Duration (weeks)	**Beta-Pert (2, 6, 10)**	**6·00**	**3·51**	**6·00**	**8·48**

* Variables that are subject to uncertainty are presented in normal font, those subject to variability are in **bold**.
† See Table 2.
‡ Fitted to simulated samples.

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mental pollution from a panel of 24 physicians and 11 environmental epidemiologists. Our procedure was similar to the VTV approach, i.e. valuation by means of interpolation on the scale of indicator diseases. In contrast to Stouthard and colleagues [49], who valued a year of life with one or more episodes of acute, reversible illness, we valued the acute condition as such, without reference to its duration. Duration is entered as one of the independent factors in the final calculations of health burden.

Acute, diarrhoeal disease

In the GBD, two severity weights are presented for infectious enteric disease. Watery diarrhoea (further specified as five episodes a day without major pain or cramps) is one of the indicator conditions, and a mean disability weight of 0·066 is assigned (median 0·054) [48]. We use a Beta-distribution with parameter values (1·5, 21), which has these characteristics, to describe the variability in individual severity weights of campylobacter-associated diarrhoea in the general population.

The case definition for the more severe cases of bacterial gastroenteritis as valued for this study is shown in Table 3. The median severity weight for this health state was 0·37 with a wide range between 0·05 and 0·97. The individual scores could be fitted with a Beta (1·23, 1·90) distribution. This weight, which is used for patients who visit their general practitioner, is much higher than previously mentioned weights for uncomplicated diarrhoea, reflecting the importance of an accurate case-definition and instructions given to the panel.

Guillain–Barré syndrome

The clinical heterogeneity of GBS requires a differentiation in disability classes. Table 3 shows the results of weighting the different functional grades of GBS and also shows fitted Beta distributions. We combined these weights with data on the clinical course of GBS (Fig. 1) to construct a composite severity weight for the clinical phase (first year after diagnosis) and the residual phase of GBS (Table 4).

Reactive arthritis

A severity weight for reactive arthritis is not available in the literature. The VTV study lists weights for three different grades of rheumatoid arthritis – mild: 0·21; moderate: 0·37 and severe: 0·94. Given the fact that most cases of reactive arthritis are relatively mild, a severity weight of 0·21 was considered appropriate. There is no information on the variability of this weight. We arbitrarily used a β-Pert distribution with most likely value 0·21, minimum 0·00 and maximum 0·42 (i.e. $\times 2$ most likely).

INTEGRATION

Uncertainty and variability in parameter values

The preceding information can now be integrated into an estimate of the health burden of infection with thermophilic *Campylobacter* spp. in the Netherlands. However, there is considerable uncertainty and variability in the available data. Here, variability is defined as the inherent randomness of a system under study. Uncertainty is defined as lack of knowledge about the system. Additional data collection can reduce uncertainty but not variability. Both uncertainty and variability can be expressed in a statistical distribution function, but require a different strategy to account for in the analysis. Table 4 shows the frequency distributions used for uncertainty and variability analysis, and some characteristic values. We considered severity and duration of disease to be variable parameters, and other parameters uncertain. We did not consider second order uncertainty (i.e. uncertainty in the parameter estimates of the distribution functions of the variable quantities). We performed uncertainty and sensitivity analysis in @RISK 3.5.1 (Pallisade Corporation [51]) as an add-on to Microsoft Excel 97. All simulations were run using Latin Hypercube sampling, and terminated when all output parameters converged at the 1% level.

The strategy to account for uncertainty and variability depended on the estimated incidence. We explain the methodology by example of the morbidity burden of gastroenteritis in the total population. This value was estimated from four distribution functions, two of which are uncertain (incidence rate of gastroenteritis, IR and attributable proportion for campylobacter, AP) and two of which are variable (duration L and severity W). In a population of size N, the (annual) incidence of gastroenteritis $I = IR \times AP \times N$ is again an uncertain distribution function, which is obtained by sampling from the underlying distributions. Each iteration (realization of the model with a set of parameters randomly drawn

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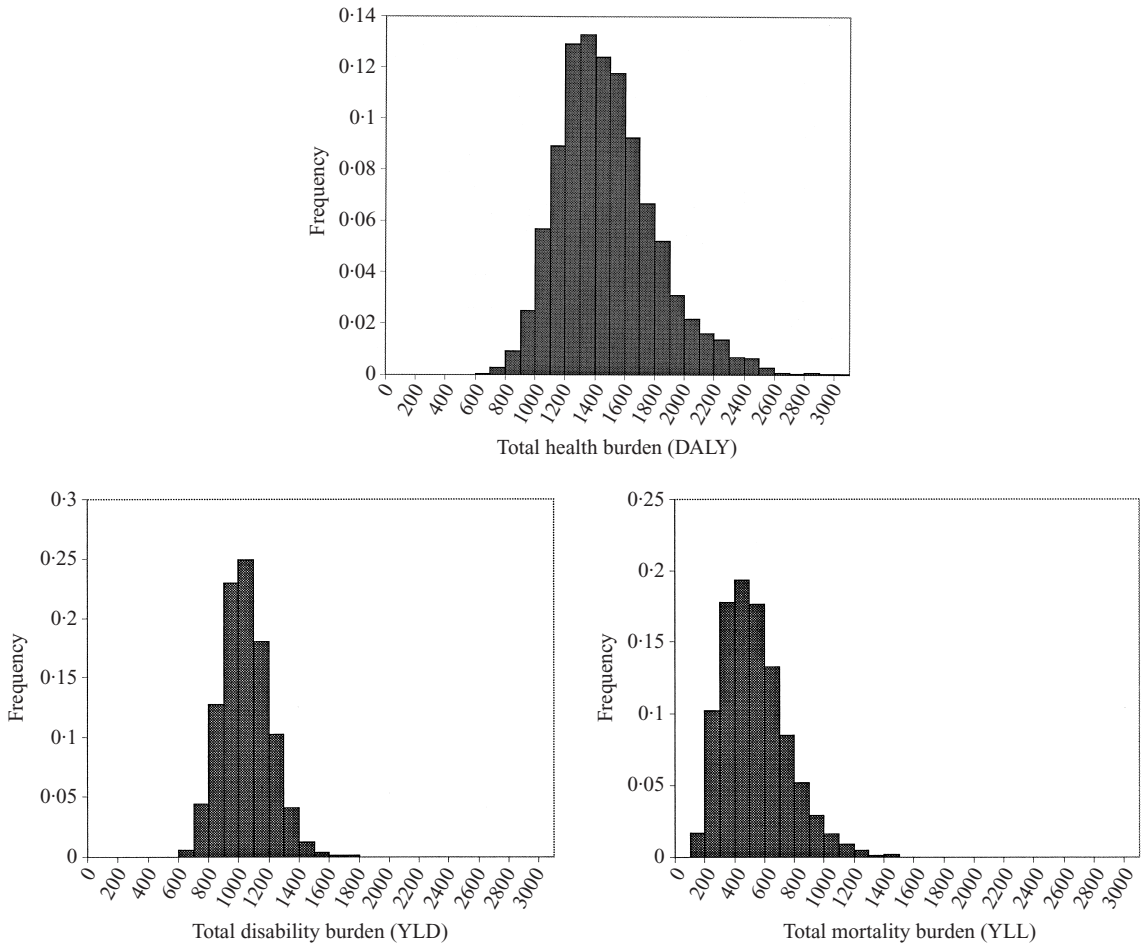

Fig. 2. Distribution of estimated total health burden of infection with thermophilic *Campylobacter* spp. in the Netherlands, and the contributing disability and mortality burden.

from the underlying distributions) represents one possible value of I cases (per year). For each case, the individual health burden yld_i is obtained by multiplying random samples from L and W. The total health burden in the population is then obtained by addition of individual estimates: $YLD = \Sigma_{i=1}^{I}\ yld_i$. For diseases with low incidence, random variation cannot be neglected, and the individual burden for each incident case in each iteration has to be simulated. According to the Central Limit Theorem, the mean value of yld_i is known with high certainty for a large population. In that case, the total population burden in a specific iteration can simply be obtained by multiplying I with the mean of yld_i.

Figure 2 show the results of the uncertainty analysis for the total health burden. The resulting distributions are characterized in Table 5. The mean annual morbidity burden of disease related to thermophilic *Campylobacter* spp. is estimated as 947 *YLD*, of which $286 + 158 = 444$ *YLD* (47%) is attributed to the effects of acute gastroenteritis. Residual disability from *GBS* is the second most important factor in the morbidity burden, contributing 338 *YLD* (36%). Mortality associated with acute gastroenteritis accounts for a mean of only 32 cases per year, but adds a significant health burden of 413 *YLL* to the total estimate. The mortality related to GBS is of minor importance. Summation of morbidity and mortality burden yields an estimate of the mean total health burden of infections with thermophilic *Campylobacter* spp. in the Netherlands of 1382 DALY per year. For a population of 15 million, this implies that approximately 0·01% of all possible healthy life years is lost by this pathogen. The results show that the uncertainty of the estimate of total health burden is relatively small, the coefficient of variation (CV = standard deviation/mean) is approx. 0·23. Figure 2 shows that the distribution is skewed to the right. The most likely range of the health burden (5th to 95th percentile) is between 927 and 1991 DALY per year.

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Table 5. *Characteristics of the output distributions of estimates of disease burden*

Output parameter	5-percentile	Median	Mean	95-percentile	S.D.
Gastroenteritis, pop					
YLD	157	277	286	442	87
YLL	126	382	413	811	214
DALY	324	658	699	1203	274
Gastroenteritis, GP					
DALY	139	158	158	178	12
GBS, clinical					
YLD	10	17	17	23	4
YLL	6	15	21	57	17
DALY	18	32	38	75	18
GBS, residual					
YLD	208	336	338	477	83
Reactive arthritis					
YLD	73	143	149	248	54
Total					
YLD	698	935	947	1222	160
YLL	145	403	435	839	215
DALY	927	1338	1382	1991	324

The major contribution to uncertainty in the overall estimate comes from uncertainty in YLL by gastroenteritis (CV = 0·49). This is mainly related to the relatively low incidence of fatal cases. The uncertainty in YLD is much smaller (CV = 0·17 of total *YLD*).

Uncertainty in model assumptions

A second source of uncertainty in the final result is the effect of the assumptions in the baseline model. Comparing the results of the baseline scenario with those obtained by alternative assumptions provides insight into the effect of these uncertainties, which are not accounted for in the distribution functions used above. We show the results of some alternative scenarios in Figure 3.

1. In the population based surveillance study [21], several case definitions for gastroenteritis were used to analyse the data. The incidence rate estimate of 447 per 1000 person years was based on a comprehensive case-definition, in accordance with WHO criteria. It was felt that this case-definition could also include many cases of gastroenteritis of non-infectious origin and a more restrictive case-definition was also applied, resulting in an incidence rate estimate of 153 cases of gastroenteritis per 1000 person years. *Campylobacter* spp. were isolated from 6 faecal samples of 52 respondents. Hence, an alternative estimate for the incidence of campylobacter-associated gastroenteritis is $(153/1000) \times 15 \times 10^6 \times (6/52) = 265000$ cases per year. This estimate would result in an overall reduction of the health burden by 13% to 1224 DALY, and would reduce the estimated burden by gastroenteritis in the total population and by reactive arthritis by 21 and 20%, respectively.

2. The baseline severity weight for gastroenteritis in the general population was based on a relatively mild case-definition of watery diarrhoea. In Annex 3 of the GBD, alternative, age-specific weights are given for 'Diarrhoeal diseases (episodes) in the treated and untreated form' [13]. These estimates range between 0·119 for the 0–4 years old to 0·086 for the 15–59 year old. An average disability weight of an episode of diarrhoeal disease of 0·09 seems to be an acceptable simplification. Applying this weight increases the DALY estimate for the general population by 14% and the total estimate by 7% to 1503 DALY per year.

3. If correction for non-response in sentinel surveillance is not applied, the DALY estimate for gastroenteritis at the general practitioner decreases by 41%, but the total DALY estimate is reduced by only 3% to 1354 DALY per year.

4. A high estimate for the incidence rate of GBS, as used in the USA, is 3·64/100000 person years [10]. This would increase the estimated health burden by GBS by 208%, and would also have a profound effect on the total estimate, which increases by 56% to 2186 DALY per year.

5. Assuming that the probability of acquiring GBS

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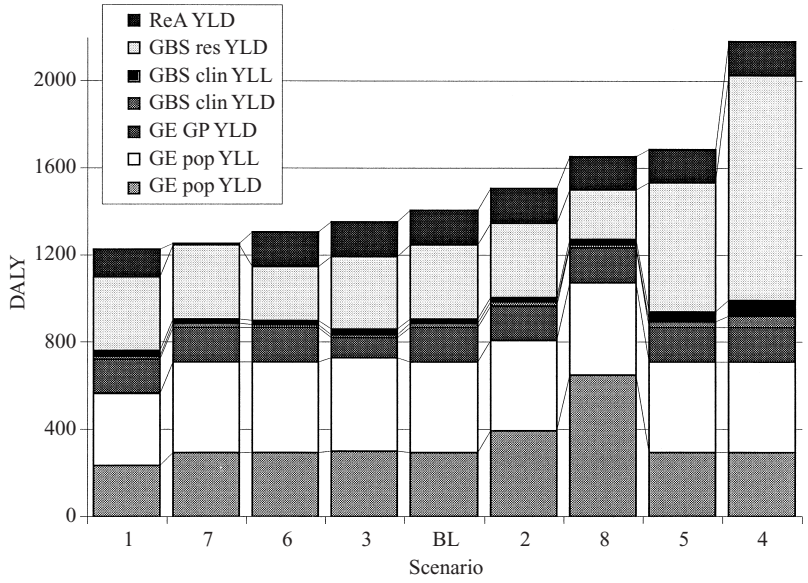

Fig. 3. Graphical representation of scenario analysis (ReA: reactive arthritis, GBS: Guillain–Barré syndrome, GE: gastroenteritis, GP: general practitioner, pop: population, *YLD*: Years Lived with Disability, *YLL*: Years of Life Lost). Scenarios: see text, BL: baseline.

Table 6. *Comparison of severity weights from the panel elicitation and from a regression model*

		Severity weight	
Health state	Euroqol 5D score	Panel*	Model†
Gastroenteritis			
General population	112211	0·07‡	0·15
General Practitioner	11321, 21321, 11311, 21331	0·39	0·40
GBS			
$F = 1$	11211	0·14	0·07
$F = 2$	21211	0·28	0·12
$F = 3$	22321	0·45	0·47
$F = 4$	33322	0·78	0·73
$F = 5$	33332	0·92	0·90

* Table 3; mean from fitted Beta distributions.

† The regression model [52] allows negative scores for health states that are considered worse than death. Actually, the predicted score for state 33333 is –0·59. In the panel elicitation, all health states were valued on a scale between 0 (best imaginable health) to 1 (worst imaginable health). Therefore, the model predictions were divided by a factor of 1·59.

‡ Mean score from Global Burden of Disease Study [48].

after campylobacter-associated gastroenteritis is 1:1058 [37] has strong effects, the GBS related health burden increases by 75% and the total estimate by 20% to 1686 DALY per year.

6. If no correction for sensitivity of the serological test for antecedent campylobacter infection in GBS patients is applied, the related health burden decreases by 26% and the total estimate by 7% to 1305 DALY.

7. If only more severe cases of reactive arthritis are taken into account (incidence 50 cases per year, with median duration 25 weeks and severity weight 0·37), the related health burden is practically negligible and the total burden is reduced by 11% to 1253 DALY per year.

8. An alternative for obtaining severity weights by direct panel elicitation is a model-based approach.

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For this purpose, health states are described by a generic, multiattribute classification system such as the Euroqol-5D system. The Euroqol-5D describes health in five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) with three levels each (no problems, some problems, extreme problems), resulting in $3^5 = 243$ possible health states. Different studies have evaluated a subset of these health states, using different valuation methods and different groups of respondents. A randomly selected sample of the general population in the UK was invited to evaluate 15 health states using VAS and TTO techniques. By varying the health states submitted to respondents, it was possible to obtain valuations for 42 EuroQol health states. Dolan [52] constructed a regression model to interpolate the other 201 health states on this scale. Table 6 shows a comparison between the modelled severity weights and the weights from the panel elicitation. In general, there is good agreement between weights for relatively severe health states, but the panel weights less severe states of GBS considerably higher than the general public. When comparing the valuations obtained by applying this model with the direct panel elicitation, several factors must be taken into account. (i) The panel elicitation was based on the PTO protocol and the model on values obtained with the TTO protocol. In general, the TTO protocol assigns slightly higher severity weights than the PTO protocol. (ii) The general public (whose values were used to develop the model) assigns a higher severity weight to any health state than (medical) professionals (in the panel). (iii) Furthermore, the general public attaches more weight to severe health states as is explicitly demonstrated in the model structure.

Therefore, it is not to be expected that the two sets of severity weights correspond exactly. The model values are another possible set of values. Substituting these severity weights for the weights in the baseline results in an increase of the overall health burden by 18% to 1653 DALY. The difference is mainly attributable to an increase of the disability burden of gastroenteritis in the general population from 291 to 652 DALY, or by 124%. This is now the most significant single cause of health burden. The disability burden of gastroenteritis leading to GP consultation increases slightly and the disability burden by GBS is reduced by 33%.

9. There is major uncertainty in the case-fatality ratio of campylobacter associated gastroenteritis and the distribution used in the baseline scenario is arbitrary. To evaluate the effect of this uncertainty more fully, we ran a series of simulations in which the case-fatality ratio (CFR) was kept constant at values of 1, 2, 3, …, 20 per 100000 cases. Figure 4 shows the results of this analysis. The mean estimate of the total health burden varies between approximately 1000 and 1800 DALY. Comparison with the mean and standard deviation of the baseline scenario demonstrates that, even though the uncertainty in the CFR has a major impact on the mean estimate, the contribution to overall uncertainty is limited.

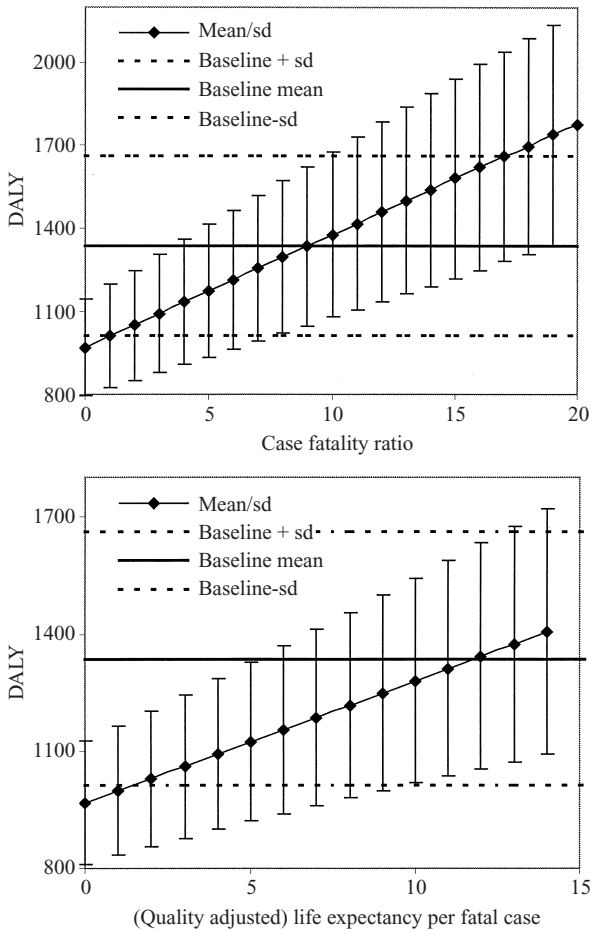

Fig. 4. Effect of uncertainty in the case-fatality ratio (top) or the life expectancy or quality of life of fatal cases (bottom) of gastroenteritis on the total health burden and the associated uncertainty.

10. It might be argued that fatal cases by gastroenteritis are not a random selection of the population, but is related to those that have underlying diseases. These might result in a reduced life expectancy, or a reduced quality of life before the fatal event. Then, attribution of the standard life expectancy to these cases or assigning a weight of 1 to the lost life years would overestimate the true

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mortality burden. Figure 4 shows the effect of assuming lower life expectancies. As above, it is clear that the assumption has a major impact on the median estimate, but does not add much to overall uncertainty.

In summary, the alternative assumptions result in variation of the median value of the total health burden between 900 and 2200 DALY per year, which is approximately the same as the range displayed in Table 5.

DISCUSSION

We used the DALY methodology to integrate all epidemiological and clinical information of outcomes of campylobacter infection with social values on the severity of different health states, to give an overall estimate on the health burden. Despite considerable uncertainty and variability in the underlying information, the final result appears to be relatively robust. The most likely value of the total health burden in the baseline scenario is approx. 1400 DALY per year with a (90%) range between 900 and 2000 DALY per year. To account for the effect of assumptions in the baseline scenario, we repeated the calculations using alternative assumptions with the mean estimate ranging between 900 and 2200 DALY per year. Hence, the overall result is also relatively robust against alternative assumptions. This is related to the fact that the total health burden is based on different disease end-points, and it is unlikely that all parameter estimates for these end-points will simultaneously have an extreme value. The relative contribution of individual diseases to the total health burden is more uncertain, but mainly from a quantitative point of view. In the baseline scenario, gastroenteritis in the general population, gastroenteritis related mortality and residual symptoms from GBS are the major determinants of health burden. In most scenarios this order is maintained. Only when extreme estimates for the incidence rate of GBS are used (such as in recent work from the USA [10]), will (residual disability from) GBS be the leading cause of total health burden. The most important causes of health burden affect patients that are not usually seen in clinical settings. Most detailed data are available from clinical studies, but these relate to diseases or disease stages that only have a small contribution to the overall health burden. This contrast is most striking for GBS. There is a wealth of data on patients in their first year after hospitalization, which adds only 40 DALY to the health burden (or 3% of the total). The residual symptoms of GBS add 330 DALY or 24% of the total burden, but only one paper is available on this stage of the disease. There is also a lack of data on severity, duration and case-fatality ratio of campylobacter-associated gastroenteritis in the general population and on all aspects of reactive arthritis. Thus, this study indicates that active surveillance for gastrointestinal pathogens, based on population studies is preferred above passive surveillance based on clinical reports. Such studies have recently been reported from the UK [53] and are in progress in the Netherlands [54, 55].

The Dutch VTV study gives a first estimate for the loss of healthy life years in the Dutch population. Because of major uncertainty in the underlying parameters, the reports do not give an estimate for the total burden, but classify diagnostic groups of diseases on the basis of different indicators: prevalence, severity, life years lost, years lived with disability and health burden as expressed in DALY. In the classification according to health burden, intestinal infections rank in the category 3000–10000 DALY per year. Other disorders in this category are meningitis, sepsis, upper respiratory infections, stomach and duodenal ulcers, Down's syndrome, violence and accidental drowning. Thermophilic campylobacter is only one of more than 50 infectious agents that may cause gastrointestinal illness, but accounts for 5% of all cases on a population basis. Extrapolating the current estimate of 1400 DALY per year to all causes of gastroenteritis would result in an estimated burden of 28000 DALY per year, which is considerably higher than the VTV estimate. This figure is probably an overestimation because (i) not all gastroenteritis is infectious in nature, (ii) not all intestinal pathogens induce severe complications such as GBS and (iii) gastroenteritis induced by many agents (e.g. viruses and bacterial toxins) is less severe and of shorter duration than campylobacter-associated gastroenteritis. Nevertheless, the results of this study indicate that the health burden associated with gastrointestinal pathogens may be underestimated if only diarrhoeal illness is accounted for. Finally, even though the total health burden associated with campylobacter is small in comparison to major diseases such as lung cancer, psychological disorders and coronary vascular diseases, the results of this study justify further efforts to reduce the incidence of foodborne disease, and campylobacteriosis in particular. In addition to the

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high direct costs, related to productivity losses and medical consumption [56], this study adds the dimension of preventable health loss.

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