CAMPYLOBACTER RISK MANAGEMENT AND ASSESSMENT

CARMA

RIVM report 250911004 / 2004

Campylobacteriosis and sequelae in the Netherlands

Estimating the disease burden and the cost-of-illness

M.J.J. Mangen[1,2], A.H. Havelaar[3], G.A. de Wit[2]

[1] Wageningen University and Research Centre, Agricultural Economics Research Institute, P.O. Box 29703, 2502 LS, Den Haag.
[2] National Institute for Public Health and the Environment, Centre for Prevention and Health Services Research, P.O. Box 1, 3720 BA Bilthoven
[3] National Institute for Public Health and the Environment, Microbiologal Laboratory for Health Protection, P.O. Box 1,

LEI WAGENINGEN UR

This investigation has been performed by order and for the account of the Ministry of Public Health, Welfare and Sports and the Ministry of Agriculture, Nature and Food Quality, within the framework of project V/250911, CARMA: Campylobacter Risk Management and Assessment.

Abstract

Campylobacteriosis and sequelae in the Netherlands - Estimating the disease burden and the cost-of-illness

Each year, approximately 80,000 persons per year (range 30,000 – 160,000) are estimated to experience symptoms of acute gastro-enteritis as a consequence of infection with Campylobacter bacteria. On average 18,000 patients consult a general practitioner and 500 patients are hospitalised; for some 30 cases the disease could be fatal. Additionally, each year some 1400 cases of reactive arthritis, 60 cases of Guillain-Barré syndrome and 10 cases of inflammatory bowel disease are associated with a previous Campylobacter infection. The disease burden and the cost-of-illness of Campylobacter infections and sequelae were estimated using a stochastic simulation model. Disease burden was expressed in Disability Adjusted Life Years (DALYs), the sum of years of life lost and years lived with disability, weighted for the severity of disease. Considered in the cost-of-illness were direct health-care costs (e.g. doctors' consultations, hospitalisation, rehabilitation), direct non-health-care costs (e.g. travel costs of patients, co-payments by patients) and indirect non-health-care costs (productivity losses), using cost estimates for the year 2000. The disease burden associated with Campylobacter infections was estimated at 1200 DALYs per year, with a 90% uncertainty interval of between 900 and 1600 DALYs per year. The costs-of-illness were estimated to total € 21 million per year with a 90% confidence interval of between € 11 million and € 36 million per year. Hence, Campylobacter infections pose an important public health problem for the Netherlands and incur substantial costs.

Preface

This report is part of the CARMA (**C**ampylobacter **R**isk **M**anagement and **A**ssessment) project. The CARMA project is mainly focused on two key questions:

1) What are the most important routes by which the Dutch population is exposed to Campylobacter and can the contribution of these routes is quantified?
2) Which (sets of) measures can be taken to reduce the exposure to Campylobacter, what is their expected efficiency and societal support?

For the Netherlands, chicken meat was defined to be a major route of human Campylobacter infections - but not the only one. Therefore within the CARMA project it was decided to focus in first instance on the chicken meat production chain. Next to a risk assessment an economic evaluation is needed in order to answer the second key question. Within the CARMA project an economic evaluation of different interventions in the chicken meat chain to reduce human Campylobacter infections will take place in the form of a cost-effectiveness analysis. The costs of the intervention applied in the chicken meat chain will be related to 'reduced' burden of disease and 'reduced' costs of illness. This will result in a cost-effectiveness ratio that should express the relative efficiency of several policy options to reduce the number of Campylobacter infections. As a first step in such an economic evaluation, the disease burden and the cost-of-illness associated with Campylobacter infections and sequelae is estimated in this research report.

More information on the CARMA project can be found at the website www.rivm.nl/carma.

The authors would like to acknowledge a number of different people for their contributions to this study. There is, first of all, Rob Bernsen from the Jeroen Bosch Hospital in s'Hertogenbosch; some of the members of the Department of Neurology at the Erasmus Medical Centre Rotterdam, especially Pieter van Doorn, Marcel Garssen, Bart Jacobs and Rinske van Koningsveld; and there is Marten Postma from the University of Groningen, all from the Netherlands. Further we would like to thank Margrit Ebinger from the University of Ulm, Germany, Timo Hannu from the Helsinki University Central Hospital, Finland, and Morten Helms and Henning Locht, both from the Statens Serum Institute, Denmark, for their contributions. And last but not least, we would like to thank our colleagues from the National Institute of Public Health and Environment for their various contributions to this study, mainly Winette van den Brandhof, Yvonne van Duijnhoven, Wilfrid van Pelt and Matty de Wit from the Centre for Infectious Disease Epidemiology, Peter Teunis from the Centre for Information and Technology and Methodology and Nancy Hoeymans from Centre for Public Health Forecasting.

Contents

Samenvatting

Naar schatting maken 80.000 personen per jaar (onzekerheidsinterval 30.000 – 160.000) een episode van gastro-enteritis door ten gevolge van infectie met Campylobacter bacteriën. Ongeveer 18.000 patiënten consulteren een huisarts, 500 patiënten worden in het ziekenhuis opgenomen en 30 patiënten overlijden als gevolg van de gastro-enteritis. Daarnaast treden er ieder jaar naar schatting 1400 gevallen van reactieve artritis op, 60 gevallen van Guillain-Barré syndroom en 10 gevallen van inflammatoire darmziekte ten gevolge van een voorgaande Campylobacter infectie. De ziektelast en de ziektegebonden kosten van Campylobacter infectie werden geschat met behulp van een stochastisch simulatiemodel. Ziektegebonden kosten in het basisjaar 2000 betroffen directe kosten in de gezondheidszorg (bijvoorbeeld consulten van een arts, ziekenhuisopname en rehabilitatie), directe kosten buiten de gezondheidszorg (bijvoorbeeld reiskosten en eigen bijdragen van patiënten) en de indirecte kosten buiten de gezondheidszorg, met name productiviteitsverlies. De ziektelast werd geschat op 1200 DALYs (Disability Adjusted Life Years) per jaar, met een 90% onzekerheidsinterval tussen 900 en 1600 DALYs per jaar. DALYs zijn de som van verloren levensjaren ten gevolge van voortijdige sterfte en jaren doorgebracht met een ziekte, gewogen naar de ernst ervan. De ziektegebonden kosten werden geschat op ongeveer 21 miljoen Euro, met een 90% onzekerheidsinterval tussen 11 en 36 miljoen Euro per jaar. Campylobacter infecties vormen dus een belangrijk volksgezondheidsprobleem in Nederland.

Executive summary

Campylobacter infections in humans may cause acute gastro-enteritis (GE), which, in most cases, is self-limiting within a few days to weeks. For some patients the disease is fatal. Guillain-Barré Syndrome (GBS), reactive arthritis (ReA) and inflammatory bowel disease (IBD) are the most significant sequelae occurring occasionally after campylobacteriosis. Human Campylobacter infections pose an important public health problem in the Netherlands.

With the availability of a more recent Dutch epidemiological study with a much lower estimated annual number of GE cases than in a study carried out in the earlier nineties, an update of a previous estimate of the disease burden associated with Campylobacter infections and sequelae in the Netherlands was necessary. This was the first objective of the current study. The second objective of this study was to estimate the cost-of-illness related to Campylobacter infections and their sequelae in the Netherlands.

Methodological approach

Using a stochastic simulation model we estimated the cost-of-illness and the disease burden associated with Campylobacter infections and sequelae. A previous disease burden estimate using **D**isability **A**djusted **L**ife **Y**ears (DALYs) was updated. We took into consideration each of the different health states associated with Campylobacter infection or its sequelae. For all four illnesses Dutch estimated disability weights were used. The estimated annual GE incidence was based on a recently conducted population study in the Netherlands (1996-1999). Estimates for symptom length and severity of GE were based on Dutch and English studies. Estimates of incidence, symptom length and severity of GBS were based on Dutch studies only. Estimates of incidence, symptom length and severity of ReA estimates were based on a recently published Finnish study (2002). The estimated incidence of Campylobacter-associated IBD was based on a recent Danish registry-based study. Estimates of symptom length and severity of IBD were based on a published Markov chain model analysis of a population-based cohort study conducted in the United States.

Following the Dutch guidelines for human health care evaluation studies, we estimated the direct health care costs, direct non-health care costs and indirect non-health care costs associated with Campylobacter infection and its sequelae, using Dutch cost estimates for the year 2000. The direct health care costs considered included e.g. general practice (GP) consultations, hospitalisation, drugs, rehabilitation and other medical services. Travel costs of patients and eventually co-payments by patients were considered as direct non-health care costs. Applying the friction cost method, we estimated the productivity losses (indirect non-health care costs) that occurred due to sickness leave and premature mortality, and also, in the case of GE, due to third persons taking care of sick persons. When the friction cost method is applied, production losses are only considered for the period that is needed to replace a sick, invalid or deceased worker, the so-called friction period.

Estimates of medical services used for the different illnesses were based, wherever available, on Dutch studies and data. In the case of ReA and IBD, we had to fall back on international literature. Despite all efforts made, information on the use of medical services and on the length of sickness leave of ReA patients was scarce.

The estimated disease burden and cost-of-illness with regard to the different illnesses associated with Campylobacter infections are presented both discounted and undiscounted. For this, we used the officially recommended discount rate in the Netherlands, which is 4%. Applying a discount rate is generally used to account for the fact that e.g. health today is valued higher than health in the future, and for the fact that there is uncertainty about future possibilities to 'better' treat diseases.

Summarising the main results

In this executive summary only the main results are shown. Details of the assumptions made in order to estimate the incidence, the disease burden and the cost-of-illness are given in Chapters 3, 4, 5 and 6 of this report for GE, ReA, GBS and IBD, respectively. In each of these chapters we also describe the different sensitivity analyses applied. Only assumptions that have an important impact on our final outcomes are discussed in this executive summary.

Estimated incidences of Campylobacter infections and associated sequelae

The annual incidence of Campylobacter-associated GE cases in the Netherlands, with a population of 16 million, was estimated to be on average 79,000 cases with a 90% confidence interval (C.I.) of 28,000 to 162,000 GE cases (Table I). In nearly 30 cases GE is fatal (90% C.I.: 20-37). For some of the GE patients the Campylobacter infections resulted in sequelae. The estimated average annual incidence of sequelae was 1400 ReA cases, 59 GBS cases, of which 2 fatal, and 11 IBD cases (Table I). Most cases of Campylobacter infection in humans would result only in GE. Complications such as ReA, GBS or IBD, respectively, or fatal GE and fatal GBS cases after a Campylobacter infection, are relatively rare. Of all sequelae related to previous Campylobacter infections, ReA is by far the most occurring sequel.

Table I. The estimated mean and the attendant uncertainty[1] of annual incidences of Campylobacter-associated GE cases, ReA cases, GBS cases, IBD cases, fatal GE cases and fatal GBS cases, respectively, in the Netherlands.

	Estimated annual incidence			
	5%	Mean	50%	95%
Morbidity				
GE cases	28,000	79,000	69,000	162,000
ReA cases	470	1,400	1,200	3,000
GBS cases	40	59	58	84
IBD cases	10	11	11	13
Mortality				
Fatal GE cases	20	28	27	37
Fatal GBS cases	1	2	2	3

[1)] The model parameters used in this study are often uncertain or are variable or both. We therefore not only show for example the average annual incidence but also the 5th, 50th and 95th percentile, representing the uncertainty in the estimated average.

Estimated disease burden due to Campylobacter infections and sequelae

The estimated disease burden associated with Campylobacter infections and sequelae for the Netherlands is considerable, with on average 1185 DALYs with a 90% C.I. of 872 to 1623 DALYs per year (Table II). More than 50% of the estimated mean disease burden associated with Campylobacter infections and sequelae in the Netherlands is due to GE cases and associated mortality. About 25% is due to GBS cases and 10-11% is due to both IBD and ReA cases (Figure I). More than a third of the total estimated mean disease burden is due to mortality (Figure II). By discounting the disease burden by 4%, mortality still accounts for nearly a third of the total estimated disease burden.

Table II. Mean and attendant uncertainty of the estimated disease burden due to Campylobacter-associated GE cases, GBS cases, ReA cases, IBD cases and the sum of all illness cases, respectively, in the Netherlands (year 2000).

Description	Disease burden							
	Not discounted				Discounted (4%)			
	5%	Mean	50%	95%	5%	Mean	50%	95%
Disability adjusted life years (DALYs)								
GE	430	635	610	924	323	499	469	776
ReA	44	126	109	271	44	126	109	271
GBS	199	298	286	413	114	169	166	234
IBD	109	127	126	151	47	55	55	66
C. infections and sequelae	872	1185	1149	1623	581	850	817	1270

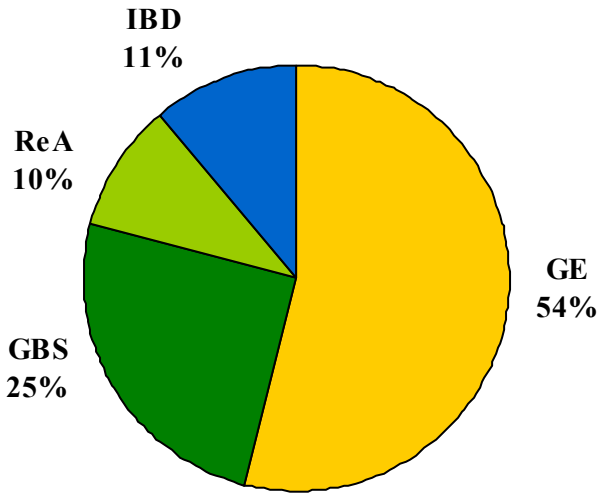


Figure I. Distribution of the estimated mean annual disease burden related to Campylobacter infections and sequelae by the different illnesses for 2000 (undiscounted figures).

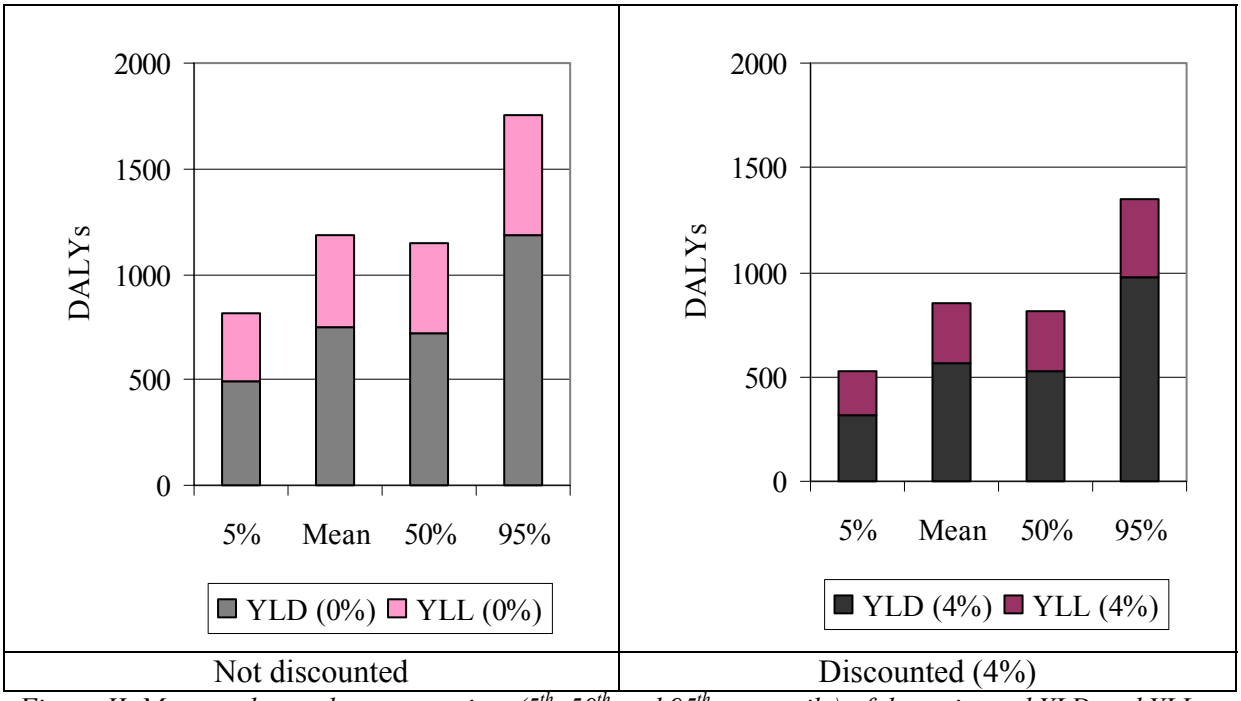


Figure II. Mean and attendant uncertainty (5th, 50th and 95th percentile) of the estimated YLD and YLL, respectively, due to Campylobacter infections and sequelae in the Netherlands (year 2000).

By dividing the average estimated DALYs by the average estimated annual incidence, we obtain an estimate of the 'average' DALYs/case. Chronic and long-lasting diseases, such as IBD and GBS, are responsible for a higher disease burden per patient than short disease episodes, such as gastro-enteritis. To obtain insight into the relative disease burden of all Campylobacter-associated diseases, we have summarised the estimated DALYs/1000 average cases for all four Campylobacter-associated illnesses and the estimated DALYs associated with Campylobacter infections and sequelae per initial GE cases. The results are summarised in Table III.

Table III. Mean estimate of DALYs/1000 cases for average GE cases, GBS cases, ReA cases and IBD cases, respectively, all associated with Campylobacter infections (year 2000).

	Not discounted DALYs/ 1000 average cases
DALYs due to GE/GE cases	8
DALYs due to ReA/ReA cases	90
DALYs due to GBS/GBS cases	5,000
DALYs due to IBD/IBD cases	11,600
DALYs due to C.-infections and sequelae/GE cases	15

Estimated cost-of-illness due to Campylobacter infections and sequelae

The estimated cost-of-illness associated with Campylobacter infections and sequelae in the Netherlands for 2000 was considerable, with on average more than € 20 million per year (90% C.I. € 11 – 36 million, Table IV). Indirect non-health care costs accounted for nearly two-thirds of the estimated average total cost-of-illness, whereas direct health care costs accounted for approximately one-third. Direct non-health care costs were only of minor importance (Table IV).

Indirect non-health care costs, which were mainly productivity losses, accounted for approximately 90% of the total cost-of-illness related to GE cases, whereas direct health care

costs accounted for approximately 70% of the estimated cost-of-illness associated with IBD and GBS cases, respectively. The direct non-health care costs were only minor (less than 1% of total costs). The indirect non-health care costs related to GE cases are by far the greatest cost category in our estimated total cost-of-illness (Figure III). Therefore it is not surprising that indirect non-health care costs accounted for approximately two-thirds of the estimated average total cost-of-illness.

Table IV. Mean and attendant uncertainty of the estimated direct health care costs, direct non-health care costs, indirect non-health care costs and total costs, respectively, all related to Campylobacter infections and sequelae for 2000 (undiscounted figures).

Description	Estimated costs (*1000 €) for the year 2000			
	5%	Mean	50%	95%
Direct health care costs	5,300	6,500	6,500	8,000
Direct non-health care costs	28	51	50	81
Indirect non-health care costs	5,300	14,000	12,600	29,300
Total costs	11,500	20,600	19,000	36,300

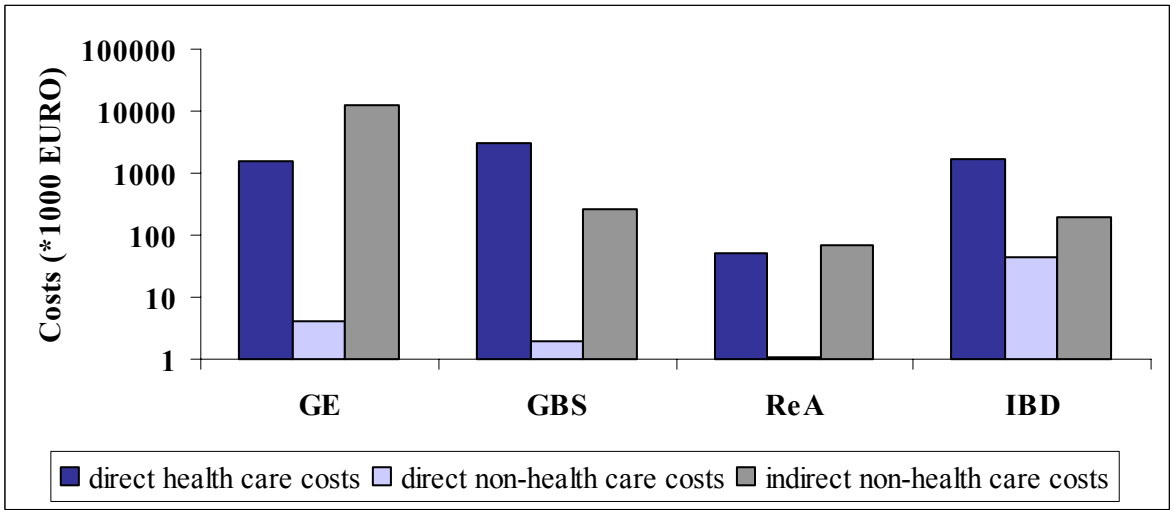


Figure III. The estimated mean direct health care costs, direct non-health care costs, and indirect non-health care costs due to Campylobacter-associated GE cases, GBS cases, ReA cases, and IBD cases, respectively, for 2000 (undiscounted figures).

For GE and ReA all costs were assumed to occur within the first year. In the case of GBS most costs would occur in the first years after disease onset and only for IBD, the associated costs of illness were assumed to be evenly spread over the remaining life years of the patients after disease onset. Given that IBD cases account for ~10% of the total costs, discounting has, as shown in Table V, only little impact on the estimated cost-of-illness related to Campylobacter infections and sequelae.

Under the current assumptions, approximately two-thirds of the estimated mean cost-of-illness related to Campylobacter infections and sequelae in the Netherlands are made by GE cases (see Figure IV). Of the estimated mean cost-of-illness about 17% were estimated to be made by GBS cases and 9% by IBD cases. ReA cases accounted for only 1% of the estimated mean cost-of-illness. However, in the current study the costs of illness related to ReA cases were probably underestimated.

Table V. Mean and attendant uncertainty of the estimated cost-of-illness associated with Campylobacter infection and sequelae in the Netherlands, total and for each illness.

Description	Estimated cost-of-illness (*10^6 €) for the year 2000							
	Not discounted				Discounted (4%)			
	5%	Mean	50%	95%	5%	Mean	50%	95%
GE	6.1	15.1	13.8	30.9	6.1	15.1	13.8	30.9
ReA	0.0[1]	0.1	0.1	0.4	0.0[1]	0.1	0.1	0.4
GBS	2.2	3.4	3.3	4.9	2.1	3.3	3.3	4.8
IBD	1.6	1.9	1.9	2.3	0.7	0.9	0.9	1.0
Total costs	11.5	20.6	19.0	36.3	10.3	19.4	17.9	35.1

[1)] Less than € 0.1 million.

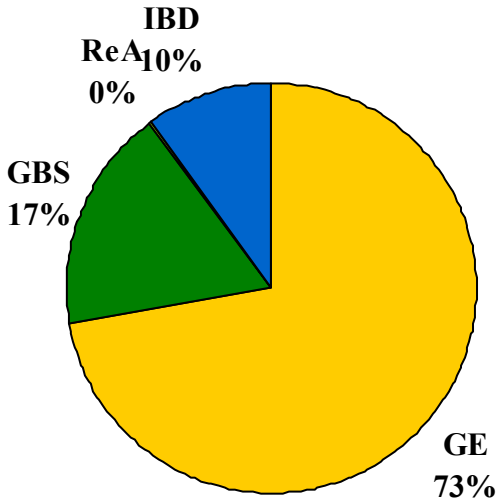


Figure IV. Distribution of the estimated mean total cost-of-illness due to Campylobacter infections and sequelae by the different illnesses for the year 2000 (undiscounted figures).

We further have summarised in Table VI the estimated mean cost-of-illness per estimated GE case, GBS case, ReA case and IBD case, respectively, for the year 2000. For GE cases, we have considered the average costs due to GE only/GE case and the average costs due to GE and sequelae/GE case. The estimated costs per estimated ReA cases might be underestimated, as already mentioned earlier. Especially chronic and long-lasting diseases such as GBS and IBD resulted in a high cost-of-illness per estimated case, as opposed to e.g. the relatively short GE episode/average case.

Table VI. Average estimate of cost-of-illness/cases for an average Campylobacter-associated GE case, GBS case, ReA case and IBD case, respectively, in the Netherlands for 2000 (undiscounted figures).

	Average cost-of-illness (€)/average case
Costs due to GE/GE case	190
Costs due to ReA/ReA case	20
Costs due to GBS/GBS case	58,000
Costs due to IBD/IBD case	173,000
Costs due to GE & sequelae/ GE case	260

Sensitivity analysis

Due to model uncertainties and the non-availability of some data, assumptions had to be made. With the help of sensitivity analyses the impact of such assumptions was analysed. Details of the different assumptions and their impact on the results are discussed in the different chapters within this report. In the following paragraph we only summarize those assumptions that had an important effect on our results.

- The assumed length of symptoms and the assumed sickness leave of GE cases *not* visiting a GP (approximately two-thirds of all GE cases) had a major impact on the assumed cost-of-illness. For example, a half-day longer (shorter) sickness leave/patient resulted in an increase (decrease) of the estimated total costs by more than € 1 million, whereas the impact on the estimated disease burden was relatively small.
- Given the large uncertainty of the population at risk to develop ReA after a Campylobacter infection, the assumed annual incidence of ReA cases had a major impact on the estimated disease burden. Assuming that on average 1400, 400 and 5800 cases would develop ReA, this resulted in an average estimated disease burden of 126, 38 and 520 DALYs, respectively.
- More detailed knowledge about medicine use and sickness leave for ReA patients would probably result in a higher estimate of the cost-of-illness. But the total estimated costs due to ReA would probably remain to be the lowest costs of all sequelae associated with Campylobacter infections.

Discussion of study results

The annual incidences of Campylobacter-associated GE cases, ReA cases, GBS cases and IBD cases in the Netherlands, with a population of 16 million, was estimated to be on average ~ 79,000, 1400, 59 and 11 cases respectively. Most cases of Campylobacter infections in humans would result only in GE. Complications such as ReA, GBS or IBD, respectively, or fatal cases after Campylobacter infections are relatively rare. Of all sequelae related to previous Campylobacter infections, ReA is by far the most occurring sequel, but in most cases also by far the less severe sequelae. Even if we would assume that only positive laboratory-confirmed Campylobacter infections could result in ReA, this would still be by far the most occurring sequel after a previous Campylobacter infection.

The estimated disease burden associated with Campylobacter infections and sequelae was, with on average nearly 1200 DALYs, slightly lower than the estimate of the previous Dutch disease-burden study, which was on average 1400 DALYs. The estimated number of fatal GE cases and the estimated YLL are in both studies comparable. In our study, disease burden due to non-fatal GE cases, ReA and GBS was always slightly lower than in the earlier study. In the case of non-fatal GE cases, the difference was mainly due to the lower annual incidence assumed in our study. Consequently the annual ReA incidence was assumed to be lower as well. Although we assumed the same annual GBS incidence, our estimate was slightly lower due to slightly elderly GBS patients. We used another more representative data set in our study that included more patients from a larger geographic area.

The greatest part of the estimated disease burden related to Campylobacter infections and sequelae was due to GE cases. But fatal GE cases, on average 30 cases, accounted for more than one-third of the total estimated disease burden related to GE cases. Further it has to be noted that patients with chronic and long-lasting illnesses, such as IBD and GBS, had a larger impact on the estimated disease burden than the large amount of non-fatal GE cases.

The population at risk for developing ReA after a Campylobacter infection needs to be better defined in future research. Assuming that: a) all Campylobacter-associated GE cases visiting a GP (BASE) develop ReA; b) only positive laboratory-confirmed Campylobacter cases develop ReA; or c) all Campylobacter-associated GE cases might develop ReA, large differences in the estimated annual incidence of ReA cases were found. Consequently, also the estimated disease burden related to ReA varied a lot. With a better estimate of the 'real' number of ReA cases, it might be expected that also the estimated cost-of-illness varies enormously. Future research is needed in order to get a more reliable estimate of the population at risk.

By applying the friction cost method, the estimated indirect non-health care costs related to chronic and/or long-lasting illnesses, and related to fatal cases, are by far lower than found in other studies. Former studies have used the human capital method, which is known for resulting in far higher estimates of productivity losses (*potentially* lost income as a consequence of disease considered). Therefore, when comparing our estimates with cost-of-illness estimates of other studies, differences in study methodology should be taken into account.

Of the average estimated € 21 million total cost-of-illness, the greatest part was due to GE cases. Of these, the productivity losses due to sickness leave of GE cases played an important role. However, when comparing the estimated average costs per average case per illness, average IBD and average GBS patients were by far costlier to the Dutch society than for example GE patients.

Given that productivity losses due to sickness leave of GE cases were among the major costs of the total cost-of-illness related to Campylobacter infections and sequelae, better estimates of the length of sickness leave of especially GE patients not visiting a GP might help to improve the estimate. In case of for example half a day shorter sickness leave the estimate will have to be corrected downwards by more than € 1 million, whereas a longer sickness leave (+0.5 days) will raise the estimate of the cost-of-illness by more than € 1 million Furthermore, newly available data, especially on ReA but also on additional aids and tools for GBS cases might help to improve the estimate of the cost-of-illness related to Campylobacter infections and sequelae. The latter cost component, however, will probably result in a higher estimate of the cost-of-illness than our estimate. Therefore, we regard the current estimate of the cost-of-illness related to Campylobacter infections and sequelae as an underestimation rather than an overestimation of the real costs.

Despite all the shortcomings of this study, we could update the previous estimate on the disease burden related to Campylobacter infections and sequelae, thereby using newly available data and knowledge. Further, this study is the first estimate of a cost-of-illness for the Dutch society considering not only Campylobacter-associated GE cases, but also associated sequelae. No earlier estimates of the cost-of-illness for the Dutch society associated with ReA, GBS and IBD were available. And although in this study we considered only the costs related to Campylobacter-associated ReA, GBS and IBD cases, our results are a first step towards estimating the cost-of-illness of ReA, GBS and IBD.

1 Introduction

1.1 Background and objective

Approximately 70% of the roughly 1.5 billion annual episodes of diarrhoea in humans and 3 million deaths of children under the age of 5 world-wide are estimated to be due to foodborne pathogens (World Health Organisation (WHO), 2003). However, differences in available technology (e.g. refrigeration), plant and livestock hygiene standards, food production practices, cultural differences and geographic or climatic differences vary greatly among countries (Buzby et al., 1997a, b). Consequently, countries are not equally at risk from foodborne disease. Persons in developing countries with inadequate supplies of safe water and poor waste disposal are particularly susceptible. But in the industrialised world, foodborne pathogens also pose a problem. Campylobacter is the most commonly reported bacterial cause of acute gastro-enteritis in the industrialised world (Williams, 1999; Rodrigues et al., 2001; Wittenbrink, 2002). Different Campylobacter species exist, but *Campylobacter jejuni* is the most common isolated Campylobacter species in faeces of patients with diarrhoea (Blaser, 1997). Only 5-10% of campylobacteriosis is caused by other Campylobacter species, e.g. *C. coli, C. lari, C. hyointestinalis*, and others (Wittenbrink, 2002). Most campylobacteriosis cases are sporadic cases, and outbreaks are rarely identified (Rodrigues et al., 2001). In the Netherlands, with approximately 100,000 cases of acute gastro-enteritis annually, Campylobacter pose a serious public health problem (Havelaar et al., 2000a, b). Although Campylobacter gastro-enteritis is generally a mild and self-limiting illness, the symptoms can range from diarrhoea and lethargy, which lasts some days, to severe diarrhoea and abdominal pain (and occasionally fever) that lasts for several weeks (Anonymous, 2001; Withington and Chambers, 1997). And for some cases, campylobacteriosis is even fatal (Havelaar et al., 2000a, b). Furthermore, Campylobacter infections in humans can lead to serious ongoing sequelae. The most common complications after Campylobacter infections are reactive arthritis (ReA); Guillain-Barré syndrome (GBS) and Miller-Fisher syndrome; inflammatory bowel disease (IBD) and bacteraemia, whereby the latter one is more common in immuno-compromised patients (Kist, 2002; Rautelin and Hanninen, 2000; Smith, 2002; Skirrow et al., 1993). Other, but less frequent post-infectious complications associated with previous Campylobacter infections described in the literature are: uveitits; haemolytic anaemia; haemolytic uraemic syndrome; carditis; encephalopathy; septic abortion; early miscarriage; polyneuropathy; cholecystitis; pancreatitis; cystitis and meningitis (Allos, 2001; Blaser, 1997; Bourke et al., 1998; Hannu et al., 2002; Kist, 2002; Peterson, 1994a). But the frequency of these latter post-infectious complications is so low that we could disregard them in the current study.

Havelaar et al. (2000a, b) estimated that campylobacteriosis and sequelae accounted for an annual loss of over a thousand healthy life years in the Netherlands in the years 1990-95, a considerable disease burden that is probably linked with a considerable economic loss. Van Den Brandhof et al. (2004) estimated the costs for patients with acute gastro-enteritis related to a Campylobacter infection to be ≈ € 9 million for the year 1999. These authors did not consider sequelae associated with Campylobacter infections. In another study where gastro-enteritis, but not sequelae, wasa considered, the costs of Campylobacter infections in the Netherlands were estimated at an annual amount of € 15 to 48 million in 1997 (Bunte et al., 2001). No estimate of the economic impact of Campylobacter infections and the consequences of its sequelae, however, is available for the Netherlands. Therefore the first objective of this study is to estimate the cost-of-illness related to Campylobacter infections

and its sequelae for the Netherlands. Given the fact that a more recent population study by De Wit et al. (2001c) with a lower estimated annual number of gastro-enteritis cases than the one used by Havelaar et al. (2000a, b) is available the second objective of this study is, then, to update the previous disease burden estimate of Havelaar et al. (2000a, b), while also consulting newly available literature and clinical data.

1.2 Outline of the report

The results of this study were summarised and discussed as executive summary at the beginning of this report. Model description and assumptions made are described in more detail in the following chapters of this report. Chapter 2 of this report explains the theoretical framework used. In Chapter 3 we focus in more detail on the estimated disease burden and cost-of-illness estimates for gastro-enteritis linked to a Campylobacter infection. Finally, we look at the different sequelae associated with Campylobacter infections, reactive arthritis, Guillain-Barré syndrome and inflammatory bowel disease, in chapters 4, 5 and 6, respectively.

2 Conceptual approach

2.1 Estimating annual incidences

In order to estimate the cost-of-illness and the disease burden associated with Campylobacter infections and sequelae for the Netherlands in the year 2000, estimates of the annual incidence of Campylobacter infections and sequelae are necessary. In the Netherlands, Campylobacter infections are reported, along with other infectious diseases of public health importance, to a surveillance program (Van Pelt et al., 2003). Acute gastro-enteritis, however, is in general a relatively mild disease and only a small proportion of patients seeks medical care. Furthermore, only a minority of cases attending their general physician (GP) require microbiological testing, only some of which lead to a positive result. The result is a pyramid of sources for surveillance of a pathogen/illness (e.g. gastro-enteritis), as shown in Figure 2.1. Consequently, such surveillance systems are incomplete compared to the true incidence of illnesses such as gastro-enteritis and others occurring in the surveyed population (McCarthy and Giesecke, 1999). Apart from laboratory reports, outbreak reports, surveillance in general practices and population-based surveys there are other data sources that might be used to estimate the annual incidence of a disease. However, according to Havelaar et al. (2000a) each data source is biased, and consequently the data must be interpreted with care.

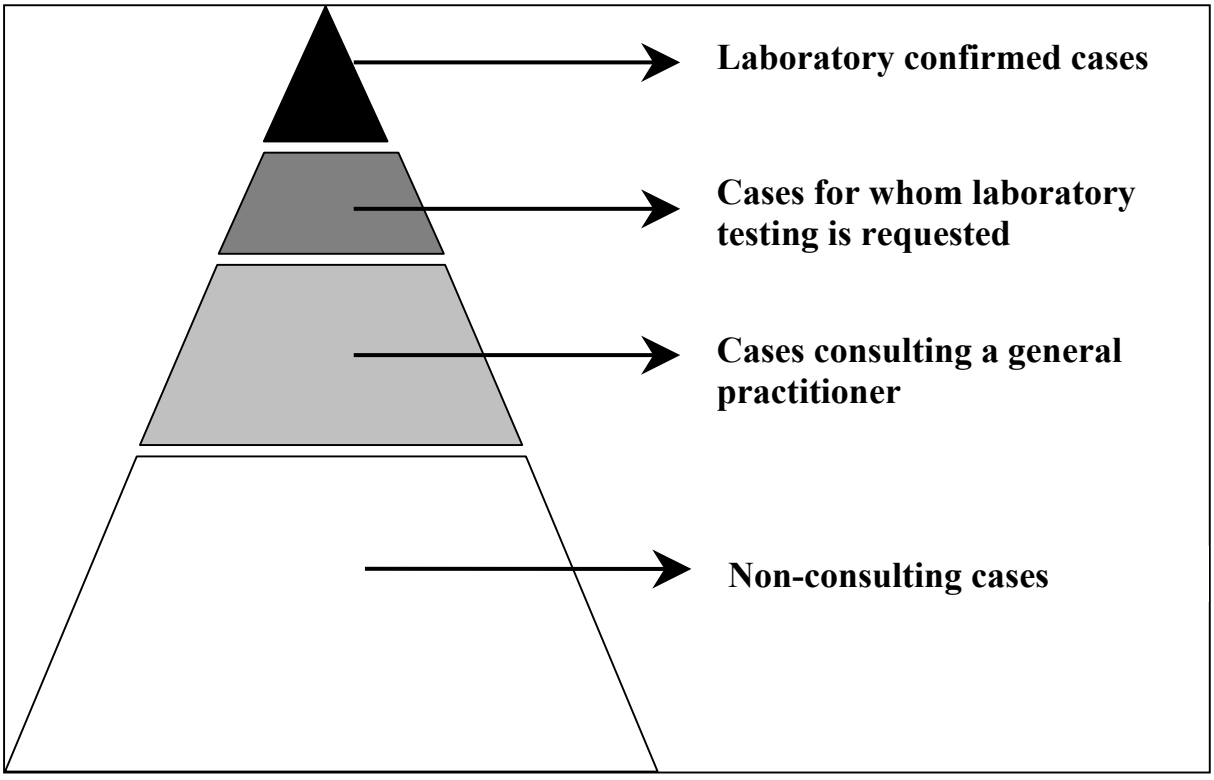


Figure 2.1. Pyramid of sources for surveillance of gastro-enteritis (Source: De Wit, 2002)

In this study we had to use different data sources in order to obtain the best possible estimate for annual incidences of acute gastro-enteritis (GE), ReA, GBS and IBD, respectively, all associated with Campylobacter infections. Specific details on the sources used in order to estimate the annual incidence for the different illnesses are given in the following Chapters.

2.2 Estimating annual disease burden and cost-of-illness

Although Campylobacter gastro-enteritis is generally a mild and self-limiting illness, symptoms can range from diarrhoea and lethargy, which lasts a few days, to severe diarrhoea and abdominal pain (and occasionally fever) that lasts for several weeks. For some cases, the Campylobacter infection is even fatal. Further, Campylobacter infections in humans can lead to serious ongoing sequelae (Anonymous, 2001; Wittenbrink, 2002), see Figure 2.2. Therefore apart of estimates on annual incidences, information on symptom severity and symptom duration is needed in order to estimate the disease burden and the cost-of-illness. Information on the assumptions made on symptom length and severity for the different illness and the different health states of illness, all associated with Campylobacter infections, is given in the following Chapters.

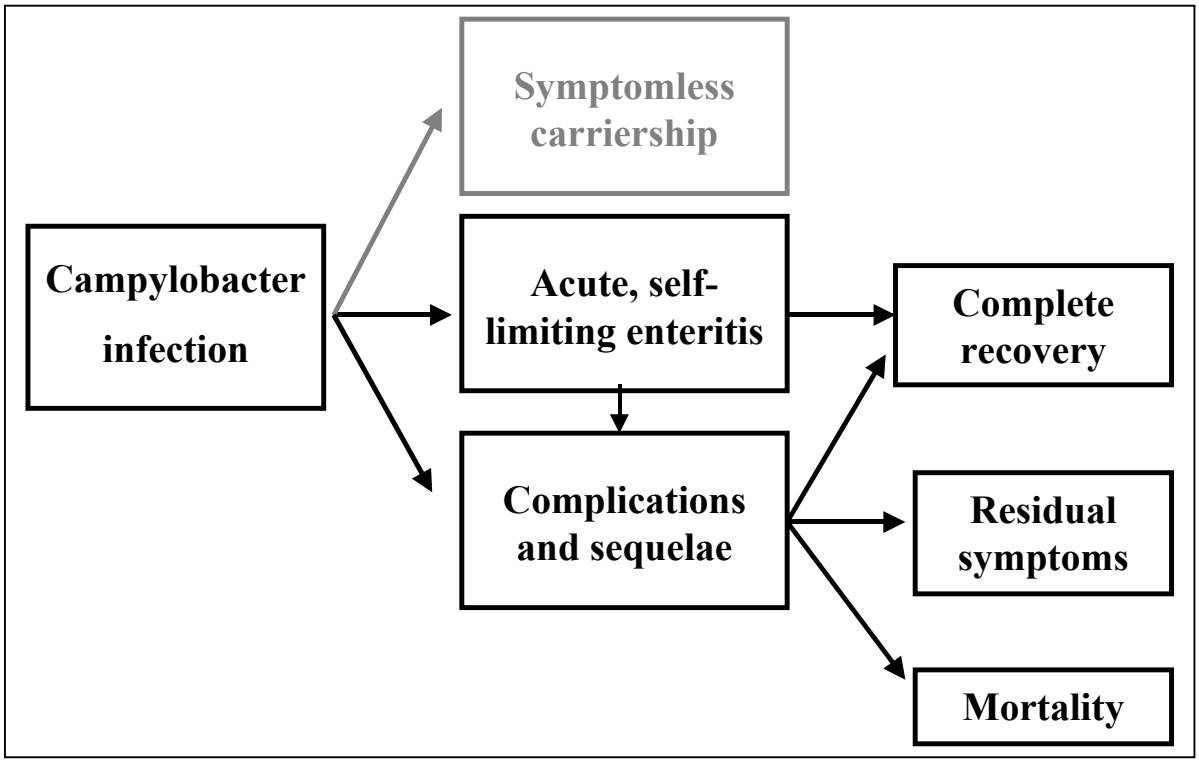


Figure 2.2. Campylobacter infection and the different illness and health states (based on Havelaar et al. (2000a)).

2.2.1 Annual disease burden (DALYs)

In order to estimate the annual disease burden, it was necessary to combine morbidity and mortality. One of the methods available to combine morbidity and mortality into one single metric unit is DALY (Disability Adjusted Life Years). The concept of DALYs aggregates the loss of health compared to 'perfect' health (Havelaar and Melse, 2003). DALYs is commonly used by the WHO to evaluate public health priorities. Further, many studies in different countries around the world are being conducted using DALYs (Lyttkens, 2003). In the Netherlands, the DALY methodology was used by the Dutch Public Health Forecasts study (Ruward and Kramers, 1997). This study estimated the disease burden in the Netherlands of 52 diseases as a combination of mortality and disability associated with these diseases.

The DALY methodology adds up the sum of years of life lost (YLL) and years lived with disability (YLD):

$$DALY = YLL + YLD$$

YLL is the number of years of life lost due to mortality. YLL is calculated by accumulation over all fatal cases and all diseases of the expected individual life span (e) at the age of death. Thus:

$$YLL = \sum_{\text{all diseases}} \sum_{\text{all fatal cases}} (e)$$

The first step in the DALY approach is then to also specify life expectancy. Within this study we use standard Dutch life expectancy for age and sex for the year 2000 as reported by Statistics Netherlands. A detailed description of the standard life table used is given in Appendix 6 of Havelaar et al. (2003).

YLD is the number of years lived with disability. YLD is calculated by accumulation over all cases and all diseases of the product of the duration of the illness (t) and the disability weight (w):

$$YLD = \sum_{\text{all diseases}} \sum_{\text{all cases}} (t * w)$$

Each health effect is weighted for its severity, with death as the most severe outcome (weight 1) and perfect health as the best outcome (weight 0). For each specific health effect, the disability weight (w) is then multiplied by the duration (t) of this specific health effect, and by the number of people affected by the particular outcome. The estimated burden of disease, attributable to one agent, is obtained by adding up all the health outcomes caused by this agent (Havelaar and Melse, 2003).

The DALY metric requires quantification of the value of different disease state relative to full health. Dutch disability weights are available from several sources. The disability weights used for IBD and ReA were obtained from Stouthard et al. (1997) and for GE and GBS disability weights were obtained from Havelaar et al. (2000a, b). Both are Dutch studies, and the second study followed the protocol described by Stouthard et al. (1997).

The disability weights used for the different disability states of Campylobacter infections and sequelae will be described in the following chapters. Also, information on duration of disability will be given in the various illnesses-specific chapters.

The estimated DALYs with regard to the different illnesses associated with Campylobacter infection are presented both discounted and not discounted. Applying a discount rate is generally used to account for the fact that health today is valued higher than health in the future, and for the fact that there is uncertainty about future possibilities to ‘better’ treat diseases.

2.2.2 Cost-of-illness

According to Hay and Hay (1992b) two different approaches are available to estimate costs of disease: the prevalence approach and the incidence approach. In the prevalence approach, illness costs are defined as ‘the stream of health care costs accruing to all patients alive during a specific time period’ (e.g., the annual disease costs for all IBD patients alive in 2000), taking into account the proportion of patients in each disease state during the specified

time period. ‘Under the incidence approach, the costs of disease are defined as the present discounted expected sum of current and future costs accruing to all incident cases of disease in a specific time period’ (e.g., the IBD incidence cohort of 2000), taking into account lifetime probabilities of transiting to each disease state (Hay and Hay, 1992b). Both methods produce the same results when aggregated across all patients and time periods. In order to estimate the costs associated with Campylobacter infections and sequelae, we mainly used the incidence approach in this study.

Following the guidelines of Oostenbrink et al. (2000), we estimate the cost-of-illness associated with Campylobacter infections and its sequelae for Dutch society as a whole. In our cost-of-illness study we consider direct health care costs and direct non-health care costs as well as indirect non-health care costs associated with Campylobacter infections and its sequelae, using cost estimates for the year 2000. The considered direct health care costs included such costs as doctor consultations (specialists and generalists), hospitalisation, drugs, rehabilitation and other medical services. Travel costs of patients and any co-payments by patients for costs such as informal care, if available, were considered as direct non-health care costs. Indirect non-health care costs, which are defined as the value of production lost to society due to disease, are considered. Production losses can be the consequences of: a) temporary absence from work; b) disability; and c) premature mortality. We estimated the productivity losses that occur due to sickness leave of sick people, and, where available, information on third persons taking care of patients. In accordance with the guidelines of Oostenbrink et al. (2000), this study does not consider ‘potential’ indirect health care costs. Indirect health care costs are the future costs of health care in life years gained through current medical intervention.

Studies that estimate indirect non-health care costs often use the human capital approach. The human capital approach estimates the value of *potential* lost production (or the potential lost income) as a consequence of disease. In the case of permanent disablement or premature death at a specific age the total productivity value (or income) from that age until the age of retirement is counted as productivity losses. But the real production losses for society might be smaller (Koopmanschap et al., 1995). In this study we therefore apply the friction cost method to estimate the indirect non-health care costs. In this method, production losses (indirect non-health care costs) are only considered for the period needed to replace a sick, invalid or dead worker, or ‘friction period’ (Koopmanschap et al., 1995; Koopmanschap and van Ineveld, 1992). The friction cost method takes into account the economic processes whereby a sick, invalid or dead person can and will be replaced after a period of adaptation (Koopmanschap and van Ineveld, 1992). The length of the friction period depends on the situation on the labour market. A high unemployment rate generally allows fast replacement of a sick, invalid or dead person, whereas in the case of a low unemployment rate, on average more time is needed to find someone on the labour market that could fill in the position of a sick, invalid or dead person. The unemployment rate in 2000 was comparable to the one in 1998. Using the estimated friction period of Oostenbrink et al. (2000) for the year 1998, we assume for the year 2000 a friction period of 123 days.

The estimations of the costs-of-illness for the different illnesses and the different health states are described in more detail in the following chapters. Results will be presented both discounted and undiscounted.

2.3 General modelling approach

Within this study we used the same modelling approach as Havelaar et al. (2003), who give a full description of the modelling approach. We therefore give here only a summary of the general modelling approach.

The formulas for disease burden and cost-of-illness are shown in basic notation:

Disease burden

Disability burden: $YLD = N \times t \times {}^{w}\!/_{365}$ (healthy life years per year)

where: Incidence of illness N (cases per year)
Duration of symptom t (days)
Disability weight w

Mortality burden: $YLL = d \times e$ (life years per year)
where: Incidence of death d (cases per year)
Expected life span at the age of death e (years)

Cost-of-illness

Direct health care costs: $DHC = \sum_i m_i \times p_i \times c_i$

where: Cases using medical service i m_i; for i = 1 to n
# of medical service i/case $p_{i;}$ for i = 1 to n
Cost/medical service i $c_{i;}$ for i = 1 to n

Direct non-health care costs: $DNHC = \sum_j r_j \times q_j \times c_j$

where: Cases using non-medical service j r_j; for j = 1 to n
# of non-medical services j/case $q_{j;}$ for j = 1 to n
Cost /non-medical service j c_j for j = 1 to n

Indirect non-health care costs: $INHC = s \times u \times v$
where Cases of sickness leave s (cases per year)
Duration of sickness leave u (days); maximum 123 days per episode
Wage costs per day v (age dependent)

The model used in this study to estimate the disease burden and the cost-of-illness associated with Campylobacter infections and sequelae is built in Excel, using the add-in software program @Risk version 3.5.2 (Pallisade Corporation, Newfield, NJ, USA). It is a second order stochastic model. Given that real-life data are often limited and/or absent, every model builder has to deal with some degree of uncertainty and methodological controversy (Drummond et al., 1997). Total uncertainty is broken down into variability and uncertainty (Vose, 2000). Variability is defined as 'the inherent heterogeneity of a system'; e.g. variations in the length of the hospital stay of different patients. Uncertainty is usually defined as 'a lack of perfect knowledge about a factor in the model that represents the system' (Vose, 2000). Variability cannot be reduced. However, with the availability of more information on a system, the uncertainty might be reduced. For example the incidence of

illness is not known but is estimated from observational data on a sample of the population. The uncertainty in the incidence rate can be represented by a statistical distribution. The mean or median of this distribution represents our best estimate of the true incidence rate, whereas the range between e.g. the 5th and 95th percentile represents our uncertainty about the true incidence. Any value that is sampled from this distribution represents one possible value of the true incidence rate, and it can be used as an input for a simulation of the variability of the disease burden over the years (Havelaar et al., 2003).

But not only is the incidence of illness uncertain, other parameters are as well. In this study we accounted for the uncertainty and variability for parameters describing the infection incidence, the illness duration and severity of campylobacteriosis and secondary sequelae. However, with regard to the costs/unit for the different cost categories to be considered in the estimation of the cost of illness and the estimates about the disability weights, costs/unit and weights/case will be considered as 'given', using their 'best guess', despite their uncertainty. For example, this means that the volumes of health care use are being treated as variable and uncertain, while costs/unit are regarded as 'given'. The different distributions used to describe uncertainty and variability of the different parameters will be described in each of the following disease-specific chapters, and are summarised in Appendix V.

According to Vose (1997) sensitivity analysis might be applied for the 'scenario uncertainty' (e.g. descriptive errors, aggregation errors, etc.) and/or model uncertainty (e.g. uncertainty due to necessary simplification of real-world processes, miss-specification of the model structure, etc.). By performing sensitivity analysis, we might identify those 'parameters' that are of most influence on the obtained results and conclusions, and also be able to quantify the extent of their influence. In this study we will pay special attention to the parameters for which a possible change in parameter values might result in a different conclusion of our study.

In order to reach the point where the percentile values for all defined outputs did change less than 1.5%, our convergence criteria, 1100 iterations were necessary. In order to account for uncertainty and variability, we run the model with 250 simulations and 1500 iterations per simulation. The time needed to run the model at least once was more than 24 hours. When doing sensitivity analysis, we therefore decided to apply only 1 simulation with 1500 iterations, using the average of uncertain parameters.

2.4 Presentation of results

The model parameters used in this study are often uncertain or are variable or both. Results were therefore not only presented as averages but attendant uncertainty and/or variability was shown as well.

A useful way to represent the output data is by a cumulative distribution plot. Figure 2.3. shows such a cumulative plot of, for example, the estimated incidence of campylobacteriosis cases in the Netherlands. The lines in the graph show the interpretation of this plot. 50% of all output data is less than or equal to the corresponding value on the x-axis. In this way, any percentile can directly be read from the plot. The dotted lines in Figure 2.3 indicate the estimated 5th and 95th percentile, and the arrow between both points represents the attendant uncertainty range (90% confidence interval) of the estimated average.

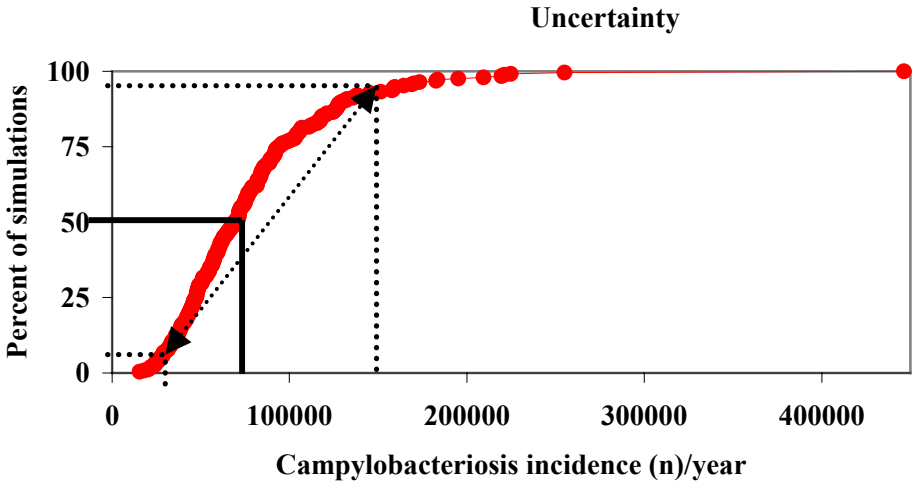


Figure 2.3. Estimated cumulative probability of annual incidence of campylobacteriosis cases.

In the graphs such as shown below, we see 4 different cumulative frequency distributions. The red diamonds represent the uncertainty in the mean disease burden, as in the figure above. The additional information in the graph represents the variability in the disease burden, that would be observed if the population would be observed for several years. This variability is less important from a decision making point of view. We have therefore chosen to present only the uncertainty in the mean burden (or cost) in the summary tables. For a more detailed description see (Havelaar et al., 2003).

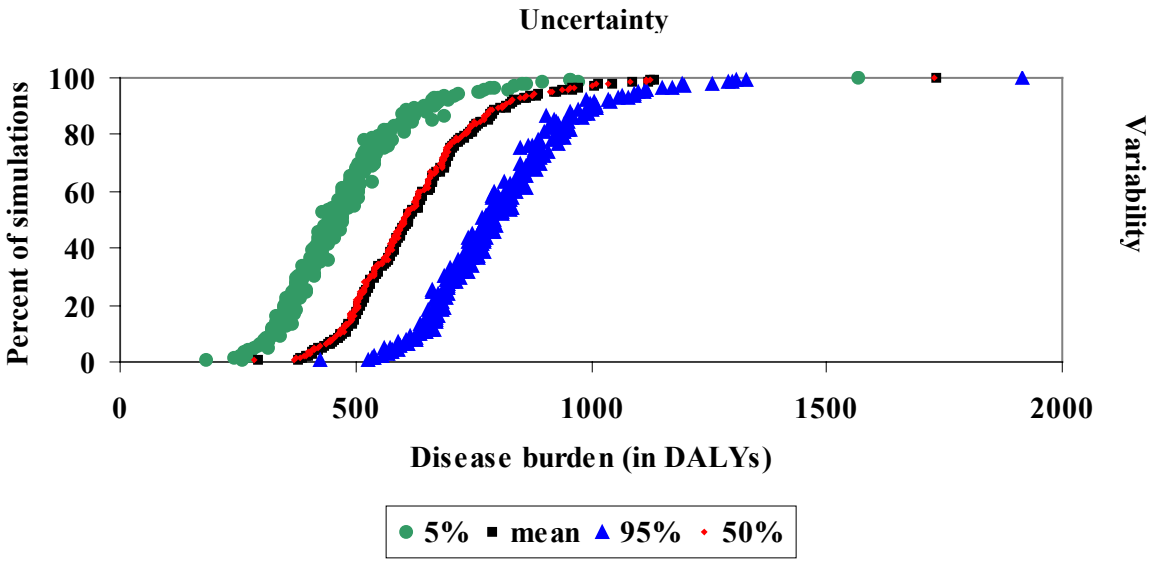


Figure 2.4. Cumulative distribution of the mean , 5th, 50th and 95th percentile of the estimated disease burden (example), breaking down the total uncertainty into variability and uncertainty.

3 Campylobacter-associated gastro-enteritis cases*

3.1 Background information

As already mentioned in the general introduction, Campylobacter is the most commonly reported bacterial cause of acute gastro-enteritis in the industrialised world (Williams, 1999; Rodrigues et al., 2001; Wittenbrink, 2002). For the most part, Campylobacter gastro-enteritis (GE) is a mild and self-limiting illness (Withington and Chambers, 1997). But for some cases, campylobacteriosis is fatal (Havelaar et al., 2000b). In the Netherlands, with approximately 100,000 cases of acute gastro-enteritis annually, Campylobacter pose a serious public health problem (Havelaar, 2002; Havelaar et al., 2000a, b).

Most campylobacteriosis cases are sporadic cases and outbreaks are rarely identified (Withington and Chambers, 1997). Farm animals, wild animals and pets are the most important reservoirs of Campylobacter. From these reservoirs food products and the environment undergo continuous contamination, resulting in many pathways by which humans can come in contact with Campylobacter (Havelaar, 2002).

Different Campylobacter species exist. *Campylobacter jejuni* is the most common isolated Campylobacter species in faeces of patients with diarrhoea (Blaser, 1997). Only 5-10% of campylobacteriosis is caused by other Campylobacter species, e.g. *C. coli, C. lari, C. hyointestinalis*, and others (Wittenbrink, 2002).

3.2 Estimating annual incidence of Campylobacter-associated GE cases

In order to estimate the annual incidence of GE associated with Campylobacter infection, including the different health states of campylobacteriosis patients, we used a variety of available data sources. The estimate of the total annual incidence in the population was based on a recent community-based cohort study known as the SENSOR study (De Wit et al., 2001c). The number of campylobacteriosis patients consulting a GP was based on General Practice (GP)-based research (De Wit et al., 2001a). Laboratory surveillance data was used to estimate: a) the number of laboratory-tested faeces samples; b) the number of hospitalised cases; c) the number of fatal cases, this in combination with the findings of Helms et al. (2003); and d) the age-specific incidences (Van Pelt et al., 2003).

The different health states of campylobacteriosis patients considered in this study are summarised in Figure 3.1.

* The authors acknowledge the support of the CIE group, namely Winette van Brandhof, Yvonne van Duijnhoven, Wilfrid van Pelt and Matty de Wit. Their data as well as their critical feedback was a valuable contribution to this study.

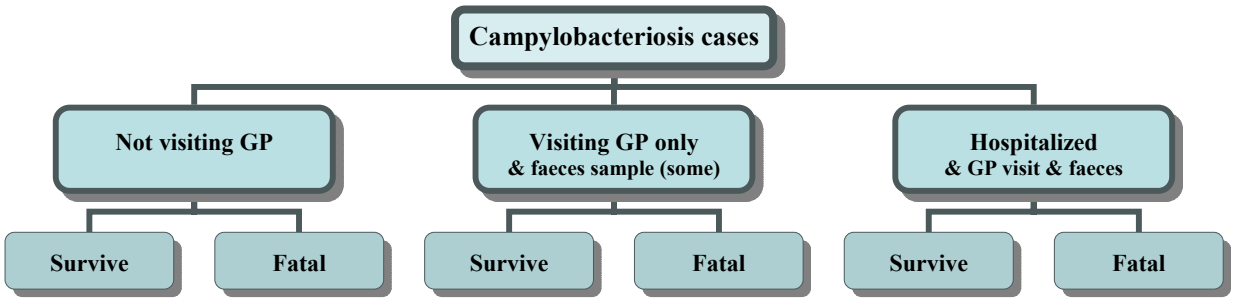


Figure 3.1. The different health states of campylobacteriosis patients.

3.2.1 Community-based cohort study

According to De Wit (2002) a community-based cohort study is the most appropriate method of obtaining information on the incidence of gastro-enteritis in the community. However, in order to obtain a sufficient number of cases, a large cohort has to be included. Consequently these studies are very expensive and time-consuming. A first population-based study on gastro-enteritis was performed in May, June and July of 1991 in four municipal health service regions in the Netherlands (Hoogenboom-Verdegaal et al., 1994). The estimated incidence of gastro-enteritis from this study was 450 episodes per 1000 person-years. Campylobacter as the triggering pathogen was detected in 4.6% of the cases, resulting in approximately 300,000 estimated campylobacteriosis cases/year for the Dutch population. A second Dutch community-based cohort study, the SENSOR study, was conducted from December 1998 to December 1999 (De Wit et al., 2001a). In the SENSOR study the standardised gastro-enteritis incidence was estimated at 283 per 1000 person-years. The number of gastro-enteritis episodes was much lower in the second study than in the first study, 283 versus 450 per 1000 person-years. According to De Wit (2002) and De Wit et al. (2001c) seasonal trends in pathogens causing gastro-enteritis make the interpretation of data covering only three months of the year (as was the case in the first Dutch study) very difficult. Other arguments to support a bias in this first study were the relatively high number of non-responses and the fact that the population-based cohort study could not be compared with other studies performed in Dutch general practices, as these were applied in other regions and at different time intervals (De Wit, 2002). In this study we therefore used only the findings of the second and more recent community-based cohort study of De Wit et al. (2001c).

De Wit et al. (2001c) detected Campylobacter as the triggering agent in only 1.3% of the gastro-enteritis episodes. This was a lower percentage than the 4.6% found in the previous cohort study by Hoogenboom-Verdegaal et al. (1994) or the 4.2% found in England by Tompkins et al. (1999). After standardisation De Wit et al. (2001c) obtained an estimated percentage of Campylobacter in gastro-enteritis episodes of 2.4%, resulting in approximately 100,000 campylobacteriosis cases/year in the Netherlands (assumed Dutch population 15.5 million). De Wit et al. (2001c) used 24 different age and sex classes when standardising. Because De Wit et al. (2001c) found only 9 Campylobacter isolates, we performed a re-standardisation with only the 6 age classes, mainly because otherwise, there would be subgroups with no observed cases. The re-estimated percentage was, at 1.7%, below the estimate of De Wit et al. (2001c) and resulted in an estimated annual average incidence of approximately 78,800 campylobacteriosis cases for the Netherlands, with a 95% C.I. of 28,231 and 168,792 (see Appendix I). The uncertainty of the estimated annual average

campylobacteriosis incidence is considered in this study. Further details on the re-standardisation can be found in Havelaar et al. (2003).

3.2.2 GP-based research

The Netherlands Institute for Health Services Research (NIVEL) maintains a network of 'sentinel' general practices that participate in the continuous morbidity registration. Gastro-enteritis (GE) was included in the continuous morbidity registration in 1992-93 and from 1996 onwards (De Wit, 2002). Although this surveillance system provided information on consultations for the clinical syndrome gastro-enteritis, no information was obtained about the pathogens responsible (De Wit, 2002). Therefore additional information was collected in case studies in 1992 and 1993 by Goosen et al. (1996) and from 1996-1999 by De Wit et al. (2001a). Goosen et al. (1996) estimated an incidence of gastro-enteritis in general practices of 90 per 10,000 person-years and an incidence of campylobacteriosis in general practices of 11.7 per 10,000 person-years. De Wit et al. (2001a) estimated an incidence of gastro-enteritis in general practices of 79.7 per 10,000 person-years, which was a little bit lower than the one estimated by Goosen et al. (1996).

De Wit et al. (2001a) detected Campylobacter as triggering agent in 10.5 % of the gastrointestinal cases visiting a GP. This estimate falls between the 9.4% reported by Palmer et al. (1996) and the 12.2% reported by Tompkins et al. (1999), who conducted similar studies for Wales and England. But we re-estimated the number of campylobacteriosis cases in the Dutch population (see Appendix I). Consequently the estimate of Campylobacter as the triggering agent within the GP-consulted gastro-enteritis cases decreased from 10.5%, the estimate of De Wit et al. (2001a), to 8.5%. This results in approximately 18,765 GP consultations per year.

Given that the number of GP consultations is strongly correlated with the number of campylobacteriosis cases in the total population, we estimated the fraction of campylobacteriosis cases that would visit a GP in the Netherlands. This was on average 23.8%. The uncertainty around this parameter was considered by using a beta distribution. This is less than found in the IDD study for England and Wales, in which it was estimated that nearly every second campylobacteriosis patient (47.1%) consulted a GP (Anonymous, 2000c; Wheeler et al., 1999).

3.2.3 Laboratory-based surveillance systems

Faecal samples tested

Despite their incompleteness, laboratory-based surveillance systems provide data on a continuous basis, which allows the monitoring of trends in the different pathogens (De Wit, 2002; Van Pelt et al., 2003). In the Netherlands, a laboratory-based surveillance system exists for the bacterial pathogens Salmonella, Campylobacter, Yersinia, Shigella and *E. coli* O157, and a separate one for rotavirus (De Wit, 2002). From the annual submitted faecal specimens between 1996 and 2000 3.46% were Campylobacter isolates in the 15 participating regional Public Health Laboratories (PHL), resulting in an estimated average annual number of laboratory-tested positive Campylobacter cases in the Netherlands of 5650 (Van Pelt et al., 2003).

Age-specific incidences

Based on the observations from 1996 until 2000 of 2 PHLs (approximately 6.4% of the population), age-specific incidences for *Campylobacter spp*. were derived (Van Pelt et al., 2003). Incidences were highest among very young children (0-4 years of age), followed by young adults (15-29 years of age). Incidence gradually decreased in those over 30 years of age (Van Pelt et al., 2003). In the youngest age group (0-4 years), 30% more males were found than females, but 60% more females were found in the age class 15-29 years (Van Pelt

et al., 2003). The age-specific incidences of gastro-enteritis cases found in the laboratory surveillance were similar to those found by NIVEL. Therefore, it was assumed that the age-specific incidences found within these 2 PHLs were representative for the Netherlands. Age-specific incidences found in the laboratory surveillance were assumed to be representative for the age-specific incidences of campylobacteriosis patients not visiting a GP, campylobacteriosis patients visiting a GP and hospitalised campylobacteriosis patients.

Hospitalised cases

Although the National Medical Register (NMR) collects data on hospital discharge diagnoses from all hospitalised patients in the Netherlands, campylobacteriosis cases are registered in a collective group of non-specified gastro-enteritis. Consequently, an estimation of hospitalised campylobacteriosis cases based on this register was not possible. However, for 2 of the 15 participating Regional Public Health Laboratories (approximately 6.4% of the population) data of the senders of Campylobacter-positive faeces are collected from 1992 (Heerlen) and 1993 (Arnhem) onwards (Van Pelt et al., 2003). In the years 1996-2000, 2442 faeces samples were positive for Campylobacter, of which 212, or on average 8.7%, were submitted by hospitals (Van Pelt, pers. communication). The uncertainty around the estimated 8.7% is estimated in this study by using the beta distribution (Beta (213, 2231)). Based on a standardised, population-based sentinel surveillance scheme, Gillespie et al. (2002) estimated that 10% of laboratory-confirmed campylobacteriosis cases would be hospitalised in England, which is a little bit higher than the estimated 8.7%. However, 8.7% of the laboratory-tested positive Campylobacter cases is equivalent with 0.6% of all campylobacteriosis cases. This is similar to the estimate of 0.6% and 0.5% used by Buzby et al. (1996) and Anonymous (2001), respectively.

Bacteraemia

In many reports is bacteraemia highlighted as a possible extra-intestinal complication of campylobacteriosis. Skirrow et al. (1993) found for England and Wales during the period 1981-1990 a total of 394 cases of Campylobacter-associated bacteraemia, which was, according to Pearson and Healing (1992), about 34 cases on average per year. Skirrow et al. (1993) estimated a bacteraemia incidence of 1.5 per 1000 reported campylobacteriosis cases. According to Pearson and Healing (1992) invasive Campylobacter infection was most common in patients more than 65 years old, and least common in those aged 1-14 years. There were ten (2.5%) deaths among the 394 patients. Most deaths were due to an underlying disease, such as a malignancy or heart disease (Skirrow et al., 1993). A variety of papers refer to this study (Kist, 2002; Smith, 2002). Another study in which the incidence of Campylobacter-associated bacteraemia cases was estimated is that of Schonheyder et al. (1995). From 1989-1994 twelve Campylobacter-associated bacteraemia cases were reported in Denmark, which was equal to an estimated incidence of 0.2 per 100,000 population-years. No information is available for the Netherlands.

The number of Campylobacter-associated bacteraemia cases in the Netherlands might be estimated from the number of Campylobacter isolates from blood samples. For 2 PHLs, Arnhem and Heerlen, data from the submitted material of Campylobacter positive isolates were collected from 1992 (Heerlen) and 1993 (Arnhem) onwards until 1998 (Van Pelt, pers. communication). From the 3230 collected samples in this time period, only six were blood samples, which is equal to less than 0.2% of all submitted and positive tested Campylobacter isolates. This is close to the findings of Skirrow et al. (1993). With an estimated average of 5650 annual laboratory-tested positive Campylobacter cases in the Netherlands (Van Pelt et al., 2003), this would be equal to about eleven Campylobacter-associated bacteraemia cases. This falls within the estimated range of Havelaar et al. (2000a), who estimated, based on the findings of Skirrow et al. (1993) and Schonheyder et al. (1995), that 9-54 Campylobacter-

associated bacteraemia cases would occur per year in the Netherlands, whereby the mortality would be less than one case per year.

Given the relatively low number of Campylobacter-associated bacteraemia cases we might, just as Havelaar et al. (2000a), assume that the public health burden due to Campylobacter-associated bacteraemia is relative small. Furthermore, bacteraemia patients fall within the number of estimated hospitalised campylobacteriosis-patients. In comparison to campylobacteriosis patients without bacteraemia, bacteraemia patients might require an intravenous application of antibiotics and/or a prolonged antibiotics cure, and as such slightly higher health care costs. However, all subsequent hospitalisation treatments are similar. Therefore, to avoid double counting, as well as for reasons of simplification, we will consider them in this study within the group of hospitalised campylobacteriosis cases. For these few patients the direct health care costs might be slightly underestimated due to the non-consideration of costs such as intravenous antibiotics.

Fatal cases

The mortality risk of campylobacteriosis cases is low, but significant in respect to disease burden. There is little information on Campylobacter-associated mortality. Estimates of campylobacteriosis cases that would be fatal, range from 0.05% to 0.005%. For example, Mead et al. (1999) assumed that 0.05% of the total estimated campylobacteriosis cases would be fatal. Based on the IID study conducted in 1995 in England, Adak et al. (2002) estimated that 0.025% of all campylobacteriosis cases in the population are fatal cases. Buzby et al. (1996) estimated that 2-6% of the hospitalised cases would die, which corresponds to 0.012-0.036% of all campylobacteriosis cases being fatal. Anonymous (2001) assumed that 1% of the hospitalised campylobacteriosis cases would die, which corresponds to 0.005%. Havelaar et al. (2000b) estimated that 0.01% of all campylobacteriosis cases would be fatal. The best data, however, were available from a Danish study.

In this study we therefore used the estimated relative mortality for patients with campylobacteriosis as obtained in the Danish study of Helms et al. (2003). Based on a registry-based, matched cohort study, Helms et al. (2003) estimated the excess mortality associated with infections with *Campylobacter* spp., *Salmonella* spp, *Yersinia enterocoliticica*, and *Shigella* spp. The authors collected data from the national registry of enteric pathogens, the Danish civil registration system, the national registry of patients, and the cancer registry between 1 January 1991 and 31 October 1999. For every patient, they randomly selected ten people matched for age, sex, and county of residence who were alive on the date the sample was received. The resulting estimated relative mortality for patients with campylobacteriosis within the first year after symptoms onset, correcting for co-morbidity, was 1.86 (range 1.56-2.20). Using age-specific mortality risks and age-specific incidences of two PHLs the estimated number of fatal cases was on average 28 with an uncertainty range from 20 to 37 (5^{th} and 95^{th} percentile). Thus, on average 0.038% of all campylobacteriosis cases would be fatal, an estimate that falls in the middle of the range of the above-mentioned studies.

3.3 Estimating disease burden due to Campylobacter-associated GE cases

According to the findings of the IID study in England, a Campylobacter infection was associated with relatively severe symptoms. In the GP component from the IID study, about 17% of adult cases had bloody diarrhoea, 92% had abdominal pain and 76% had a high temperature/fever (Anonymous, 2000c). This is also in accordance with De Wit et al. (2001a),

who reported that infection with Campylobacter species in a GP cohort study were more common in the group having high fever, having blood in the stool, having abdominal cramps and having a higher frequency of stools per day. From laboratory confirmed cases, it is also known that diarrhoea (95-98%), abdominal pain (76-88%) and fever (80-81%) are common in Campylobacter-infected patients, and about 1/3 of these patients also report bloody diarrhoea, apart from other symptoms (Kapperud et al., 1992; Gillespie et al., 2002; Locht and Krogfelt, 2002; Hannu et al., 2002). Similar findings are also reported for Campylobacter infections in the community component of the IID study (Anonymous, 2000c). But Campylobacter infected patients not only have more severe symptoms, but also the duration of the illness is longer for bacterial infections than for viral infections (Anonymous, 2000c).

The number of patients with Campylobacter infections found in the population-based cohort study of De Wit et al. (2001c) was with nine cases too small to use as base to estimate the disease length according to symptom severity, without risking great uncertainty in the results. In the English IID study, which was conducted in the years 1993-1996, Campylobacter was identified 32 times as the triggering agent in the cohort component and 353 times in the GP case control component (Tompkins et al., 1999). Furthermore 23 of the 32 campylobacteriosis patients of the cohort component and 192 of the 353 campylobacteriosis patients in the GP case control component resubmitted the socio-economic questionnaire (Anonymous, 2000c; Roberts et al., 2003). Therefore, the English IID study was one of the most complete studies that we could identify in the literature. We therefore based our assumptions of symptom length and sickness leave length on their findings, according to the different health states of campylobacteriosis patients.

3.3.1 Duration of illness

The effect of illness due to a Campylobacter infection on the person who was ill as reported for the GP component and the community component in the English IDD study are summarised in Appendix II. For our study, however, we wanted to know what would be the effect of illness due to a Campylobacter infection on the person who was ill and a) did not visit a GP; b) did visit a GP but was not hospitalised; and c) did visit a GP and was hospitalised. Although, the English IDD study is one of the most complete studies found in the literature, this information was not given as such. We therefore had to adapt the study results slightly in order to obtain the necessary information. We assumed that patients visiting a GP, hospitalised or not hospitalised, would have the same overall mean for the period ‘at home because of the illness’ and the period ‘feeling ill but able to do normal daily activities (work/school/shops)’, as shown in Appendix II. However, hospitalised patients would have on average an additional 4.67 days of illness before recovering (for details see Appendix II). This resulted in average illness duration of 9.72 days for campylobacteriosis patients visiting only a GP and an average illness duration of 14.39 days for hospitalised campylobacteriosis patients. The English IDD study found that approximately 47% of all campylobacteriosis cases would visit their GP (Anonymous, 2000c). Based on this estimate, we then calculated the average duration of illness of campylobacteriosis patients not visiting a GP to be 3.22 days. Based on 6,948 laboratory-confirmed campylobacteriosis cases Gillespie et al. (2002) estimated that the duration of illness for campylobacteriosis cases would be 11 days. This estimate falls in between our assumed duration of illness for patients visiting a GP only (9.72 days) and for hospitalised patients (14.34 days). Information on the duration of illness for patients not visiting a GP as a separate group, however, was not available in the literature. We therefore will perform some additional sensitivity analysis in order to define the impact of the assumed duration of illness for patients not visiting a GP on the estimated disease burden.

For each fatal case the age at death is simulated and the expected life span is sampled from the standard life table as reported by Statistics Netherlands for the year 2000. No distinction between men and women was made. The expected life span is equal to the years of life lost due to the premature death. For further model details see Appendix 6 in Havelaar et al. (2003).

3.3.2 Disability weights

Specific disability weights for Campylobacter-associated GE and the different health states are hard to find in the literature. Within this study we therefore will use those defined and applied by Havelaar et al. (2000a, b). The disability weight per illness and per case used, the estimated average years lived with disabilities per illness and per case and the average estimated annual disability weight per case are summarised in Table 3.1.

Table 3.1. Disability weight (annual profile), duration of illness (years) and yld/episode/year for campylobacteriosis patients not visiting a GP, visiting a GP only and being hospitalised, respectively.

	Campylobacteriosis patients		
	not visiting GP	visiting GP only	hospitalised
Disability weight/case (annual profile)	0.067	0.393	0.393
Duration of illness (years)	0.009	0.027	0.039
Disability weight/case/year	0.0006	0.010	0.015

The disability weight for fatal cases is equal to 1. Hence, the sum of years of life lost is multiplied by 1, resulting in the disease burden associated with premature death due to Campylobacter-related gastro-enteritis.

3.4 Estimating cost-of-illness due to Campylobacter-associated GE cases

3.4.1 Direct health care costs

The only direct health care costs of patients not visiting a GP are those for over-the-counter medicines. Patients visiting a GP, whether hospitalised or not, also use over-the-counter medicines. But apart from these medicines, patients might also have a prescription from their doctor for antibiotics or the like. Hardly any information was available on the drug use for campylobacteriosis patients, neither over-the-counter medicine nor other drugs. We therefore based our assumptions on the findings from the SENSOR study, in which data on the drug use in the Netherlands of gastro-enteritis cases not visiting a GP and gastro-enteritis cases visiting a GP were collected (Van Den Brandhof et al., 2004). The percentage of patients using medicines is summarised in Table 3.2. The uncertainty for each of these point estimates was considered with the help of beta distributions (Appendix V).

Table 3.2. Percentage of patients not visiting a GP and patients visiting a GP, respectively, using painkiller, ORS, anti-diarrhoea, antibiotics and other medicines.

	Over-the-counter medicine			Prescription medicine	
	Painkiller	ORS	Anti-diarrhoea	Antibiotics	Others
Not visiting a GP	31%	5%	5%	n.a.	n.a.
Visiting a GP	59%	33%	5%	27%	14%

For patients visiting a GP we assumed one GP consultation/case. For some cases, a faecal sample is submitted for laboratory testing in order to determine the triggering agent. We assumed that for each hospitalised patient a faecal sample was always submitted for laboratory testing. Subtracting the estimated hospitalised campylobacteriosis cases from the total number of estimated laboratory-tested positive campylobacteriosis cases, we obtained the number of laboratory-tested positive campylobacteriosis cases within the group of patients that visited only a GP.

In the Dutch public health system where the GP is the 'gatekeeper', hospitalised patients were assumed to have visited their GP first before being transferred to a hospital. The average hospital stay was assumed to be 5.9 days, according to the reported average length for 'other (bacterial) foodborne diseases' in the year 2000 (Prismant, 2003). Campylobacter infections were one of the possible bacterial foodborne illnesses registered within this category. Based on the total number of Dutch hospital beds, we assumed that approximately 14% of the patients would be admitted to a university hospital and 86% would be admitted to a general hospital (Oostenbrink et al., 2000). According to the Dutch system, we calculated for each patient admitted to the hospital a 'short subscription'[1] for an internist specialist. The different costs assumed per medical unit are given in Table 3.3. For most medical services we used the cost estimates of Oostenbrink et al. (2000) and updated them to the year 2000.

Table 3.3. Cost estimates per medical service unit (year 2000)

Medical service	Costs/unit (in €)	Source
GP visit	17.8	Oostenbrink et al. (2000)
Faecal sample	62.3	Van Den Brandhof et al. (2004)
University hospital/day	354.9	Oostenbrink et al. (2000)
Regular hospital/day	252.5	Oostenbrink et al. (2000)
'Short subscription fee' for an internist	25.6	Anonymous (2000a)

We did not calculate the direct health care costs for fatal cases separately. These patients were already considered in one of the other sub-groups of campylobacteriosis patients.

3.4.2 Direct non-health care costs

In our study we assumed that no additional travelling was required in order to buy over-the-counter medicines. Further, medicines on prescription will be bought in a pharmacy. However, this will generally be done on the way back from the GP. Therefore additional travel costs were not considered here. Travel costs were considered when visiting a GP and when being hospitalised. According to Oostenbrink et al. (2000) the average distance from a patient's home to GP in the Netherlands is approximately 1.8 km and from a patient's home to hospital approximately 7 km. The cost of travelling with public transport or private car was assumed to be approximately € 0.12/km in 2000. The cost of travelling by car or public transport in order to visit a GP is estimated to be € 0.44 /visit, and travelling to a hospital/specialist is estimated to cost € 1.70/visit. However, no information was available about what transport services patients might use. Given the severity and given the longer

[1] In the Netherlands, apart from their consultation fee and their medical services specialists charge their patients a so-called 'subscription fee'. This could be either a 'short subscription fee' or a 'yearly subscription fee.' The short subscription fee, which for most specialists is valid for about 2 months, and if patients return after those 2 months a 'additional subscription fee' is charged which is then valid for the rest of the year. Patients who need treatments from specialists over a longer period are charged the yearly subscription fee. These 'subscription fees' vary from specialist to specialist. However, only one specialist is allowed to charge these subscription fees per illness. A second specialist involved in the treatment of the illness can only charge what is referred to as a 'clinical subscription fee', which is less than the normal subscription fee. For more details see Anonymous (2000b).

distance, we therefore assumed that hospitalised patients would always use either a car or public transport, while for patients visiting their GP, we did assume that most likely half of the patients would bike or walk, whereas the other half would take a car or public transport, following the assumption made by Van Den Brandhof et al. (2004). However, given the uncertainty of this assumption we included a Perth distribution with 50% being the most likely, and 10% and 90% the minimum and maximum estimates.

There was also no information available on the time spent off work in order to visit a GP. Given uncertainty, we applied a uniform distribution in order to estimate the time spent off work, ranging from 0 to 0.25 days/consultation for a GP.

No information was available on informal care, for example time costs of a neighbour taking care of the sick child. Therefore no additional costs were considered here.

3.4.3 Indirect non-health care costs

In order to determine the indirect non-health care costs, we had to determine the duration of sickness leave for the different patient groups. In our study we estimated productivity losses due to absence from work of sick persons as well as of third persons taking care of sick persons.

The assumed effect of illness due to a Campylobacter infection on the person who was ill and did not visit a GP, did visit a GP but was not hospitalised, and did visit a GP and was hospitalised, was 3.22, 9.72 and 14.39, respectively. Details are given in section 3.3.1. The effect of illness is composed of a period in which patients are at home because of the illness, and a period in which patients feel ill but are able to do normal daily activities (work/school/shops). The duration of sickness leave corresponds only to the length of the period in which patients are at home because of the illness.

Only nine campylobacteriosis cases were observed in the Dutch population-based cohort study of De Wit et al. (2001c). We therefore based our estimates, just as for the assumed effect of illness, on the English IID study conducted in the years 1993-1996. Based on the English IDD study, we assumed that patients visiting a GP, hospitalised or not, would on average feel sick 1.81 days but in that time they would be able to do their daily activities (Anonymous, 2000c). Due to a lack of data we assumed that for patients not visiting a GP this would be 0.91 days, which is equal to the overall mean obtained for campylobacteriosis patients in the community cohort of the English IDD study (Anonymous, 2000c). These 0.91 days were based on campylobacteriosis patients visiting and not visiting a GP (see Appendix II). However, if here we make the same calculation as we did it in order to obtain the duration of illness for patients not visiting a GP, then we obtain a Figure close to zero days, which we consider not realistic. In order to obtain the average duration of sickness leave for the different patient groups, we then subtracted the period in which patients felt sick but were able to do their daily activities from the total duration of the illness. The resulting average duration of sickness leave for the different patient groups were summarised in Table 3.4. Given the fact that we do know the age of the patients, but not whether they work or not, we calculated productivity losses for patients in the working life only. The assumed productivity losses per day per person used were based on the salary of an average ‘person’ in that age class. The applied productivity losses per day per average ‘person’ were based on Oostenbrink et al. (2000), and are summarised in Appendix III.

Table 3.4. Estimated duration of sickness leave for patients not visiting a GP, patients visiting only a GP, and hospitalised patients.

	Campylobacteriosis patients		
	not visiting GP	visiting GP only	hospitalised
Duration of sickness leave (in days)	2.31	7.92	12.59

The Dutch Sensor study investigated, depending on the age of the patients, the number of third persons that were absent from their work in order to take care of a sick person with gastro-enteritis (Van Den Brandhof et al., 2004). Within their study Van Den Brandhof et al. (2004) distinguished between patients that had visited a GP and those that had not visited a GP. However, only a few patients had visited a GP (68), and only six patients within this group were 12 years or older. We therefore decided to add both groups together, with as a consequence more observations per age group. We then estimated, depending on the age of the patient, the percentage of patients that needed a third person to be absent from his/her work in order to take care of the sick person (see Table 3.5). Using beta-distributions, we estimated the uncertainty around these point estimates (see Appendix V). We assumed the same duration of sickness leave of a third person taking care of a sick person, as would this be the case for the sick person herself. When calculating productivity losses for third persons being absent from work in order to take care of a sick person, we used the average salary of an average 'working person' (Appendix III).

Table 3.5. Estimated percentage of third persons being absent from their work in order to take care of a sick person, depending on the age of the patient.

Patients age groups	0-4 years	5-9 years	10-14 years	≥ 15 years
Percentage of patients needing care from a 3rd person	13%	19%	11.8%	5.2%

For fatal cases in the working life years (15-64 years), we assumed for each case a friction period of 123 days, implying that we consider productivity losses for the period needed to replace a deceased worker (Koopmanschap et al., 1995; Koopmanschap and van Ineveld, 1992). Given that these patients do not die on the first day of the onset of symptoms, the productivity losses for this group might be slightly overestimated.

3.5 Results

3.5.1 Estimated annual incidence of campylobacteriosis cases

The cumulative distribution of the estimated annual incidence of Campylobacter infections in the Netherlands is shown in Figure 3.2. The mean and the attendant uncertainty for campylobacteriosis cases and the different health states are summarised in Table 3.6. Only seven of the estimated average 28 fatal cases were younger than 65 years (results not shown). Most fatal cases are 65 years or older.

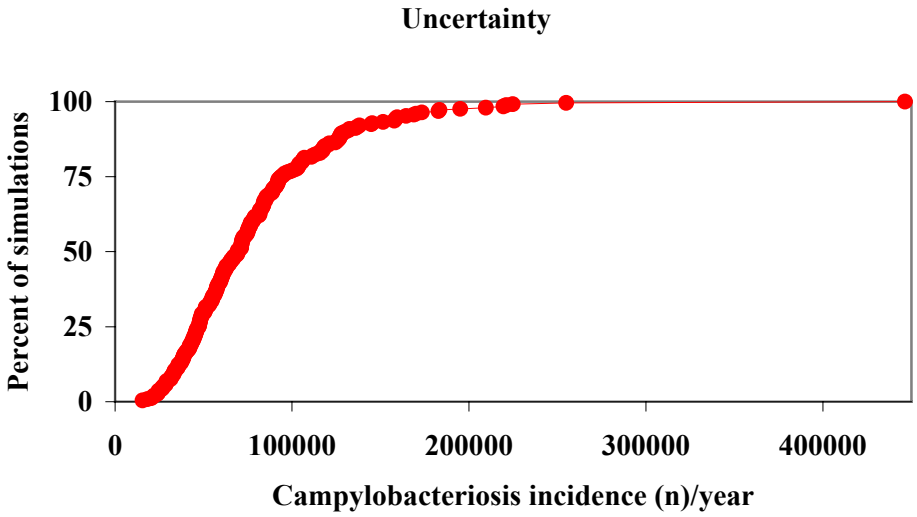


Figure 3.2. Cumulative distribution of the estimated annual incidence of campylobacteriosiscases in the Netherlands.

Table 3.6. Estimated mean and attendant uncertainty[1] of annual incidence of campylobacteriosis cases in the Dutch population, including the different health states of the disease.

	Estimated annual incidence in the Netherlands			
	5%	Mean	50%	95%
Total campylobacteriosis cases	27,924	78,785	69,298	162,219
Not visiting GP	21,244	60,031	52,663	123,732
GP visits only	6,180	18,261	16,227	38,757
Hospitalised cases	441	493	492	546
Fatal cases	20	28	27	37

[1)] The model parameters used in this study are often uncertain or are variable or both. We therefore not only show for example the average annual incidence but also the 5th, 50th and 95th percentile, representing the uncertainty in the estimated average.

3.5.2 Estimated disease burden due to Campylobacter-associated GE cases

Given the large number of Campylobacter-associated GE cases in the population the variability surrounding symptom length and symptom severity would average out. We therefore decided to use only averages in our study. The cumulative distribution of the estimated annual disease burden (DALYs) associated with GE cases is shown in Figure 3.3, breaking down the total uncertainty into a variability-related component and an uncertainty-related component. Results of YLL, YLD and DALYs, discounted and not discounted, related to the estimated annual number of GE cases are summarised in Table 3.7. In Figure 3.4 the average estimated DALYs are distinguished according to the different health states of GE cases considered in this study. Looking at Table 3.7 it becomes clear that the largest part of disease burden related to GE cases is due to life years lost (YLL), so to fatal cases.

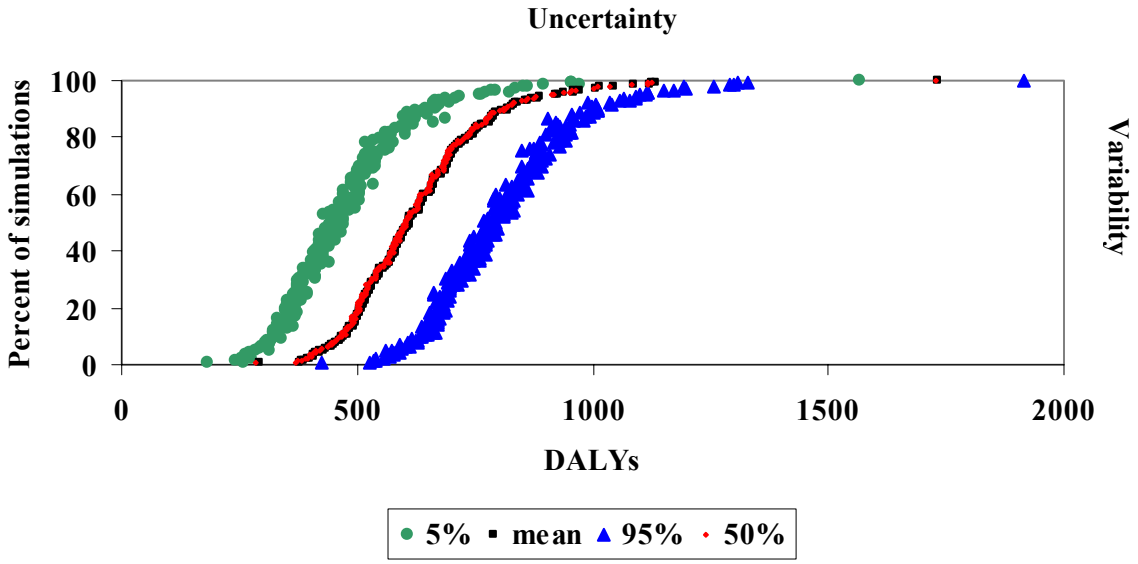


Figure 3.3. Cumulative distribution of the mean , 5th, 50th and 95th percentile of the estimated DALYs due to the annual number of Campylobacter-associated GE cases in the Netherlands, breaking down the total uncertainty into variability and uncertainty.

Table 3.7. Estimated mean and attendant uncertainty of YLL, YLD, DALY, discounted and not discounted, associated with the annual number of Campylobacter-associated GE cases in the Netherlands.

Description	YLD, YLL or DALY, respectively			
	5%	Mean	50%	95%
YLD (not discounted)	85	234	210	486
YLL (not discounted)	288	400	392	536
DALY (not discounted)	430	635	610	924
DALY (discounted with 4%)	323	499	469	776

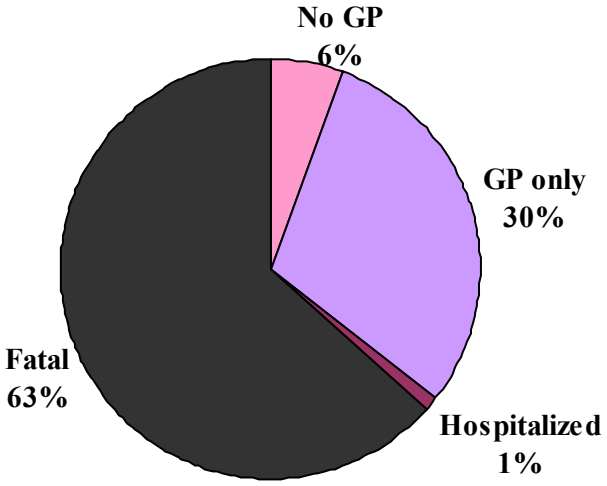


Figure 3.4. The estimated mean DALYs for GE patients not visiting a GP, GE patients visiting a GP, hospitalised GE patients and fatal GE cases, respectively.

3.5.3 Estimated cost-of-illness due to Campylobacter-associated GE cases

Given the large number of Campylobacter-associated GE cases in the population, the variability surrounding symptom length, duration of sickness leave and length of hospitalisation stay would average out. We therefore also used only averages here. The cumulative distribution of estimated cost-of-illness associated with GE cases is shown in Figure 3.5, breaking down the total uncertainty into a variability-related component and an uncertainty-related component. The mean and the attendant uncertainty of the estimated total cost-of-illness and the different cost categories associated with GE cases are summarised in Table 3.8. In Table 3.9, the estimated mean of the different cost categories is shown for the different health states of GE patients. Figure 3.6 shows the distribution of the total costs between the different cost categories.

Approximately half of the direct health care costs are incurred by patients visiting only a GP, whereas the other half of the direct health care costs are incurred by hospitalised patients. Direct health care costs for patients not visiting a GP are minor, while the group of patients not visiting a GP accounts for nearly half of the productivity losses. The other half of the productivity losses are due to sickness leave of GE patients visiting a GP. Given the relative low number of hospitalised patients, this group accounts only for approximately 2% of the productivity costs. Productivity losses due to fatal cases are minor. Reasons for this are: a) there are only a few fatal cases and most of them are older than 64 years; and b) we calculate only the friction period, which is equal to 123 days for fatal cases in the working life age.

Given that all costs occur within the first year, discounting of the costs is not needed in order to estimate the net present value (NPV).

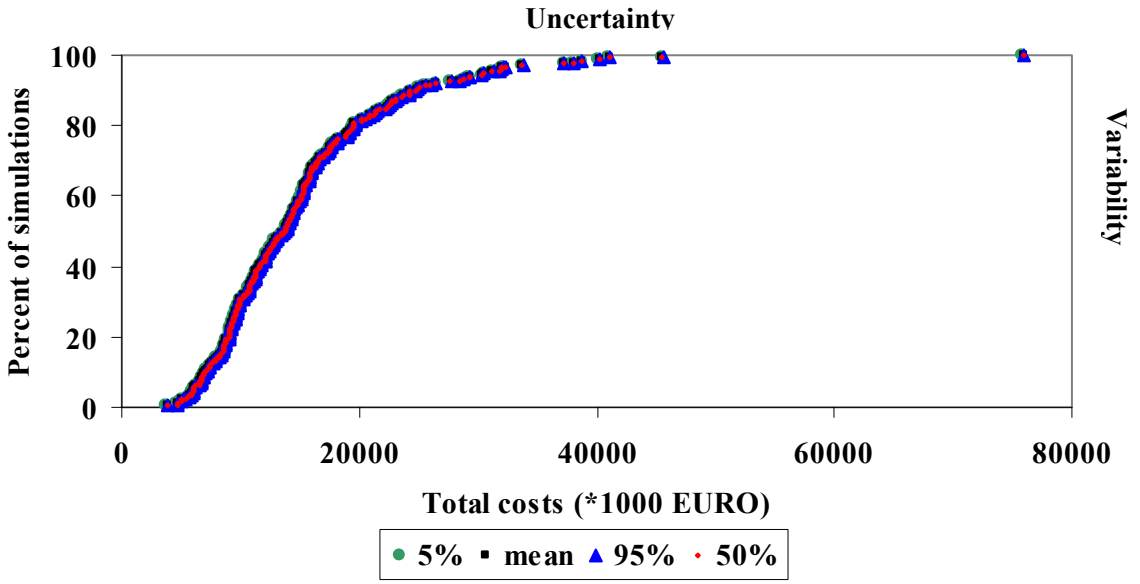


Figure 3.5. Cumulative distribution of the mean , 5th, 50th and 95th percentile of the estimated cost-of-illness due to Campylobacter-associated GE cases in the Netherlands, breaking down the total uncertainty into variability and uncertainty.

Table 3.8. Estimated mean and attendant uncertainty of the cost-of-illness due to Campylobacter-associated GE cases in the Netherlands (year 2000).

Description	Estimated costs (*1000 €)			
	5%	Mean	50%	95%
Direct health care costs	1,302	1,644	1,573	2,221
Direct non-health care costs	2	5	4	10
Indirect non-health care costs	4,800	13,490	12,152	28,769
Total costs	6,096	15,139	13,793	30,902

Table 3.9. Estimated mean total costs, direct health care costs, direct non-health care costs and indirect non-health care costs associated with all GE cases, GE cases not visiting GP, GE cases visiting GP only, hospitalised GE cases and fatal GE cases (year 2000)

Description	Mean costs/year (*1000 €)			
	Total costs	Direct health care costs	Direct non-health care costs	Indirect non-health care costs
GE cases	15,139	1,644	5	13,490
Not visiting GP	6,469	22	0	6,447
GP-visits only	7,520	798	4	6,725
Hospitalised cases	1,122	852	1	289
Fatal cases	42	n.a.	n.a.	42

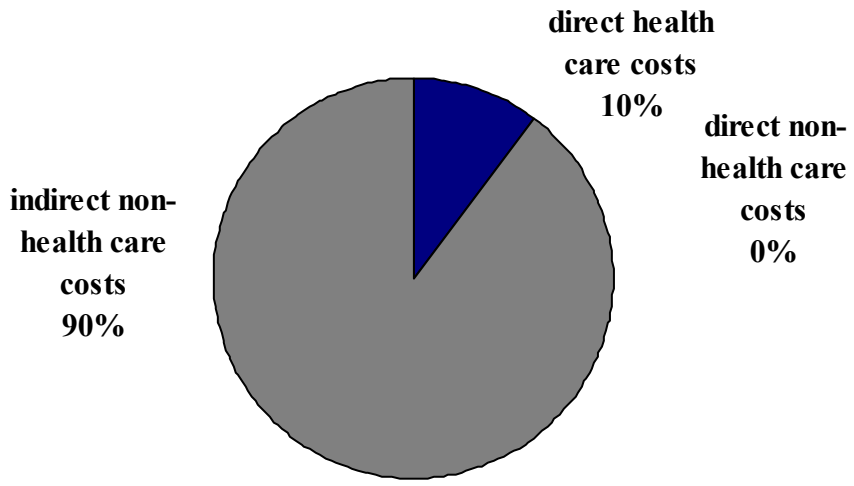


Figure 3.6. Distribution of the estimated mean cost-of-illness due to Campylobacter-associated GE cases between the different cost categories.

Finally, in Table 3.10, we calculated the estimated average costs for an 'average' Campylobacter-associated GE case and for the different health states.

Table 3.10. Estimated average costs for an average GE case in the population, GE case not visiting GP, GE case visiting GP only, hospitalised GE case and fatal GE case (year 2000).

Description	Estimated average costs/average case (€)		
	Direct health care costs	Indirect non-health care costs	Total costs
GE case in population	21	171	192
GE case not visiting GP	0.4	107	108
GE case visiting GP only	43	368	412
Hospitalised GE case	1,688	585	2,275
Fatal GE case	n.a.	1,516	1,516

3.5.4 Sensitivity analysis

Given our uncertainty on the effect of illness with regard to GE patients not visiting a GP, we did some additional sensitivity analysis. We assumed that the effect of illness would be 0.5 and 1 day longer and shorter than the assumed 3.22 days. The estimated average difference of DALYs and indirect non-health care costs associated with GE cases not visiting a GP are summarised in Figure 3.7.

A shorter or longer effect of illness of GE patients not visiting a GP has little impact on the estimated disease burden. But a shorter or longer effect of illness of GE patients not visiting a GP has a considerable impact on the estimated average indirect non-health care costs, and as such also on the estimated average cost-of-illness associated with GE in the Netherlands. A half a day shorter (or longer) effect of illness results in a half a day shorter (or longer) duration of sickness leave of GE patients not visiting a GP and being in the working age (15 to 64 years) with a decrease (or increase) of the average estimated cost-of-illness associated with GE cases by more than € 1 million.

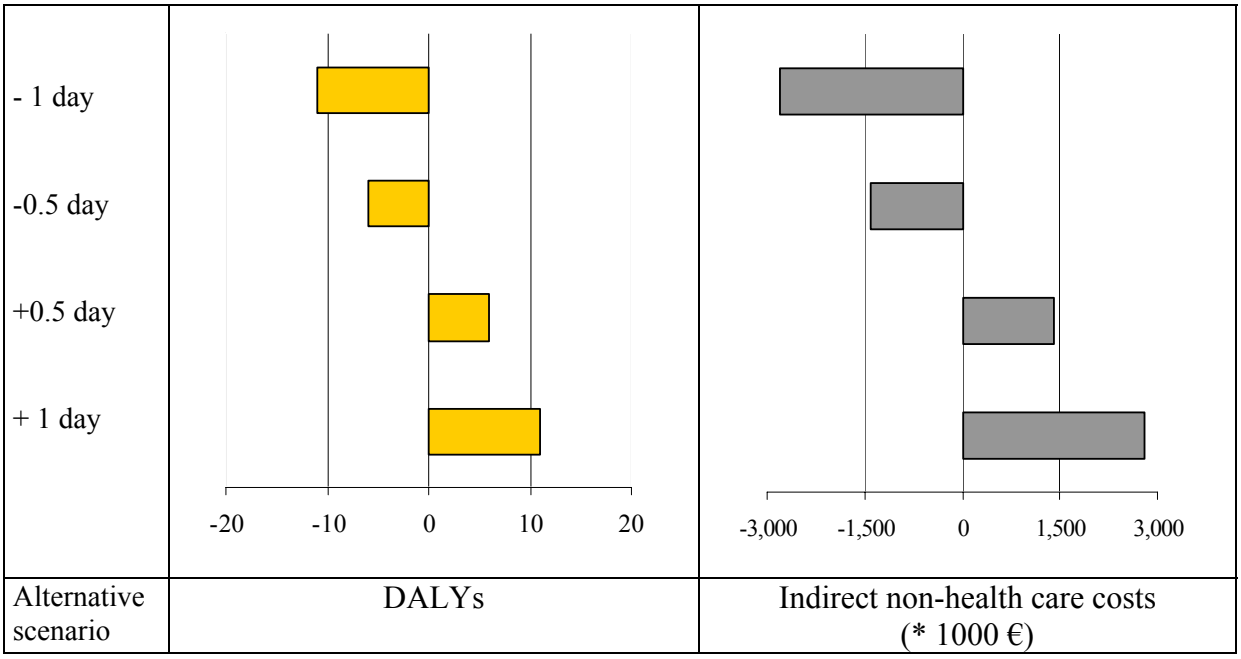


Figure 3.7. Estimated mean difference of DALYs and indirect non-health care costs associated with GE cases not visiting a GP, when assuming that the effect of illness of GE patients not visiting a GP would be 1 and 0.5 days longer and shorter than the assumed 3.22 days.

3.6 Discussion

In this study we used a lower estimate of the annual Campylobacter-associated GE cases in the Netherlands than did Havelaar et al. (2000a, b) in an earlier study. Despite this, our estimate of DALYs associated with campylobacteriosis is relatively close to the estimate of Havelaar et al. (2000a, b). The estimated number of fatal GE cases and the estimated YLL in both studies are comparable. The difference between both studies lies mainly in the estimated number of GE patients visiting a GP and not visiting a GP. The average number of estimated GE patients visiting a GP was in our study slightly higher than in the study of Havelaar et al. (2000a, b). This group accounted on average for 159 YLDs in the study of Havelaar et al. (2000a, b), whereas we obtained an estimated average of ~190 YLD. Although the number of GE cases not visiting a GP was much lower in our study, the higher estimated incidence of GE patients visiting a GP influenced the results enormously. Apart from the GE patients visiting and not visiting a GP, we also considered hospitalised GE patients in this study. These, however, accounted for only 8 DALYs (results not shown).

At € 15 million for the year 2000, the average estimated cost-of-illness is for the year 2000 slightly higher than the estimated average € 9 million in Van Den Brandhof et al. (2004) for the year 1999. Van Den Brandhof et al. (2004) did an estimation of the cost-of-illness associated with all gastro-enteritis cases in the Netherlands. The proportion of campylobacteriosis patients who did not consult a GP and the proportion of campylobacteriosis patients consulting a GP were determined based on the SENSOR study and the GP-study of De Wit et al. (2001a). The cost-of-illness associated with Campylobacter infection was estimated using the indirect method. This entailed that the costs for gastro-enteritis cases using the health care system was multiplied by the proportion of Campylobacter patients consulting a GP, resulting in € 4.8 million. Further, the costs for gastro-enteritis cases not consulting the health care system was multiplied by the proportion of Campylobacter patients not visiting a GP, resulting in € 4.4 million. The average number of annual campylobacteriosis cases was comparable in both studies. The difference between both studies is probably due to the assumed length of sickness leave. Van Den Brandhof et al. (2004) assumed that 23% of adult patients were absent for an average of 5 days, which is equal to an overall mean sickness leave of only 1.15 days per adult patients. But we assumed a longer sickness leave of adult campylobacteriosis patients (see Table 3.4).

Our estimate of the cost-of-illness due to Campylobacter infections was also far lower than the estimate of Bunte et al. (2001) for the year 1997. Bunte et al. (2001) based his assumption of the annual incidence of campylobacteriosis cases on the first community-cohort study conducted in the Netherlands with an estimated 7 million gastro-enteritis cases per year. From all gastro-enteritis cases he assumed that Campylobacter would be the triggering agent in 4.5% and 14%, resulting in 310,000 and 980,000 Campylobacter cases, respectively. The 4.5% was based on a community-based cohort. But the 14% was based on GP-based cohort, which is not necessarily representative for the whole population. The annual incidence of campylobacteriosis used was far higher than the one used in our study. Furthermore, Bunte et al. (2001) used the human capital method in order to estimate the indirect non-health care costs; therefore a comparison of the indirect non-health care costs is not possible. The assumption made in order to estimate the direct health care costs also differs from ours. The assumed costs per Campylobacter case visiting a GP are comparable in both studies. But the assumed costs for drug use/patients of Bunte et al. (2001) are far higher than ours. Bunte et al. (2001) used the average drug costs/patients of all enteritis and gastro-intestinal drugs declared in the health insurance system. First of all, not all of these drugs can be linked to gastro-enteritis only. And secondly, campylobacteriosis cases not visiting a GP might for

example use some over-the-counter drugs such as painkillers, but without a prescription from their doctor, which would be necessary for most other medicines, no other drugs. Therefore these costs seemed to be highly overestimated in Bunte et al. (2001). Furthermore, the hospitalisation costs also seemed to be overestimated. Bunte et al. (2001) related all hospitalisation costs where a gastro-enterologist was the consulting doctor for gastro-enteritis. But not all patients treated by a gastro-enterologist are enteritis patients.

Within our study the productivity losses are by far the largest part of the costs. Given the large number of GE cases not visiting a GP, even though these are the patients with the shortest sickness leave, it is not surprising that this group has the largest impact on the assumed productivity losses. If the assumed sickness leave would on average be a half a day longer or shorter, the productivity losses would increase or decrease by more than € 1 million. It is therefore crucial for future studies to get a better and more reliable estimator on the effect of illness and on the duration of sickness leave for this group of patients.

Given the fact that we considered the friction method, the estimated average cost per average campylobacteriosis patients is much lower than for studies using the human capital method. For example, Anonymous (2001) estimated the average costs/average campylobacteriosis patients to be USD 284 in 2000, whereas we obtained an estimate of € 192.

With on average approximately € 1700 /case, hospitalised GE patients are responsible for more than 50% of the total health care costs. Direct non-health care costs are only minor. Considering informal care might have resulted in slightly higher direct non-health care costs.

4 Campylobacter-associated reactive arthritis cases

4.1 Background information

4.1.1 General background information

The term reactive arthritis (ReA) was introduced in 1969 by Aho to describe an acute aseptic arthritis triggered by an infection elsewhere in the body, such as infections in the gut or in the urogenital tract (Yu and Thomson, 1994). In this sterile, reactive arthritis, elevated antibody levels to the triggering organisms are present in the host, but triggering organisms are not found in the affected joints and also no rheumatoid factor is present (McDowell and McElvaine, 1997). Triggering agents are mostly different sero-types of Salmonella, Yersinia, Shigella, Chlamydia and Campylobacter; (Hannu et al., 2002; Keat, 1983; Yu and Thomson, 1994), as well as Escheria species (Locht and Krogfelt, 2002). Infections associated with these agents appear to give rise to a number of chronic joint diseases which include reactive arthritis (ReA), Reiter's syndrome (RS) and ankylosing spondylitis (AS) (Bunning et al., 1988; McDowell and McElvaine, 1997; Raybourne et al., 2003).

ReA develops one to three weeks after onset of the bacterial infection (William, 2003b). ReA is an acute, non-purulent, aseptic arthritis and Reiter's syndrome is a form of ReA (Bunning et al., 1988). In the case of RS urethritis and conjunctivitis (Yu and Thomson, 1994) may occur alongside other cutaneous manifestations (Peterson, 1994b) apart from the arthritis. However, RS-associated foodborne illness is similar to ReA with respect to articular features and may only have one extra-articular feature (Raybourne et al., 2003). Therefore in this study we will use the term ReA to cover both entities. AS is the most chronic form of the spondyloarthropathies and it is mainly characterised by progressive degeneration of the lumbar spine (Raybourne et al., 2003). Some studies have shown that ReA and RS can progress to AS in some individuals (Raybourne et al., 2003). A more detailed description of the ReA family can be found in (William, 2003a;b), and other medical and rheumatoid textbooks.

4.1.2 Genetic predisposition for ReA?

According to a number of authors, there is evidence of genetic predisposition for reactive arthritis, in particular the presence of the HLA-B27 antigen. But in addition to genetic factors, environmental factors, possibly related to the number of organisms ingested and the severity of enteritis, might also be of importance in determining the subsequent development of reactive arthritis (Eastmond et al., 1983). In a population study based on laboratory-confirmed Campylobacter cases, Hannu et al. (2002) found a frequency of 14% (6 patients) HLA-B27 positive ReA patients. The same frequency is found in the general population in Finland. According to Hannu et al. (2002), most studies with a high reported frequency of HLA-B27 ReA patients were usually hospital-based series of patients with more severe and complicated disease. Their hypothesis is that at the community level, where most cases of ReA are mild, the presence of HLA-B27 seems to be less important as a risk factor for ReA. Further, the authors found no difference between the negative HLA-B27 ReA cases and the 6 positive HLA-B27 ReA cases with regard to the duration of ReA or the size of the affected joints. In a recent review of the role of bacteria and HLA-B27 in the pathogenesis of reactive arthritis Yu and Kuipers (2003) concluded that 'HLA-B27 occurs in 95% of Caucasian patients with AS, for which it is an essential gene'. However, the degree to which HLA-B27 contributes to ReA is questionable. 'The most systematic evaluation has been carried out using 198 consecutive patients infected with Salmonella, comparing the data to 100 healthy

controls. HLA-B27 is not more frequent in those with joint symptoms. In contrast, of the eight patients with physician-confirmed reactive arthritis, 75% are HLA-B27 positive. This is strong evidence that HLA-B27 is a major player in ReA; however, unlike AS, it is not essential' (Yu and Kuipers, 2003). Therefore, within this study we will follow the hypothesis of Hannu et al. (2002) and assume that at the community level most cases of ReA are mild, whereby the presence of HLA-B27 antigen is not important.

4.2 Estimating annual incidence of Campylobacter-associated ReA cases

ReA is triggered by genital infections as well as enteric infections. Based on previous studies Keat (1983) concluded that ReA occurred in 2% to 3% of all patients with Shigella, Salmonella, and Campylobacter infections. Yu and Thomson (1994) thought that referral bias and other methodological flaws might probably have resulted in a low estimate of foodborne associated ReA cases. When reviewing more recent studies, Yu and Thomson (1994) suggested that at minimum, Salmonella-associated enteritis would result in 6-10% ReA cases. Raybourne et al. (2003) reported incidence figures between 6.4% and 15% from studies having estimated ReA incidence after Salmonella outbreaks in North America and Europe.

One of the first authors reporting an ReA case triggered by *Campylobacter jejuni* was Berden et al. (1979). Other case reports followed. Although most studies focus on *Campylobacter jejuni, C. coli* and other C. species might also result in a gastro-enteritis, as well as in ReA as a secondary infection sequelae. Hannu et al. (2002) found no statistically significant difference between *C. jejuni* or *C. coli* and the occurrence of ReA. Therefore, in this study we will not distinguish between the different Campylobacter species.

A first estimation of Campylobacter-associated ReA prevalence was done by Keat (1983). Based on earlier studies, including some case-reports, Keat (1983) estimated the prevalence of ReA at 2.4%. Based on Campylobacter outbreak data Eastmond et al. (1983), Bremell et al. (1991) and Melby et al. (2000) studied the prevalence of ReA in Campylobacter-associated GE patients (see Table A in Appendix IV for details). Using physician records, Eastmond et al. (1983) estimated the probability of developing ReA after a Campylobacter infection at 1.1% (95 C.I. 0.03-5.43). However, this might be an underestimation, as mildly affected ReA patients might not consult a physician. When interviewing campylobacteriosis patients 2 years after an outbreak, 20% (7/35) of campylobacteriosis patients reported to have had rheumatologic complaints (Bremell et al., 1991). The symptoms were mainly mild, and only one patient (2.9%) reported absence from work due to the severity of the symptoms (Bremell et al., 1991). With the help of a questionnaire Melby et al. (2000) reported that 21% and 9% of the campylobacteriosis patients of a Campylobacter outbreak had joint swelling and joint pain, respectively. The authors reported further that of the 330 estimated campylobacteriosis cases only two developed ReA (0.6%). However, no information was given on a) the severity grade of ReA; and b) what those two ReA cases were based on (physician records, clinical examination, other criteria).

In the eighties, Kosunen et al. (1980) and Johnsen et al. (1983), and more recently Hannu et al. (2002) and Locht and Krogfelt (2002) studied the incidence of Campylobacter-associated ReA cases in the population (see Table B in Appendix IV for details). Kosunen et al. (1980) and Johnsen et al. (1983) used hospitalized and laboratory-confirmed campylobacteriosis patients to analyze the occurrence of ReA after Campylobacter infections. Based on the information supplied with the samples Kosunen et al. (1980) observed eight patients (2.3%)

who developed ReA. However, given that the ReA patients were diagnosed based on medical records, we might assume that these ReA patients were more serious ReA cases, who would have consulted a doctor because of ReA. In the study of Johnsen et al. (1983), there were seven self-reporting patients with joint symptoms, however only five (13.5%) cases were considered to have had ReA. The arthritis was short-lasting (3-7 days) in all 5 patients. Two patients (two boys) were hospitalised with the diagnosis of rheumatic fever. Hannu et al. (2002) and Locht and Krogfelt (2002) estimated the incidence of ReA cases by sending questionnaires on enteric and extra-intestinal symptoms to laboratory confirmed Campylobacter infection cases.

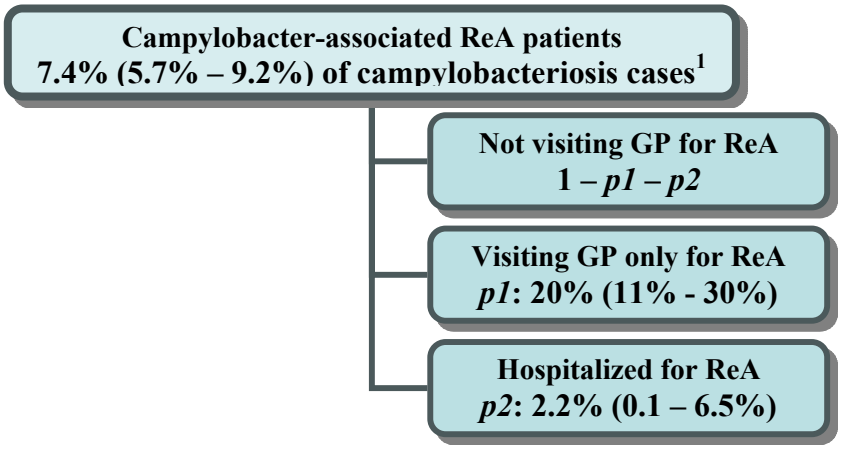
The study of Locht and Krogfelt (2002) is a retrospective study, whereby an overlap in reported physician visits, absence of work and the use of medicines because of campylobacteriosis or because of rheumatoid symptoms might have occurred. In this study, 21% of the campylobacteriosis cases reported ReA-related symptoms, and 16% of the campylobacteriosis cases were considered to have had ReA. Whereas in Hannu et al. (2002), a prospective study, 38% (220 of 582) of campylobacteriosis patients and 24% (185/758) of controls reported recent joint or other musculoskeletal symptoms. Some of the subjects having reported symptoms in Hannu et al. (2002) were clinically examined and some other specific tests were applied at a mean of eleven weeks (range 3 – 37) after disease onset. This was done for 51% (113) of the campylobacteriosis patients and for 17% (31) of the controls. Hannu et al. (2002) defined 45 (7%) ReA cases as well as some cases of reactive tendinitis, enthesopathy or bursitis (ReTEB). A total of 9% (10% in adults and 0% in children) showed inflammatory low back pain with peripheral arthritis; reactive tendinitis, enthesopathy or bursitis. This is lower than the estimates of Locht and Krogfelt (2002), but close to the estimate of Johnson et al. (1983), who estimated, based on a small population-based study with only 52 subjects from Norway, an incidence of ReA of 8%.

From the 45 defined ReA patients in Hannu et al. (2002), nine patients (~20%) had consulted a GP. This corresponds with ~1.5% of all campylobacteriosis cases. This again is substantially lower than the estimated 46% of all ReA cases, or 7-8% of all campylobacteriosis cases, of Locht and Krogfelt (2002). However, it falls within the range of the estimated ReA consultations of 1.1% by Eastmond et al. (1983) and of 2.3% by Kosunen et al. (1980; 1981). Both studies considered only patient's records. Further, Hannu et al. (2002) reported that one of the 45 ReA patients was hospitalised.

The study of Hannu et al. (2002) is one of the more complete studies related to Campylobacter-associated ReA, and we therefore base our assumptions mainly on this study. By using beta-distributions (see Appendix V), we estimated the uncertainty around the point estimates for the percentage of campylobacteriosis patients developing ReA, ReA patients visiting a GP and ReA patients being hospitalised, which are summarised in Figure 4.1.

Hannu et al. (2002) and Locht and Krogfelt (2002), both found in their studies that the Campylobacter-infected patients who develop rheumatologic complaints had more severe and prolonged diarrhoea than those with enterocolitis only. However, patients with a mild Campylobacter infection might also develop ReA (Locht, 2003, personal communication). Nevertheless, a question remains (model uncertainty): Are the ~7% of Campylobacter-associated ReA cases a) only related to laboratory-confirmed positive Campylobacter cases; b) only related to campylobacteriosis cases visiting a GP; or c) related to all campylobacteriosis cases in the population? From the English IDD study we know that about 33% of adults in the GP component reported joint problems/stiffness, 5% reported joint

swelling and 44% reported back/neck pain within the 3 first weeks after disease onset (Anonymous, 2000c). Although the self-reported 33% with joint problems/stiffness might be a little bit lower than the self-reported 38% with recent joint or other musculoskeletal symptoms in the study of Hannu et al. (2002) we thought that this indication was strong enough to allow the assumption that on average 7.4% of campylobacteriosis patients visiting a GP might develop ReA. However, in our sensitivity analysis we will consider the impact of this assumption on the estimated disease burden and the cost-of-illness.



[1)] For our base case we assumed that only campylobacteriosis patients visiting a GP or being hospitalized might develop ReA. In the sensitivity analysis, however, the number of campylobacteriosis patients that might develop ReA was equal to a) laboratory-confirmed positive Campylobacter infection cases, and b) all campylobacteriosis cases in the population.

Figure 4.1. Number of Campylobacter-associated ReA cases and the different ReA severity groups modelled in this study (average and 90% C.I.).

4.3 Estimating disease burden due to Campylobacter-associated ReA cases

4.3.1 Symptom length

Not much information is available about the clinical course of Campylobacter-associated ReA and the impact of ReA on activities of daily life. According to Yu and Thomson (1994), the clinical course of ReA can be divided into four patterns: a) a monophasic course which spontaneously resolves within 4-16 weeks; b) recurrence and remission of ReA with spontaneous resolution of symptoms; c) waxing and waning course but no true remission; and d) chronic unremitting cases. 30-50% of the ReA-cases would have a monophasic course, which spontaneously resolves within a few weeks (Yu and Thomson, 1994). In the population-based study of Hannu et al. (2002), the 44% of ReA patients who recovered in less than 6 months after onset of ReA symptoms, falls within this range. For the group with ReA symptoms that last less than 6 months, Hannu et al. (2002) found that 50%, 15%, 5%, 25% and 5% had symptoms for ≤ 1, 1-2, 2-3, 3-4 and 4-6 months, respectively. Unfortunately, Hannu et al. (2002) followed their ReA patients for only 6 months. Others studies that followed ReA patients for a little longer were Keat (1983), Locht and Krogfelt (2002) and Soderlin et al. (2003).

In a prospective population-based study Soderlin et al. (2003) studied adult patients with arthritis of less than three months duration who had consulted primary health care centres. Of the 71 patients included, 27 had reactive arthritis. The majority were triggered by Campylobacter infections. In the six-month follow-up period Soderlin et al. (2003) observed that 71% of patients with ReA due to *C. jejuni* were in remission (6 to 9 months after symptoms onset). In the retrospective population-based study of Locht and Krogfelt (2002), the median duration of joint symptoms was 60 days (interquartile range 29-180 days) and only five of the 27 patients (18.5%) claimed to have had symptoms for longer than one year. Based on earlier clinical studies Keat (1983) estimated that the mean duration of symptoms of ReA patients lasted eighteen weeks, whereby 79.4% had arthritis symptoms for less than six months, but 4.8% had symptoms for more than one year.

Based on the findings of Hannu et al. (2002) on the duration of ReA symptoms of ReA patients who recovered during the first six months after disease onset (44% of all ReA patients), and on the findings of Soderlin et al. (2003), Locht and Krogfelt (2002) and Keat (1983) for the following months, an exponential distribution was fitted to the data. The estimated mean duration of this fitted distribution was 0.608 years.

None of the studies distinguished between duration and severity. Due to the non-availability of data, we therefore will assume that ReA duration is independent of the severity of symptoms. For the hospitalised ReA patients we randomly draw the duration length from an exponential distribution with β being 0.608 years. But given the relatively large number of ReA patients not visiting a GP and of ReA patients visiting a GP, the variability surrounding symptom length would average out. We therefore estimated the disease burden due to ReA cases by using the average ReA symptom length of 0.608 years/case for these two subgroups.

4.3.2 Symptom severity and quality of life

Disability weights for ReA are not available in the literature. Within the framework of the Dutch VTV project three different grades of rheumatoid arthritis were defined (Stouthard et al., 1997). The disability weights associated with these three grades were 0.21 (95% C.I.: 0.127; 0.303) for mild rheumatoid arthritis[2]; 0.37 (95% C.I.: 0.219; 0.515) for moderate rheumatoid arthritis[3] and 0.94 (95% C.I.: 0.920; 0.961) for severe rheumatoid arthritis[4], whereby in all three cases it was assumed that the symptoms would be chronic (whole year). However, the ReA symptoms described in Hannu et al. (2002) are very mild symptoms. We though that an EQ 5D+ classification of 111211[5] might be more appropriate for ReA patients not visiting a GP. Considering the lower estimated 95% C.I. of the disability weight for 'mild' rheumatoid arthritis of Stouthard et al. (1997), 0.127 as disability weight for ReA cases not visiting a GP seemed a better estimate. For ReA patients visiting a GP, we took the average disability weight of 'mild' rheumatoid arthritis of Stouthard et al. (1997), which was

[2] Mild rheumatoid arthritis was described with an EQ 5D+ classification of 122211. For explications on the EQ 5D+ classification system see footnote 5.
[3] Moderate rheumatoid arthritis was described with an EQ 5D+ classification of 222211.
[4] Severe rheumatoid arthritis as described with an EQ 5D+ classification of 222331 (50%) and 333331 (50%).
[5] The EQ-5D questionnaire comprises five questions (items) relating to problems in the dimensions 'mobility', 'self-care', 'usual activities', 'pain/discomfort', and 'anxiety/depression'. Responses in each dimension are divided into three ordinal levels, coded as follows: (1) no problems; (2) moderate problems; and (3) extreme problems. This part, called the EQ-5D self-classifier, provides a five-dimensional description of health stats, which can be defined by a five-digit number (Gregor et al., 1997). The EQ-5D+ is a six-dimensional extended EuroQol classification, whereby the 6th item (questions) is related to 'cognitive functioning' (Stouthard et al., 1997). For example the state '122211' would indicate no problems in mobility, anxiety/depression and cognitive functioning, but moderate problems in self-care, usual activities and pain/discomfort.

0.21. And for hospitalised ReA patients, we used the estimated mean disability weight of 0.37 for 'moderate' rheumatoid arthritis of Stouthard et al. (1997). The disease burden for each ReA case is estimated by multiplying the estimated annual disability weights (w) with the symptom length (t).

4.4 Estimating cost-of-illness due to Campylobacter-associated ReA cases

Locht and Krogfelt (2002), reported that 67% of ReA patients took analgesics. According to the authors themselves, this might be an overestimation. No further information was collected on the medicine use itself (Locht, 2003, pers. communication). Due to the non-availability of data, we therefore found it preferable for the purposes of this study to disregard costs for medicine use in the case of ReA patients, knowing that this is an underestimation. But apart from the non-availability of data on drug use, information on other medical services and sickness leave was also scanty. For example, Hannu et al. (2002) reported that 20% of all ReA patients had consulted a physician, whereas Locht and Krogfelt (2002) reported that 46% of all ReA patients had visited a physician. Although according to the authors themselves, the estimate in the latter study might be an overestimation due to a possible overlap in the consultation with the physician due to enteritis symptoms or due to ReA symptoms. In Hannu et al. (2002) only one of the 45 ReA patients (2%) was hospitalised, whereas Locht and Krogfelt (2002) found no hospitalisation at all. In 2000 the average hospitalisation stay for neck and back pain in the Netherlands was 9.1 days (Prismant, 2003). ReA might fall within this category. We therefore assumed that the average hospital stay for ReA patients would be 9.1 days.

No information was available on patients' means of travel to their GP and to the hospital. We therefore assumed, just as for GE cases, that patients travelling to/from hospital would either use a car or public transport. For patients visiting their GP we did assume that most likely half (range 10% to 90%) of the patients would bike or walk, whereas the other half would take a car or public transport.

Sickness leave of ReA patients was reported in only two studies. Bremell et al. (1991) noted that only one ReA patient (2.9% of all campylobacteriosis cases) had reported absence from work due to the severity of the symptoms. However, in Locht and Krogfelt (2002) 26% of the ReA patients self-reported a temporary absence from work. The authors could not exclude that there might be a possible mix-up in whether the temporary work absence was due to enteritis symptoms or ReA symptoms. Neither study provided information on the duration of absence from work. According to Chorus (2001) the average length of sickness leave for patients with inflammation of the joints (ReA is one of the illnesses within this category) was 40 days. For the general population this was only fourteen days. However, the percentage of people who had to take days off due to illness was similar in both groups. In order to determine the length of sickness leave related to ReA only, we therefore used the difference between these two groups, which was 26 days. Using the productivity losses per day for an 'average' person during working life (see Appendix III), we estimated the indirect non-health care costs related to ReA associated with Campylobacter infections. Further, no information was available on the time that patients would be absent from work in order to consult their GP. We thought that patients might spend 0 to 0.25 days/consultation off work in order to visit a GP. By using a uniform distribution, ranging from 0 to 0.25 days/consultation, we modelled the uncertainty of this assumption.

In this study we had to make some simplified assumptions, knowing that the true cost-of-illness due to Campylobacter-associated ReA cases might be underestimated:

- For ReA patients not visiting a GP, no direct health care costs were calculated. Further we assumed that the symptoms were so mild that patients might continue their daily life activities, e.g. working, despite their disabilities due to the ReA symptoms.
- For ReA patients visiting a GP, we assumed: a) one GP consultation/patient; b) travel costs to/from the GP; and c) work absence during the GP consultation.
- For ReA patients being hospitalised, we assumed: a) one GP consultation/patient, according to the Dutch system where the GP is the 'gatekeeper' to other medical services; b) travel costs to/from the GP; c) travel costs to/from the hospital; d) costs for hospitalisation, assuming that 14% of the patients would stay in a university hospital and 86% in a general hospital (Oostenbrink et al., 2000); e) 'short subscription' for the attending rheumatologist of € 88.9 /patient, according to the Dutch system; f) an average sickness leave of 26 days.

4.5 Results

4.5.1 Estimated annual incidence of Campylobacter-associated ReA cases

The cumulative distribution of the estimated annual Campylobacter-associated ReA cases is shown in Figure 4.2, breaking down the total uncertainty into a variability-related component and an uncertainty-related component. The estimated mean and the attendant uncertainty of the total number of ReA cases, the number of ReA cases not visiting a GP, the number of ReA cases visiting a GP only and the number of hospitalised ReA cases, are summarised in Table 4.1.

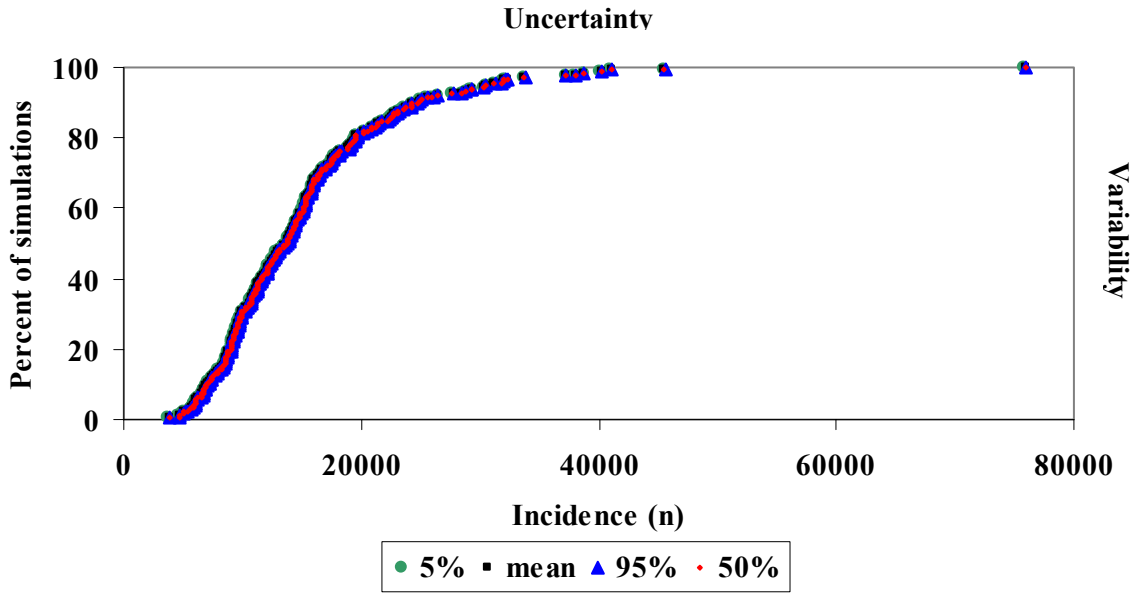


Figure 4.2. Cumulative distribution of the mean , 5th, 50th and 95th percentile of the estimated annual Campylobacter-associated ReA cases, breaking down the total uncertainty into variability and uncertainty

Table 4.1. Estimated mean and attendant uncertainty of annual incidence of ReA cases in the Dutch population, including the different health states of the disease.

Description	Estimated annual incidence			
	5%	Mean	50%	95%
Not visiting GP for ReA	385	1,134	968	2,457
GP visits only for ReA	79	251	182	626
ReA hospitalised cases	1	30	18	109
Total ReA cases	469	1,386	1,166	3,013

[1)] The model parameters used in this study are often uncertain or are variable or both. We therefore not only show for example the average annual incidence but also the 5th, 50th and 95th percentile, representing the uncertainty in the estimated average.

4.5.2 Estimated disease burden due to Campylobacter-associated ReA cases

Due to the relatively large number of ReA patients not visiting a GP and ReA patients visiting a GP, we used average disability weights and average duration of illness for those two groups. For hospitalised ReA patients, the duration of illness was randomly drawn for each individual ReA patient. The cumulative distribution of the estimated disease burden due to ReA cases associated with a previous Campylobacter infection is shown in Figure 4.3. Here the total uncertainty is broken down into a variability-related component and an uncertainty-related component. The estimated mean and the attendant uncertainty of the disease burden related to ReA cases are summarised in Table 4.2. Given the assumption made that the severity grade has hardly any influence on symptom length and given the relatively large number of ReA patients not visiting a GP, it is not surprising that this group of ReA patients accounts for the largest part of the disease burden due to ReA cases (see Figure 4.4).

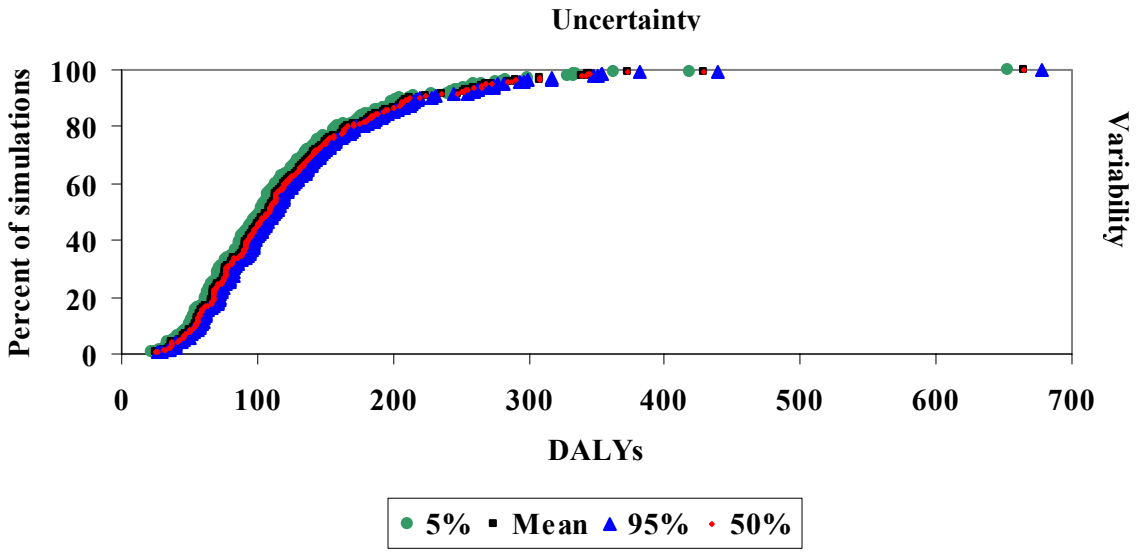


Figure 4.3. Cumulative distribution of mean, 5th, 50th and 95th percentile of the annual disease burden estimate due to Campylobacter-associated ReA cases, breaking down the total uncertainty into variability and uncertainty.

Table 4.2. Estimated mean and attendant uncertainty of the disease burden due to Campylobacter-associated ReA cases.

Description	Estimated DALYs			
	5%	Mean	50%	95%
ReA cases	44	126	109	271

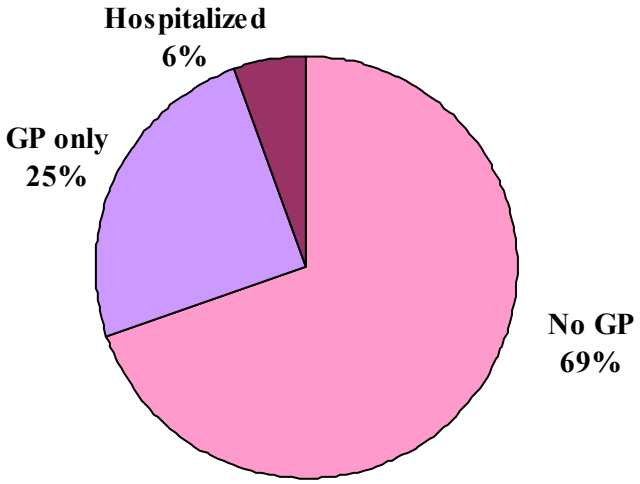


Figure 4.4. Breakdown of the estimated mean disease burden (DALYs) due to Campylobacter-associated ReA cases into the different severity groups, namely ReA cases not visiting a GP, ReA cases visiting a GP and hospitalized ReA cases.

Given that we assumed for ReA cases not visiting a GP and ReA cases visiting a GP an average duration length of symptoms of 0.608 years and given that we randomly draw for the few hospitalised ReA cases a duration length from an exponential distribution with β being 0.608 years, nearly all ReA cases recovered from the illness within one year after illness onset. Only very few patients might experience some symptoms in the second year after disease onset. Therefore, the disease burden was not discounted.

4.5.3 Estimated cost-of-illness due to Campylobacter-associated ReA cases

Due to the lack of data we had to make some assumptions in order to estimate the cost-of-illness due to ReA cases associated with Campylobacter infections. Theses assumptions, however, might have resulted in an underestimation of the cost-of-illness due to ReA cases. The cumulative distribution of the estimated cost-of-illness due to ReA cases is shown in Figure 4.5. Here the total uncertainty was broken down into a variability-related component and an uncertainty-related component. The estimated mean and the attendant uncertainty of the different cost categories related to ReA cases are summarised in Table 4.3.

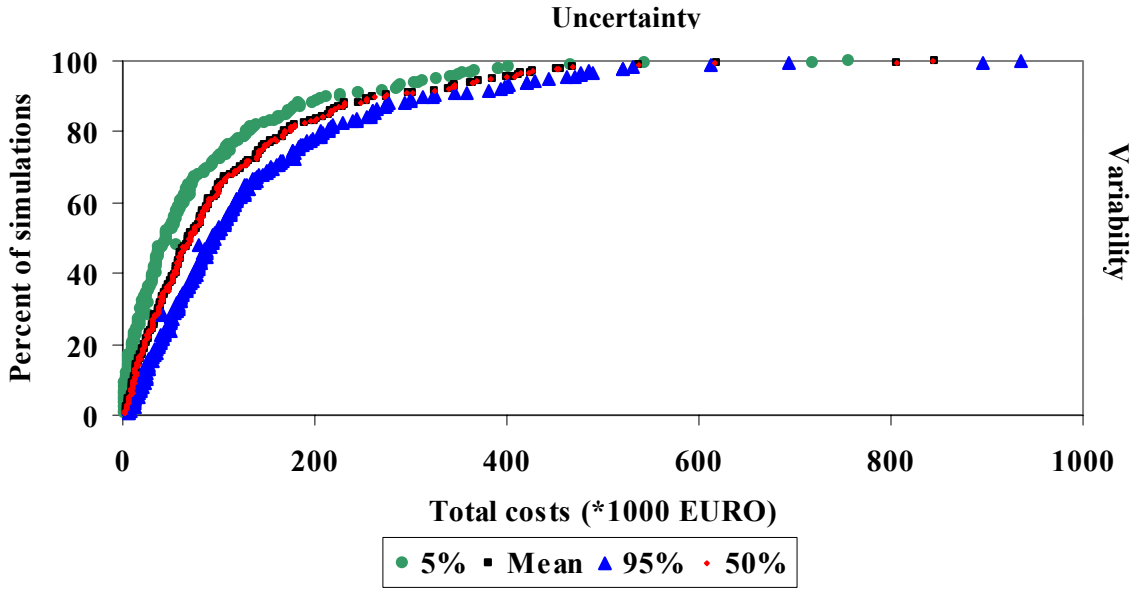


Figure 4.5. Cumulative distribution of mean, 5th, 50th and 95th percentile of the estimated annual cost-of-illness due to Campylobacter-associated ReA cases (year 2000), breaking down the total uncertainty into variability and uncertainty.

Table 4.3. Estimated mean and attendant uncertainty of cost-of-illness, direct health care costs, direct non-health care costs and indirect non-health care costs, respectively, due to Campylobacter-associated ReA cases in the Netherlands (year 2000).

Description	Estimated costs (*1000 €)			
	5%	Mean	50%	95%
Direct health care costs	5	82	50	281
Direct non-health care costs	0.02	0.12	0.09	0.30
Indirect non-health care costs	2	32	20	112
Total costs	7	114	70	394

Under the current assumptions, hospitalised patients are responsible for ~95% of the estimated cost-of-illness due to ReA. About >70% of the total costs are direct health care costs. Direct non-health care costs are negligible. For ReA cases all costs related to the disease are assumed to occur within the first year after disease onset. As a consequence, discounting was not applied.

4.5.4 Sensitivity analysis

Given that running the model requires a considerable amount of time, we considered uncertain parameters as 'given' when doing sensitivity analysis. The 'average' value of the distributions describing uncertain parameters were considered as being 'best guesses'.

As highlighted in section 4.2, the question remains (model uncertainty) of whether the ~7% of Campylobacter-associated ReA cases are a) only related to laboratory-confirmed positive Campylobacter cases, b) only related to campylobacteriosis cases visiting a GP; or c) related to all campylobacteriosis cases in the population. We decided to consider as ***base scenario*** that approximately 7% of campylobacteriosis cases that would visit a GP, whether hospitalised or not, would develop ReA. However, in our sensitivity analysis we have analysed the impact of this assumption on the estimated disease burden and cost-of-illness due to ReA cases. Therefore, apart from our ***base scenario*** we simulated two additional

scenarios, namely a) the ***laboratory scenario***, assuming that only laboratory-confirmed positive Campylobacter cases might develop ReA; and b) the ***population scenario***, assuming that all gastro-enteritis cases in the population and associated with Campylobacter infections might develop ReA. Allowing variability as the only uncertain factor, the estimated mean, 5th and 95th percentile of the annual incidence number of ReA cases, the disease burden due to ReA cases and the estimated cost-of-illness related to ReA cases are summarised for all three scenarios in Table 4.4.

Table 4.4. Estimated mean and attendant variability of the annual incidence of Campylobacter-associated ReA cases, disease burden due to ReA cases and cost-of-illness due to ReA cases, in the Dutch population.

Description	Base[1]			Laboratory[2]			Population[3]		
	5%[4]	Mean[4,5]	95%[4]	5%[4]	Mean[4,5]	95%[4]	5%[4]	Mean[4,5]	95%[4]
Annual incidence	1,325	1,386	1,443	386	418	452	5,701	5,824	5,949
Disease burden	120	126	132	35	38	42	508	520	532
Costs (*1000 €)	84	114	148	19	35	52	420	485	550

[1)] Assuming that only Campylobacter-associated GE cases visiting a GP (base) might develop ReA.
[2)] Assuming that only laboratory-confirmed positive tested Campylobacter-associated GE cases (laboratory) might develop ReA.
[3)] Assuming that all Campylobacter-associated GE cases (population) might develop ReA.
[4)] The 'average' value of the distributions describing uncertain parameters were considered as being 'best guesses'. Only variability was considered as an uncertain factor.
[5)] Mean or median. After rounding up we obtained for both the same values.

Another model uncertainty was the assumption made on sickness leave of ReA patients. For the ***base scenario*** we assumed that only hospitalised ReA patients have a longer sickness leave (26 days/case). For non-hospitalised ReA patients, only the visit of a GP might result in a short sickness leave (0 to 2 hours/case). However, if ReA symptoms are so severe that patients consult a GP, a longer sickness leave for patients of this group might not be excluded. We therefore considered in our sensitivity analysis the impact of a longer sickness leave of ReA patients visiting a GP only (***longer sickness leave scenario***). We assumed, just as for hospitalised ReA cases, a sickness leave of 26 days. The results are summarised in Table 4.5. A longer sickness leave would always influence the estimated indirect non-health care costs. In our case the indirect non-health care costs and the cost-of-illness due to ReA of the longer sickness leave scenario (alternative scenario) would have been ~ 8 times higher and ~ 3 times higher, respectively, than in the base scenario. In the case of a longer sickness leave for ReA patients visiting a GP only, the relative share of the indirect non-health care costs in the total costs would increase from 28% to 78%, and the relative share of the direct health care costs in the total costs would decrease from 71% to 22% (results not shown).

Table 4.5. Estimated mean, 5th and 95th percentile of total costs, direct health care costs, direct non-health care costs and indirect non-health care costs due to Campylobacter-associated ReA cases.

Description	Costs (*1000 €)					
	Base[1)]			Longer sickness leave[2)] for ReA patients visiting GP only		
	5%[3]	Mean[3, 4]	95%[3]	5%[3]	Mean[3, 4]	95%[3]
Direct health care costs	60	82	106	60	82	106
Direct non-health care costs	0.1	0.1	0.1	0.1	0.1	0.1
Indirect non-health care costs	24	33	42	254	284	313
Total costs	84	115	148	325	366	404

[1)] Assuming that only hospitalised ReA patients have a longer sickness leave (26 days/case). For non-hospitalised ReA patients, only the visit of a GP might result in a short sickness leave of 0 to 2 hours/case.
[2)] Assuming that both groups, hospitalised ReA patients and ReA patients visiting a GP only, have a longer sickness leave (26 days/case).
[3)] The 'average' value of the distributions describing uncertain parameters were considered as being 'best guesses'. Only variability was considered as an uncertain factor.
[4)] Mean or median. After rounding up we obtained for both the same values.

4.6 Discussion

With an average estimate of nearly 1400 Campylobacter-associated ReA cases in the Netherlands for the year 2000, our estimate is by far higher than the 40 ReA cases named in Chorus (2001). The estimate given in the study of Chorus (2001) was based on the POLS study conducted in 1997. POLS stands for 'Permanent Onderzoek Leefsituatie' and is an annual population study conducted by Statistics Netherlands. However, in order to get identified as an ReA case within the POLS study, ReA symptoms would need to be much more severe than as described by Hannu et al. (2002), Locht and Krogfelt (2002) and other studies focusing on foodborne pathogen-associated ReA cases. In this study, the main assumptions on ReA incidence and also on the symptom length were based on Hannu et al. (2002). According to the assumption made on ReA severity, the majority of cases would not consult a doctor and only very few ReA cases would need to be hospitalised. This latter category might be closer to the category of ReA cases identified in the study of Chorus (2001).

In a previous study, Havelaar et al. (2000a, b) estimated the disease burden associated with Campylobacter infections and sequelae. In this study, the authors also considered ReA cases as one of the complications related to Campylobacter infections in humans. However, this previous study assumed that the average annual incidence was 300,000 Campylobacter-associated GE cases. In the current study , which is based on a more recent Dutch community-cohort study, the estimated average incidence was less than 80,000 campylobacteriosis cases/year. Consequently the estimated number of Campylobacter-associated ReA cases/year should be, and is indeed, much lower than the estimate of Havelaar et al. (2000a, b).

But despite the lower incidence of ReA cases, the estimated average disease burden is with 126 DALYs not so much lower than the estimated average disease burden of Havelaar et al. (2000a, b), which was 159 DALYs. The difference is mainly due to the fact that in our study we assume that the average symptom length is 0.6 years, whereas Havelaar et al. (2000a, b) assumed only an average symptom length of 0.1 years. Another difference between the two studies is the disability weights used per case. We handled 3 different disability weights,

depending on symptom severity. Havelaar et al. (2000a, b) used only one disability weight. However, the disability weights used per case do not differ so much from each other and have a lower impact on the estimated disease burden. The main difference is the earlier described assumption made on symptom length. The assumed symptom length within this study, however, was based on more recent studies.

By applying retrospective or prospective study on laboratory-confirmed Campylobacter infections, Hannu et al. (2002) and Locht and Krogfelt (2002) determined the incidence of Campylobacter-associated ReA cases. Both studies concluded that campylobacteriosis cases who developed ReA symptoms also had longer gastro-enteritis symptoms than those cases that did not develop ReA. Given that generally only more severe gastro-enteritis cases visit a GP, the question of which patient group is at risk of developing ReA after a Campylobacter infection remains. Will all GE cases that visit a doctor (base scenario) develop ReA? Or only laboratory-confirmed Campylobacter cases? Or everyone infected with Campylobacter? As shown in the sensitivity analysis this is and remains an important question, which probably can only be answered by further research. Further studies should use a clearer definition of ReA, and longer follow-up might help to get a more appropriate estimate on symptom length.

When estimating the disease burden, we had to use disability weights of rheumatoid arthritis as no disease-specific disability weights were available. More disease-specific disability weights would be useful, together with a good description of the actual symptoms severity.

No information was available about the medicine use of ReA cases, as well as about the sickness leave of ReA cases. We therefore had to make some basic assumptions in order to be able to get an estimate of the cost-of-illness related to Campylobacter-associated ReA cases. When making the assumptions, we were very careful and preferred to opt for assumptions that would underestimate rather than overestimate the costs related to ReA cases. However, as shown in the sensitivity analysis, our estimate is strongly related to these assumptions. And when assuming that not only hospitalised ReA patients, but also ReA patients with less severe ReA symptoms might suffer from a long sickness leave, the total costs increased enormously. In order to get a better estimate of the cost-of-illness related to ReA cases, we would recommend that future studies follow studies such as Hannu et al. (2002) and Locht and Krogfelt (2002), and also focus on factors such as medicine use, sickness leave, medical service use and informal care, and ensure that the patients don't mix up medicines, such as the medicine used for gastro-enteritis and the medicine used for ReA symptoms.

Despite all its shortcomings, this study shows the range of the possible Campylobacter-associated ReA incidence and associated disease burden. The cost-of-illness estimate might and should be improved as soon as new data becomes available.

5 Campylobacter-associated Guillain Barré syndrome cases*

5.1 Background information

Guillain-Barré syndrome (GBS) is a neurological disease frequently preceded by an acute infectious illness, mainly upper respiratory infections and gastrointestinal infections. According to Allos (1997), GBS is preceded in 10%-30% of cases by GE infections. Campylobacter infections were not reported in association with GBS until 1982, mainly because Campylobacter species were not routinely tested for. Therefore, earlier cases of Campylobacter-associated GBS might have been unrecognised (Allos, 1997).

According to Hughes and Rees (1997), the term GBS refers to a set of clinical syndromes, but the main characteristics for GBS are an acute or sub-acute weakness of at least two limbs, which progresses for up to four weeks (> 95% of patients have completed the progressive phase within this time) and then reaches a plateau, the nadir. The neuropathy usually affects the motor, sensory, and autonomic nerves supplying the limbs. Further, the respiratory muscles and facial, bulbar, and ocular motor nerves might also be affected. Affected patients might need artificial ventilation (Hughes and Rees, 1997). In another subtype of GBS, which is most frequently reported as Miller Fisher syndrome (MFS), cranial nerve dysfunction is the most prominent feature (Van Koningsveld, 2001).

The functional status of patients with GBS is scored on a seven-point disability scale, the details of which are given in Table 5.1. GBS patients with an F-score at nadir of < 3 (able to walk unaided at nadir) are considered to be mildly affected. GBS patients with an F-score of ≥ 3 (unable to walk unaided at nadir) are considered to be severely affected (Van Koningsveld, 2001). Paralysis from GBS is generally reversible over time, but some patients are bedridden for life and others die prematurely. Most GBS cases are found among adults, although patients with GBS have ranged in age from nine months to 97 years (Buzby et al., 1997b).

Table 5.1. The Hughes disability scale - scoring system for functional status of GBS patients.

F-score	Definition
0	Healthy
1	Minor signs or symptoms of neuropathy but capable of running
2	Able to walk without support or a stick but incapable of running
3	Able to walk with a stick, appliance, or support
4	Confined to bed or chair-bound
5	Requiring artificial ventilation
6	Death

* We would like to thank Rob Bernsen from the Jeroen Bosch Hospital in s'Hertogenbosch for providing us data on the rehabilitation of GBS patients and for his critical feedback. Further we thank Rinske van Koningsveld from the Erasmus Medical Centre Rotterdam for abstracting data on hospitalisation from the MC Erasmus GBS database. We acknowledge the critical feedback of Rinske van Koningsveld on behalf of the GBS group from the Erasmus Medical Centre Rotterdam.

5.2 Estimating annual incidence of Campylobacter-associated GBS cases

Van Koningsveld (2001) reviewed thirteen studies on the incidence of GBS. In these studies, the crude incidence varied between 0.8 and 2.0 per 100,000 persons per year. Hughes and Rees (1997) analysed 35 series of GBS patients over the last 40 years. In these series the annual incidence varied from 0.4 to 4 cases/100,000 population, with a median of 1.3. Both reviews concluded that the incidence of GBS had not changed over the years. Further, Van Koningsveld (2001) and Hughes and Rees (1997) both found no trend in the incidence of GBS in relation to factors such as race, standard of living, season or climate.

Rees et al. (1998) estimated for Southeast England a crude annual GBS incidence rate of 1.2/100,000 population (95% C.I. 0.9-1.4). When adjusted for undetected cases, the estimated annual GBS incidence rate was 1.5/100,000 population (95% C.I. 1.3-1.8). Sedano et al. (1994) estimated for Cantabria (Spain) a crude average annual GBS incidence rate of 0.95 per 100,000 population (95% CI: 0.72-1.17). In the USA, the annual incidence of GBS cases is estimated to be 1-3.64/100,000 population, according to Buzby et al. (1997a, b), and 0.6 to 2.4/100,000 population according to Nagpal et al. (1999). Based on a retrospective study applied in the Southwest Netherlands for the years 1986-1997, Van Koningsveld et al. (2000) estimated the crude annual GBS incidence rate for the Netherlands to be 1.18/100,000 population. The authors of the latter study think that the estimated incidence might have been underestimated as they had to leave out eighteen patients because symptoms were too weak. Nevertheless, the crude annual GBS incidence rate estimated for the Netherlands of 1.18/100,000 population falls within the range of the studies cited above.

Sedano et al. (1994), Hughes and Rees (1997), Nachamkin et al. (1998) and Nagpal et al. (1999) noted that in almost all series, males were more commonly affected by GBS than were females. However, Rees et al. (1998) found that the age-adjusted incidence rates were roughly similar in females (1.3 (0.9-1.5) and males (1.1 (0.7-1.4). Van Koningsveld et al. (2000) estimated a crude incidence rate of 1.42 (95% C.I. 1.26-1.59) for men and 0.94 (95% C.I. 0.82-1.09) for women. However, according to Van Koningsveld et al. (2000) the numerous differences between men and women are not only based on biological factors but also on environmental origin. It is difficult to speculate about the origin of this gender difference and the cause and determinants of GBS. Therefore, for the sake of simplicity we will assume in this study that men and women are at equal risk of contracting GBS after a Campylobacter infection.

According to Rees et al. (1998), 14% of a total of 79 GBS cases had mild symptoms. Whereas Sedano et al. (1994) found that 37% of a total of 58 GBS patients were mildly affected, Van Koningsveld (2001) cited three other studies with an estimated percentage of mildly affected GBS patients of 19, 23 and 24 respectively. In the retrospective study applied by Van Koningsveld et al. (2000), data were available for 436 patients of which 121 (28%) were mildly affected ($F < 3$) and 315 (72%) were severely affected ($F \geq 3$). This estimate falls between the estimates of Rees et al. (1998) and Sedano et al. (1994). In a subsequently conducted Dutch prospective study, Van Koningsveld et al. (2002) found only 14% of the GBS patients to be mildly affected and 86 % severely affected in the Netherlands. However, in this latter study MFS patients, which are mainly mildly affected cases, were not included. This might explain in part the lower percentage found in this latter study. The authors themselves considered the study population within the prospective study to be representative. But they thought that the percentage of mildly affected patients might have been

underestimated in this study. We therefore based our assumptions mainly on the retrospective study of Van Koningsveld et al. (2000).

Different authors have studied the relationship between GBS and campylobacteriosis. Due to the time elapsed between the acute enteritis and the onset of GBS, as well as the possible use of antibiotics, the probability of isolating the Campylobacter spp. from faeces is rather small. Serology as a marker of recent infection with *Campylobacter spp*. might be more appropriate (Nachamkin, 1997). Based on small serological studies, Mishu et al. (1993) concluded that one-third to one-half of the patients with GBS had increased levels of *Campylobacter jejuni* antibodies at the time of onset of GBS. Different case-control studies demonstrated *Campylobacter jejuni* infections in 14% to 36% of GBS patients (Jacobs et al., 1998). This is in agreement with the findings of Havelaar et al. (2000a, b), which summarises some of these studies. In the summarised studies, 11% to 38% of GBS cases were linked to Campylobacter infection. Based on serology, Jacobs et al. (1998) linked 32% of the severely affected Dutch GBS patients (unable to walk) to a previous Campylobacter infection. Although much information is available on severely affected patients, relatively few studies focus on mildly affected patients. In the retrospective study of Van Koningsveld et al. (2000), the authors found some serological evidence for *Campylobacter jejuni* as the antecedent infection in 33% of the severely affected GBS patients (F≥3) and in 21% of the mildly affected GBS patients (F<3). However, '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' (Havelaar et al., 2000a). Several authors report the sensitivity of ELISA methods to be in the range of 60-75% when testing convalescent sera of patients with uncomplicated, culture-positive Campylobacter-associated-enteritis. Correcting the results of the retrospective study of Van Koningsveld et al. (2000) for published performance characteristic of the serological tests, Havelaar et al. (2000a) estimated that the incidence of *Campylobacter jejuni* associated Guillain-Barré syndrome in the Netherlands would be 59 cases per year (10 mild cases and 49 severe cases). These estimates form the basis for the current study.

Based on 29,567 reported laboratory-confirmed *Campylobacter jejuni* infections in Sweden, McCarthy and Giesecke (2001) estimated that one case of GBS among every 3,285 *Campylobacter jejuni* cases (95 % C.I.: 1,729, 7,210) would occur, whereas for the United States Allos (1997) estimated that 1 of every 1,058 cases of *Campylobacter jejuni* infection is followed by GBS. Combining our estimate of 59 GBS cases per year with the estimate of the incidence of Campylobacter-associated GE (~79,000 cases per year) this leads to the following conditional probabilities:
Risk of GBS given *C. jejuni* enteritis: 1 per 1,300 campylobacteriosis cases.
This estimate falls in between the estimates of McCarthy and Giesecke (2001) and Allos (1997).

Some studies report a bimodal age distribution with a peak in young adults and in the elderly (Hughes and Rees, 1997; Nagpal et al., 1999; De Pedro-Cuesta et al., 1996; Rees et al., 1998). Van Koningsveld et al. (2000) reported a linear increase in incidents with age without an additional peak around 20-30 years. In our study the estimated incidence range for mild and severely affected GBS cases was based on the retrospective study of Van Koningsveld et al. (2000). Based on the findings of Van Koningsveld et al. (2000), we assumed that age plays a role and patients under 50 years of age are more frequently found in the mildly affected group than elderly GBS patients (≥ 50 years).

5.3 Estimating disease burden due to Campylobacter-associated GBS cases

5.3.1 Duration of illness

GBS is self-limited, whereby patients experiencing the worst symptoms within a month of disease onset, followed by a slow recovery (Mead et al., 1999; Nachamkin et al., 1998). Partial or complete recovery takes place over weeks to months (Mead et al., 1999; Nachamkin et al., 1998). After 2-3 years, for most cases no further recovery is expected (Bernsen et al., 2002). 15 to 20% of GBS patients are left with severe neurological deficits (Buzby et al., 1997a, b; Nachamkin et al., 1998). Increasing age is significantly associated with a poor outcome (Rees et al., 1998). For some cases, GBS is even fatal. Reported case-fatality rates of GBS in the literature range from 2% to 8% (Mead et al., 1999).

Visser (1997) has shown that the probability of reaching the stage of independent locomotion after six months ($F \leq 2$) is smaller for patients over 50 years of age. According to Van Koningsveld et al. (2000) age plays a role and patients under 50 years of age are more frequently found in the mildly affected group than elderly GBS patients (≥ 50 years). Further, six months after onset of GBS, elderly GBS patients had on average a worse outcome than younger GBS patients (< 50 years) (Van Koningsveld et al., 2000).

Within this study we will make the same assumption on the duration of illness of GBS cases as was done in the study of Havelaar et al. (2000a, b). Following Havelaar et al. (2000a, b) we will distinguish between mildly and severely affected GBS patients, and within each group we will further distinguish between young and elderly GBS patients (see Figure 5.1). Within this study, the age at disease onset for each simulated GBS case is randomly drawn from the observed age distribution of Dutch GBS cases.

Havelaar et al. (2000a, b) found only little information on mildly affected patients and their recovery. Clinical experience at the outpatient department of Erasmus Medical Center Rotterdam suggested that after six months, 50% of the patients had fully recovered (F=0), whereas virtually all patients had reached F=1 (Havelaar et al., 2000a). From this information, Havelaar et al. (2000a) constructed a model for the clinical course of mildly affected patients, assuming simple exponential decrease of the number of patients in states F2 and F1 (for details see Appendix 6 in Havelaar et al. (2000a)). According to this model, 79% of patients would have fully recovered after one year whereas 21% would still suffer from minor symptoms (F=1). Havelaar et al. (2000a) found further that the initial ratio of patients in F-scores 1 and 2 was independent of age. In the absence of further information, we will assume, similar as Havelaar et al. (2000a, b), that the time course of recovery is similar for patients younger or older than 50 years.

Havelaar et al. (2000a, b) based their estimation on the recovery process of severely affected GBS patients on information collected from patients from the Dutch IVIg trial of (Van Der Meché et al., 1992). Van Der Meché et al. (1992) followed these patients during the first six months of their illness. According to Havelaar et al. (2000a, b), 60% of these randomised patients had an F-score of 4 when admitted to hospital. At nadir, approximately 20% of the patients even had an F-score of 5. After having reached the nadir, patients recovered, which is reflected by a gradual increase of the percentage of patients in F-score 0-2. Virtually all patients recover from the need for intensive care treatment, but after half a year (the end of follow-up in the clinical trial), a sizeable proportion were still severely affected (17% in F-

scores 3 and 4). In a follow-up study, Bernsen et al. (1997) evaluated the residual health status of these patients after a period of 31 months to six years after illness onset. According to Havelaar et al. (2000a) there were no significant differences in residual functional health status related to the time since the acute phase. Havelaar et al. (2000a, b) assumed therefore that the health status at follow-up will persist life-long, as we will also assume within this study. This study showed that only 25% of all patients reached an F-score of 0 (fully recovered) but continued to report psychosocial impairment, whereas 44% of patients continued to suffer from minor symptoms (F-score = 1). 31% of the severely affected patients continued to suffer from functional limitation (F-scores 2-4). For further details see Havelaar et al. (2000a).

Van Der Meché et al. (1992) observed a case-fatality ratio of only 2%. However, other studies report higher ratios. Van Koningsveld et al. (2000) found in the retrospective study for Southwest Netherlands sixteen fatal cases among 476 GBS cases, which is equal to a case-fatality ratio of 3.4%.

5.3.2 Disability weights

In this study we used the definition of disability weights from Havelaar et al. (2000a, b). The clinical heterogeneity of Guillain-Barré syndrome requires a differentiation in disability severity stage classes. The disability classes were in accordance with the F-scores and are summarised in Table 5.2.

Table 5.2. Disability weights of Guillain-Barré syndrome in different functional grades (Source: Havelaar et al. (2000a)).

F-score	Case-definition	EuroQol 5D score	Disability weight		
			Median	Range	Beta-distr.
1	Completely recovered from an episode of GBS, but having problems of insomnia, fatigue and related emotional and social constraints	11211	0.10	0.00-0.61	0.66, 4.13
2	Muscle weakness in legs and arms, able to walk 10 m or more without a walking aid, but unable to run	21211	0.30	0.04-0.65	2.16, 5.62
3	Muscle weakness in legs and arms, and only able to walk 10 m or more with a walking aid	22321	0.44	0.20-0.80	5.50, 6.70
4	Severe muscle weakness in legs and arms, not able to walk, bedridden or in a wheelchair	33322	0.80	0.25-0.95	5.55, 1.53
5	Severe muscle weakness in legs and arms, not able to walk, bedridden and requires artificial ventilation for at least part of the day	33332	0.94	0.75-0.99	18.35, 1.63

Mildly affected GBS patients have an F-score of 1 or 2 at nadir. Mildly affected GBS patients that would not fully recover from the illness were assumed to reach an F-score of 1.

Severely affected GBS patients have an F-score of 3, 4 or 5 at nadir. The recovery process is gradual. Some of these severely affected GBS patients will recover fully from the illness, whereas others will have symptoms until the end of their lives. As already mentioned in the previous section, within this study we assume that approximately 25% of all patients would reach an F-score of 0 (fully recovered) but would continue to report psychosocial impairment. 44% of patients would continue to suffer from minor symptoms (F-score = 1) and 31% of the severely affected patients would continue to suffer from functional limitation (F-scores 2-4) until the end of their lives (Havelaar et al., 2000a). Disability weights are estimated based on the frequencies of F-score reported in Table 5.2 for the different groups and multiplied by the

expected life expectancy. In some cases GBS can be fatal. For fatal cases, we modelled the expected life expectancy of each fatal GBS case individually, using Dutch life tables.

5.4 Estimating cost-of-illness due to Campylobacter-associated GBS cases

When estimating the cost-of-illness related to GBS, we used both published and unpublished studies. However, for some medical services no information was available. In order to get at least a best guess, we consulted the GBS group from the Erasmus Medical Center Rotterdam, a group that has been actively involved in clinical trials on GBS for many years. Furthermore, we checked the assumptions on rehabilitation with Rob Bernsen, a neurologist in the Jeroen Bosch Hospital in s' Hertogenbosch, who analysed the recovery process of GBS patients 3 to 6 years after disease onset.

Given the relationship found between age and severity of GBS, as well as between age and recovery, we will distinguish between a) mildly affected GBS patients and b) severely affected GBS patients. Within each severity group, we will further distinguish between two age groups: a) GBS patients <50 years; and b) GBS patients ≥ 50 years (see Figure 5.1). For severely affected and non-fatal GBS cases, we further distinguish whether: a) artificial ventilation is needed; b) inpatient rehabilitation is needed or if patients return home after discharge from hospital, whereby a few patients might need outpatient rehabilitation; c) and the recovery status reached at 3 to 6 years after disease onset (see Figure 5.2).

5.4.1 Direct health care costs

Diagnostic costs

In accordance with the Dutch system, where the GP is the 'gatekeeper' to all further medical services, we assume that all GBS patients visit their GP first. The GP refers the patient to an outpatients' clinic. In order to confirm the diagnosis, a spinal puncture and an EMG examination are performed by the neurologist. In the Netherlands, all GBS patients are admitted to the hospital (GBS group Rotterdam, pers. communication). The length of the hospitalisation and the applied treatment, however, depend on the severity grade and the age of the patient. Within this study we assume, according to the country-wide number of hospital beds, that 14% of the patients would be admitted to a university hospital and 86% would be admitted to a regular hospital (Oostenbrink et al., 2000). For each GBS patient it is randomly determined if the patient is referred to a university hospital or to a regular hospital.
The assumed costs/unit for medical services linked to the diagnostic process of the illness are summarised in Table 5.3.

Table 5.3. Assumed cost estimates/unit for medical services linked to the diagnostic process of GBS (year 2000).

Medical service	Costs/unit (€)	Source
GP-visit	17.8	Oostenbrink et al. (2000)
Outpatients' clinic visit in regular hospital	43.7	Oostenbrink et al. (2000)
Outpatients' visit in university hospital	77.7	Oostenbrink et al. (2000)
EMG examination (including costs for specialist)	38.4	Anonymous (2000a)
Spinal puncture (including costs for specialist)	48.4	Anonymous (2000a)

Figure 5.1. The different severity grades of Campylobacter-associated GBS patients modelled in this study. A distinction between young GBS patients (<50 years) and elderly GBS patients (≥ 50 years) is made. The estimated mean and attendant uncertainty of cases/year is shown.

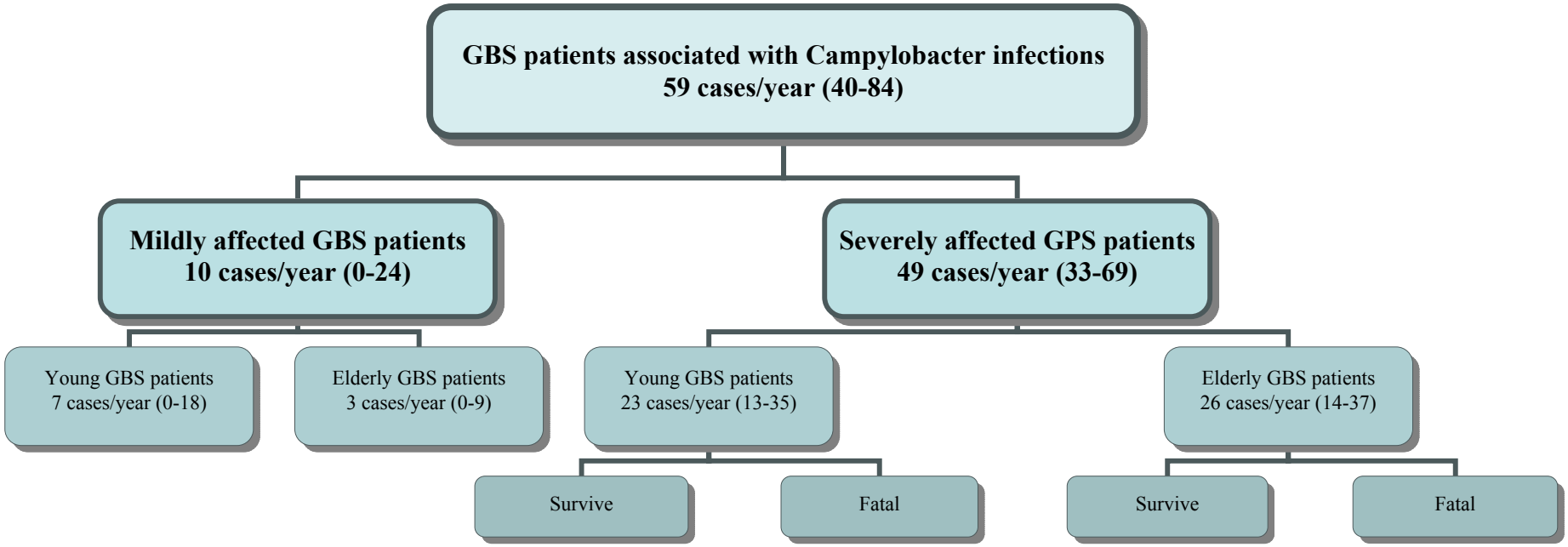
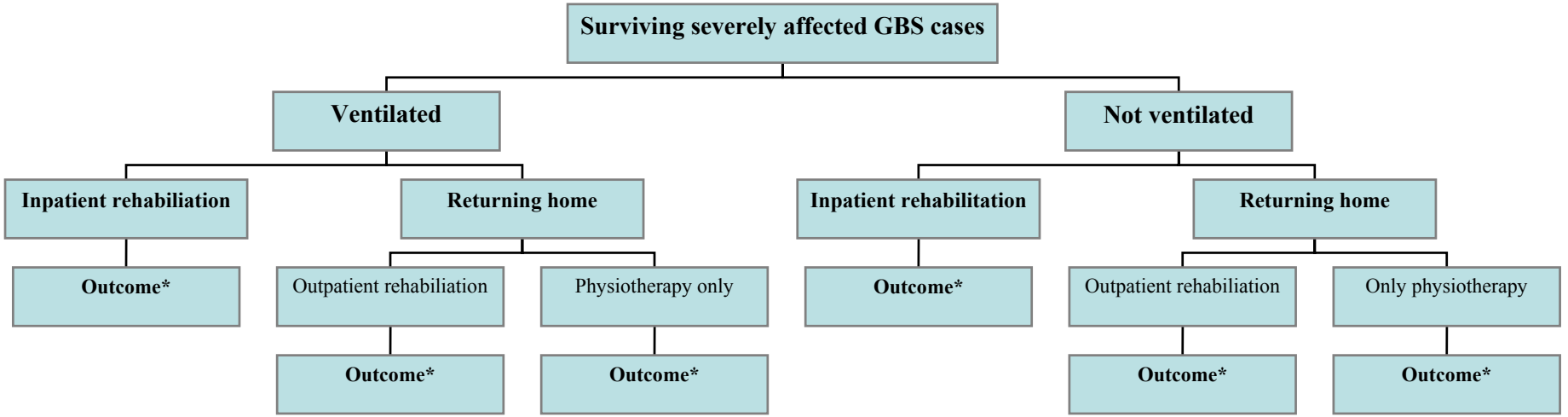
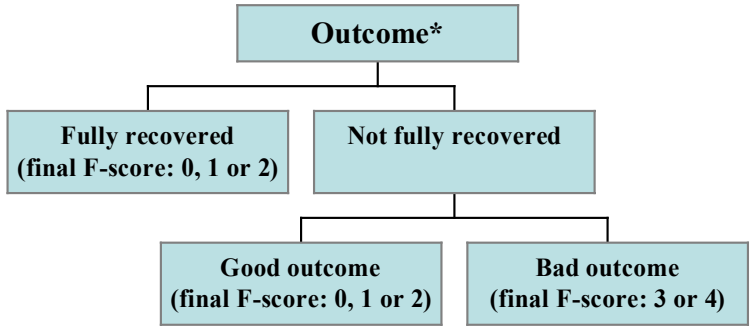


Figure 5.2. Severely affected and surviving GBS patients and the different health states modelled.



* Outcome:



Note: GBS patients had reported themselves to have 'fully recovered' or 'not fully recovered' from the disease. Whereas the final F-score was based on medical criteria. We considered three groups because: fully recovered GBS cases returned earlier to their work than GBS cases with a good outcome but that had not fully recovered from the disease

Mildly affected GBS patients

Based on the retrospective Dutch study of Van Koningsveld et al. (2000), we estimated the average stay in hospital to be fourteen days for young and mildly affected GBS patients and twenty days for elderly and mildly affected GBS patients. In this study the variation in the length of the hospitalisation is considered by using exponential distributions (see Appendix V).

It is assumed that 30-50% of mildly affected GBS patients would receive an IVIg treatment (GBS group Rotterdam, pers. communication). By using a uniform distribution, we consider the uncertainty around this parameter and with the help of a Bernoulli (p) distribution, the variation between the patients is considered in this study. Assuming a five-day application of IVIg with a daily dose of 0.4 g/kg live weight (GBS group Rotterdam, pers. communication), the costs for an IVIg treatment in 2000 are estimated to be about € 5000 per treatment for an average person. In order to stimulate the mobilisation of GBS patients, it is assumed that every day during the hospitalisation stay half an hour of physiotherapy is applied (GBS group Rotterdam, pers. communication). Furthermore, it is assumed that for every mildly affected patient a rehabilitation doctor is consulted at least once during the hospital stay (GBS group Rotterdam, pers. communication).

After hospital discharge, it is expected that about 60-75% of mildly affected GBS patients would need physiotherapy for approximately twelve weeks (GBS group Rotterdam, pers. communication). The number of physiotherapy consultations varies between one, two and three times/week, with equal probabilities (Duniform distribution). A few mildly affected GBS patients would need additional consultations in order to improve their mobility (GBS group Rotterdam, pers. communication). In this study we therefore assumed that approximately 5% of mildly affected GBS patients would need nine additional physiotherapy consultations. Furthermore, it is assumed that two additional consultations with the neurologist by the patients would occur as follow-up. For each consultation we calculate the costs for an outpatients' clinic visit, according to the guidelines in Oostenbrink et al. (2000). Furthermore, according to the Dutch system, we calculate a short subscription fee for the first consultation of the neurologist. Given the long duration of the illness, an additional subscription fee for the neurologist is assumed. All costs are assumed to occur within the first year after disease onset.

The assumed costs/unit for medical services of hospitalised mildly affected GBS patients and for follow-up by the neurologist are summarised in Table 5.4.

Table 5.4. Assumed costs/unit for medical services of a mildly affected GBS patient (year 2000)

Medical service	Costs (€)/unit	Source
IVIg treatment (average per treatment)	5,000	Anonymous (2000a)
Regular hospital room fee (per day)	252.5	Oostenbrink et al. (2000)
University hospital room fee (per day)	354.9	Oostenbrink et al. (2000)
Physiotherapy/consultation	19.4	Oostenbrink et al. (2000)
Consultation of specialist in regular hospital	43.7	Oostenbrink et al. (2000)
Consultation of specialist in university hospital	77.7	Oostenbrink et al. (2000)
Medical subscription fee (rehabilitation doctor)	54.9	Anonymous (2000a)
Short subscription fee (neurologist)	61.7	Anonymous (2000a)
Additional subscription fee (neurologist)	75.3	Anonymous (2000a)

Severely affected GBS patients

Based on data collected during the retrospective Dutch study of Van Koningsveld et al. (2000), we estimated the average stay in hospital to be 33 days for young, severely affected and *not* mechanically ventilated GBS patients and 47 days for elderly, severely affected and *not* mechanically ventilated GBS patients. Approximately 21% of severely affected GBS patients needed mechanical ventilation during their hospital stay. Mechanically ventilated GBS patients had on average a longer hospital stay with an average of 88 and 104 days for young and elderly GBS patients, respectively. Both young and elderly severely affected and mechanically ventilated GBS patients stayed on average 40 days in the Intensive Care Unit (ICU). Apart from the stay in ICU, young and elderly mechanically ventilated GBS patients stayed on average 42.5 and 62.0 days, respectively, in regular hospital rooms. GBS patients with a long stay in ICU generally have a slow recovery process, and will therefore also stay hospitalized for a longer period once dismissed from the ICU. In the model this correlation was considered by assuming that young, severely affected and ventilated GBS patients and elderly, severely affected and ventilated GBS patients would stay in a regular hospital for approximately 1.05 times and 1.2 times their stay in ICU, respectively. In this study, the variation in the length of the hospital stay is considered by using exponential distributions (Appendix V). For patients in an ICU unit, we assume a medical subscription fee for an anaesthesiologist. The daily room fees for ICU in a regular or an university hospital are € 1218, including the costs for specialists. But apart from these costs, according to Anonymous (2000a), additional costs for a neurologist and an anaesthesiologist should be considered during the first days of a mechanically ventilated patient. These additional costs were calculated and are summarised in Table 5.5.

Table 5.5. Cumulative additional costs for every mechanically ventilated GBS patient in ICU, depending on the length of ICU stay. Based on Anonymous (2000a).

	Days in intensive care								
	1	2	3	4	5	6	7	8	9
Cumulative costs (€)	340	506	673	839	1,006	1,061	1,116	1,170	1,225
	Days in intensive care (suite)								
	10	11	12	13	14	15	16	17	>17
Cumulative costs (€)	1,280	1,335	1,390	1,445	1,500	1,527	1,554	1,581	1,581

It is assumed that in 100% of the cases an IVIg and a methylprednisolon (MP) treatment is applied (GBS group Rotterdam, pers. communication). In about 3.8% of the severely affected GBS cases a second or even third treatment with IVIg is needed (Van Koningsveld, pers. communication). Just as with mildly affected GBS patients, a half an hour of physiotherapy per day in order to stimulate the mobilisation of the GBS patients (GBS group Rotterdam, pers. communication) is assumed.

Some severely affected GBS patients do recover quickly and can return to their home after hospital discharge, whereas the other GBS patients will need additional rehabilitation when leaving hospital. Most GBS patients returning home after hospital discharge require additional physiotherapy at the end of their stay in order to increase their mobility. We therefore assume that this group of patients would have two physiotherapy consultations per day in their last week in hospital (GBS group Rotterdam, pers. communication).

After leaving hospital, it is assumed that three additional visits to the neurologist by all severely affected GBS patients would occur as follow-up (GBS group Rotterdam, pers. communication). One or two, and in extreme cases even three yearly subscription fees for

consultations of a neurologist are assumed, depending on the length of hospitalisation and follow-up period.

Bernsen et al. (1997, 2001, 2002) followed 122 of the 150 severely affected GBS patients of the Dutch IVIg trial of Van Der Meché et al. (1992) for up to six years after disease onset. For 111 of the 122 patients we know if patients returned home or were admitted to a rehabilitation centre. But, for the patients returning home, we do not know if they had outpatient rehabilitation or only physiotherapy. According to these data, for young and elderly severely affected but *not* mechanically ventilated patients, 16% and 31% respectively would be transferred to a rehabilitation centre. Of the young and elderly severely affected and mechanically ventilated patients, 26% and 46% respectively would be admitted to inpatient rehabilitation. This is a little bit lower than the 40% of hospitalised GBS patients requiring admission to inpatient rehabilitation mentioned by Meythaler (1997). By using beta distribution we consider the uncertainty around the assumed percentage of inpatients rehabilitation and with the help of a Bernoulli (*p*) distribution, the variation between the patients is considered in this study (see Appendix V). No significant difference was found for the length of rehabilitation between *not* mechanically ventilated and mechanically ventilated patients. There was also no significant difference between the two age groups, but with a p-value of 0.076, there seems to be a tendency. We therefore estimated the length of the stay in the rehabilitation centre for the two age groups separately. For young and severely affected GBS patients, the average length was 115 days and for elderly and severely affected GBS patients, the average length was 225 days. Using an exponential distribution, the variation of the length of the stay in the rehabilitation centre is considered in our study (Appendix V). Based on Meythaler et al. (1997) we assume that all patients receive three to four hours of rehabilitation exercises daily (DUniform distribution). The costs for the rehabilitation doctor are considered in the room fees of the rehabilitation centre (Oostenbrink et al., 2000).

After leaving the rehabilitation centre, it is assumed that three additional visits to the rehabilitation doctor by the patient would occur as follow-up (GBS group Rotterdam). One or two, and in extreme cases even three yearly subscription fees for consultations of rehabilitation doctors are assumed, depending on the rehabilitation length.

Additional physiotherapy might be needed when leaving the rehabilitation centre. However, no information was available. We therefore had to make some assumptions. It was assumed that patients with a good outcome (F-score 0 or 1) would in most cases recover very fast, and therefore half a year of physiotherapy was considered to be sufficient for these patients. Patients with a moderate outcome were assumed to need physiotherapy for about one year, and patients with a bad outcome (F-score 3 or 4) would probably need longer physiotherapy, whereby at the weekly frequency of physiotherapy consultations will decrease over time. We therefore assumed that these patients would need physiotherapy for about two years, but with on average only one consultation per week (Rob Bernsen, pers. communication). The number of GBS patients in the different groups was based on the observed final F-score at three to six years after illness onset by Bernsen et al. (2002). These findings and the assumptions made are summarised in Table 5.6.

Table 5.6. Number and percentage of young severely affected GBS patients and elderly severely affected GBS patients with a final F-score of 0 or 1, 2 and 3 or 4; and the assumptions made about length of physiotherapy and the number of visits/week.

F-score at the end	Young GBS patients		Elderly GBS patients		Assumed physiotherapy	
	n	%	n	%	Years	visits/week
0 or 1	40	78	44	62	0.5	1 or 2[1]
2	9	18	15	21	1	1 or 2[1]
3 or 4	2	4.0	12	17	2	1

[1)] Using a DUniform distribution in our model.

However, severely affected elderly GBS patients with a high F-score at hospital discharge and a high probability of a bad outcome (final F-score of 3 or 4) might not be admitted to inpatient rehabilitation, but might be admitted directly to a nursing home (GBS group Rotterdam, pers. communication). In our model we therefore assumed that severely affected GBS patients older than 75 years and who would have a bad outcome (poor recovery) would be admitted to a nursing home. It was assumed that during the first two years of admission in the nursing home, physiotherapy would be applied. Furthermore, it is assumed that three additional consultations with the patients by the rehabilitation doctor would occur as follow-up. GBS patients admitted to a nursing home were assumed to stay in a nursing home for the rest of their life.

For severely affected patients returning home and using ambulant rehabilitation facilities, no information is available. We assumed, independently of age, that approximately 10-15% of severely affected GBS patients (Bernsen, personal communication), would use ambulant rehabilitation facilities. Due to a lack of data, we will assume a similar length of ambulant rehabilitation as for patients admitted to inpatient rehabilitation. However, unlike patients admitted to a rehabilitation centre, we assume that ambulant rehabilitation patients would require ambulant rehabilitation only three days per week (Bernsen, pers. communication). Just as for patients admitted to inpatient rehabilitation, it is assumed that ambulant rehabilitation patients would also have three to four hours of rehabilitation exercises daily. After finishing the ambulant rehabilitation, it is assumed that three additional visits to the rehabilitation doctor by the patient would occur as follow-up (GBS group Rotterdam). One or two and in extreme cases even three yearly subscription fees for consultations with rehabilitation doctors are assumed , depending on the rehabilitation length. Additional physiotherapy might be needed when finishing rehabilitation. However, no information was available. We therefore make the same assumption as for patients admitted to inpatient rehabilitation; see Table 5.6.

No information is available for severely affected GBS patients returning home after hospitalisation and not needing ambulant rehabilitation. We therefore assume, just as for the other severely affected GBS patients, that depending on the expected end F-score these patients would get physiotherapy during half a year, one year or two years after hospital discharge (see Table 5.6). Furthermore, it is assumed that after hospital discharge these patients would have three additional visits to the rehabilitation doctor as a follow-up, requiring a one-year subscription fee for rehabilitation doctors.

Due to a lack of data, it was assumed that 50-100% of GBS patients transferred to a rehabilitation centre and 100% of GBS patients transferred to a nursing home would be transported by ambulance.

The assumed costs/unit for medical services of severely affected GBS patients are, apart from those medical services already listed in Table 5.5, summarised in Table 5.7.

Table 5.7. Assumed costs/unit for medical services of a severely affected GBS patient (year 2000).

Medical service	Costs (€)/unit	Source
IVIg treatment	5,000	Anonymous (2000a)
MP treatment	75	Anonymous (2000a)
ICU fee (per day)	1,218	Oostenbrink et al. (2000)
Regular hospital room fee (per day)	252.5	Oostenbrink et al. (2000)
University hospital room fee (per day)	354.9	Oostenbrink et al. (2000)
Physiotherapy/consultation	19.4	Oostenbrink et al. (2000)
Consultation of specialist in regular hospital	43.7	Oostenbrink et al. (2000)
Consultation of specialist in university hospital	77.7	Oostenbrink et al. (2000)
Medical subscription fee (anaesthesiologist)	54.4	Anonymous (2000b)
Yearly subscription fee (rehabilitation doctor)	69.0	Anonymous (2000b)
Short subscription fee (neurologist)	61.7	Anonymous (2000a)
Additional subscription fee (neurologist)	75.3	Anonymous (2000a)
Room fee for inpatient rehabilitation/day	286.9	Oostenbrink et al. (2000)
Rehabilitation/hour[1]	85.5	Oostenbrink et al. (2000)
Room fee for nursing home/day	65.5	Oostenbrink et al. (2000)
Transport by ambulance	155.9	Oostenbrink et al. (2000)

[1)] Costs for rehabilitation are accounted for inpatient as well as for ambulant rehabilitation.

5.4.2 Direct non-health care costs

No information was available on how patients would travel to their GP and to the hospital. We assumed, therefore, just as with GE cases (see 3.4.2) and ReA cases (see 4.4), that patients travelling to/from hospital always use either a car or a public transport. Most likely half of the patients visiting a GP would bike or walk, whereas the other half would take a car or public transport. No information was available on how patients would travel to their physiotherapist, specialist or to the outpatients' clinic. In the Netherlands specialists are mostly linked with hospitals, as are outpatients' clinics, and consultations do take place within the hospital. We therefore make the same assumptions for outpatient care visits/specialist visits as for hospitalised patients. For physiotherapy no information was available on the distance between patient home and physiotherapist. Like GPs, physiotherapists are spread across the communities and are not concentrated in hospitals only. We therefore assumed the same distance from patient home to physiotherapists as for the GP visit. Here, too, we assumed that about 50% of the patients would take a car or public transport in order to visit their physiotherapist. The uncertainty of this factor was also considered in this study. Travelling with public transport or private car was assumed to cost approximately € 0.12 / km in 2000 (Oostenbrink et al., 2000). Travelling with a car or public transport in order to visit a GP is estimated to cost € 0.44 /visit, and travelling to a hospital/specialist are estimated to cost € 1.70/visit.

Given the severity of the symptoms many patients receive informal care (Bernsen, pers. communication). However, no information is available here.

In the study of (Bernsen et al., 2002) patients were also asked to report whether they had bought additional aid/tools after hospital and/or inpatient rehabilitation discharge. Part of these costs, however, would be paid by the health insurance and might therefore be

considered as direct health care costs, but part of these costs would have to be paid by the patients themselves (direct non-health care costs). However, only a few patients had filled in these questions. Furthermore, according to Bernsen (pers. communication), some of the patients that filled in these questions forgot to enumerate all the additional tools used. For example, one of the patients reported that he needed crutches as an additional tool after dismissal, but forgot to mention that he also got an extra bed for the first months after dismissal. Necessary amendments to changes of the house or part of the house due to the invalidity of the patients, for example reconstructing the bathroom, were not reported at all by the patients. However, such changes would be more expensive than most of the additional tools enumerated. Given the fact that we had insufficient information on the real number of additional aids and tools needed as well as home remodelling applied, we would highly underestimate the real costs for additional aid/tools and home remodelling. By considering only a part of these costs, however, we might create a wrong impression. We therefore decided not to consider them at all.

5.4.3 Indirect non-health care costs

No information is available on the duration of sickness leave of mildly affected and working GBS patients. According to the Rotterdam GBS group mildly affected GBS patients will stay off work for some time after hospital discharge. Their suggestion was to also calculate the total friction period of 123 days for these mildly affected GBS patients. However, given the relatively mild symptoms, we thought that this would result in an overestimation. Some of these mildly affected GBS patients might return immediately to their work after discharge from hospital. Given our uncertainty about the sickness leave of mildly affected GBS patients, with the help of a uniform distribution we modelled a sickness leave ranging from only hospitalisation to the whole friction period (123). Additional sensitivity analysis will be applied. Mildly affected GBS patients, however, once returning to their work, need some additional time off work in order to visit their physiotherapist or their neurologist. Given our uncertainty, we applied a uniform distribution in order to estimate the time spent off work, ranging from 0 to 0.25 days/ consultation for a GP or physiotherapy, and 0.25 to 1 days/consultation for a specialist/outpatient hospital visit, just as was done for the calculation of indirect non-health care costs related to GE and ReA.

In the follow-up study of Bernsen et al. (2002, 2001, 1997), 82 severely affected GBS patients were working before their illness. Because of GBS, 31 of these 82 GBS patients experienced a change in their working life. Nine of these 31 patients had a small change in their working life, whereas the other 22 patients experienced a considerable working life change. Three of the nine patients with a small working life change had ‘another job but with the same job requirements’, and six had ‘the same job, but lower job requirements’ (Bernsen et al., 2002). Of the 22 patients with a considerable working life change, five patients started working again, but at a lower level and were declared partly disabled, while the seventeen other patients had to stop working and never returned to work during the three to six years follow-up period (Bernsen et al., 2002). Of these 22 patients six severely affected GBS patients had a bad outcome (F-score of 3 or 4) three to six years after disease onset. Five of these six patients were declared fully disabled, and the sixth person was declared to 75-100% disabled. Within this study we will assume that severely affected GBS patients with a bad outcome are considered completely disabled. In this study we further assume that on average 20% of severely affected GBS patients with a relatively good outcome (F-score 0, 1 or 2) would become fully or partly disabled for the rest of their lives due to GBS. However, given that we use the friction cost method (see 2.2.2), we calculate productivity losses only for 123

days, using the age-specific salary of an average person (see Appendix III). No further productivity losses will be considered for the patients subsequently declared disabled.

Furthermore, invalid GBS patients in the working life age are followed up by social authorities, resulting in some additional costs. But unemployed people are also followed up by social authorities, and savings can be achieved by replacing the GBS patients declared disabled with some of them. From the social perspective, these additional costs are washed out by the additional savings. We therefore did not consider these costs within this study.

However, for severely affected GBS patients in the working life and not considered as disabled, we consider a sickness leave of a maximum of 123 days, according to the friction cost method. And once returned to work, we make the same assumption for time spent off work in order to visit their physiotherapist or specialist as was assumed for mildly affected GBS patients. In the follow-up study of Bernsen et al. (2002, 2001, 1997), 49 severely affected GBS patients reported full recovery from the illness at three to six years after disease onset and approximately 72 severely affected GBS patients reported not to have fully recovered from the illness three to six years after disease onset. The time period between disease onset and start of work was significantly different for fully recovered patients and not fully recovered patients. The average time spent between disease onset and starting work, part-time or full-time, was 160.7 days (24 patients) and 317 days (19 patients) for fully recovered and not fully recovered patients, respectively. In order to consider variability an exponential distribution was used.

5.5 Results

5.5.1 Estimated annual incidence of Campylobacter-associated GBS cases

The estimated cumulative probabilities of the mean, the 5^{th}, 50^{th} and the 95^{th} percentile of the annual incidence of GBS cases associated with Campylobacter infections in the Netherlands are shown in Figure 5.1. Here the total uncertainty is broken down into a variability-related component and an uncertainty-related component. The mean and attendant uncertainty for all GBS cases and the different health states are summarised in Table 5.8.

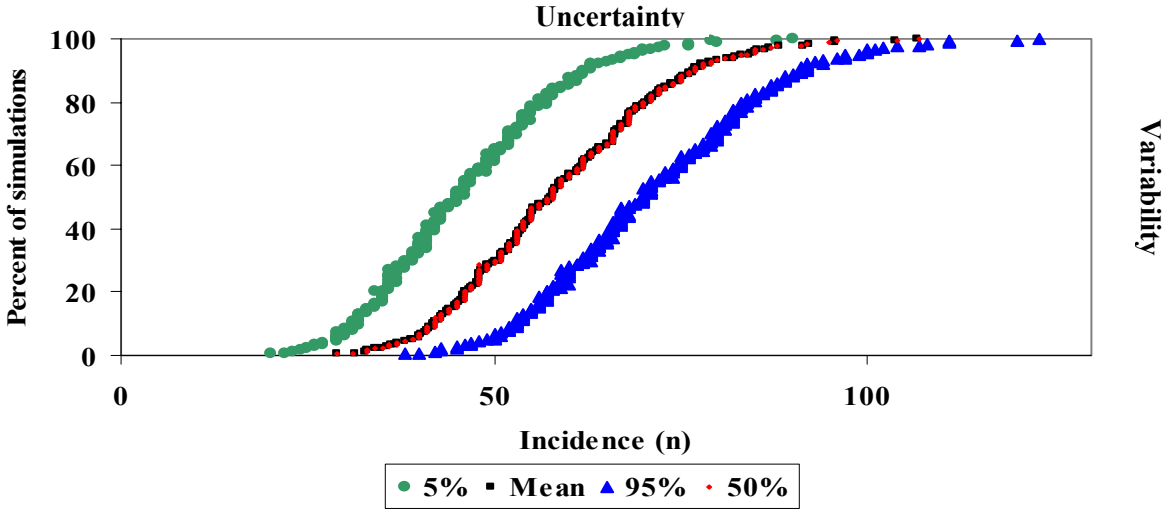


Figure 5.1. Estimated cumulative probabilities of the mean, 5th, 50th and 95th percentile of annual incidence of Campylobacter-associated GBS cases in the Netherlands, breaking down the total uncertainty into variability and uncertainty.

Table 5.8. Estimated mean and attendant uncertainty[1] of annual incidence of Campylobacter-associated GBS cases in the Dutch population, including the different health states of the disease.

	Estimated annual incidence			
	5%	Mean	50%	95%
Mild GBS cases	0	10	9	24
Sever GBS cases	33	49	48	69
Fatal cases	1	2	2	3
GBS cases (all)	40	59	58	84

[1)] The model parameters used in this study are often uncertain or are variable or both. We therefore not only show for example the average annual incidence but also the 5th, 50th and 95th percentile, representing the uncertainty in the estimated average.

5.5.2 Estimated disease burden due to Campylobacter-associated GBS cases

The estimated cumulative distribution of DALYs related to the estimated number of annual Campylobacter-associated GBS cases is summarised in Figure 5.2. Here the total uncertainty is broken down into a variability-related component and an uncertainty-related component. The estimated mean and the attendant uncertainty for the outcomes of YLL, YLD and DALYs related to the estimated annual GBS cases is summarised in Table 5.9, discounted and not discounted. In Figure 5.3 the estimated average number of DALYs related to GBS cases is separated out into a) mildly affected GBS cases, b) severely affected and surviving GBS cases and c) severely affected and fatal GBS cases. Looking at the tables and figures it becomes clear that the largest part of the estimated disease burden of GBS cases is caused by the group of severely affected and surviving GBS cases. Although most severely affected and surviving GBS cases will partly recover from their illness within the first year after disease onset, most patients will have some remaining symptoms for the rest of their lives. As a consequence, quality of life will be reduced for the remaining life expectancy of each of these

patients. The range of these 'remaining' symptoms is wide, ranging from not being able to concentrate for a longer period to being bedridden for life.

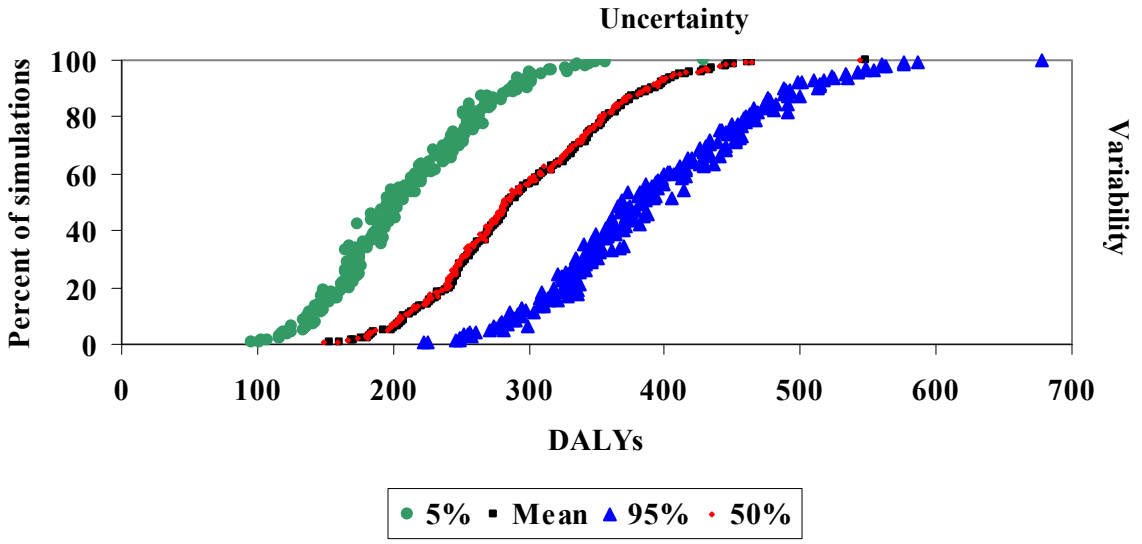


Figure 5.2. Estimated cumulative distribution of the mean, 5th, 50th and 95th percentile of disease burden due to Campylobacter-associated GBS cases in the Netherlands, breaking down the total uncertainty into variability and uncertainty (undiscounted figures).

Table 5.9. Estimated mean and attendant uncertainty of discounted and not discounted YLD, YLL and DALYs of Campylobacter-associated GBS cases in the Netherlands.

Description	Disease burden							
	Not discounted				Discounted at 4%			
	5%	Mean	50%	95%	5%	Mean	50%	95%
YLD	172	265	254	371	100	149	145	205
YLL	17	33	31	56	11	20	20	35
DALY	199	298	286	413	114	169	166	234

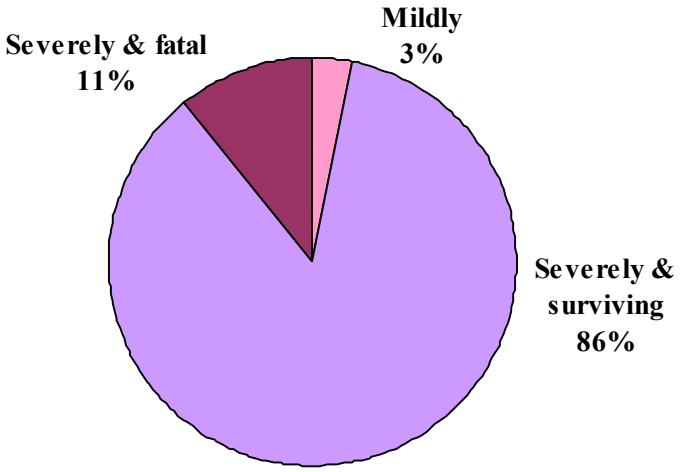


Figure 5.3. Distribution of the mean disease burden estimate due to Campylobacter associated GBS cases, broken down into: mildly affected GBS cases, severely affected and surviving GBS cases and severely affected and fatal GBS cases.

5.5.3 Estimated cost-of-illness due to Campylobacter-associated GBS cases

The estimated cumulative distribution of cost-of-illness due to Campylobacter-associated GBS cases is shown in Figure 5.4. Here the total uncertainty is broken down into a variability-related component and an uncertainty-related component. The estimated mean and the attendant uncertainty of the total cost-of-illness associated with GBS cases are summarised in Table 5.10, discounted (4%) and not discounted. Most costs occur within the first years after disease onset. Therefore discounting, if used at all, does not have a significant impact on the estimated costs. The direct health care costs account for the bulk, more than 90%, of the total cost-of-illness (see Figure 5.5). The costs of hospitalisation and rehabilitation are the two most important subcategories within the category of direct health care costs. Rehabilitation and physiotherapy, and as such rehabilitation costs, depend on the severity grade of the symptoms at nadir. Mildly affected GBS patients have, for the most part, only hospitalisation costs and some expenditure for additional physiotherapy (see Table 5.11). For severely affected GBS patients the rehabilitation costs are considerable (see Table 5.11).

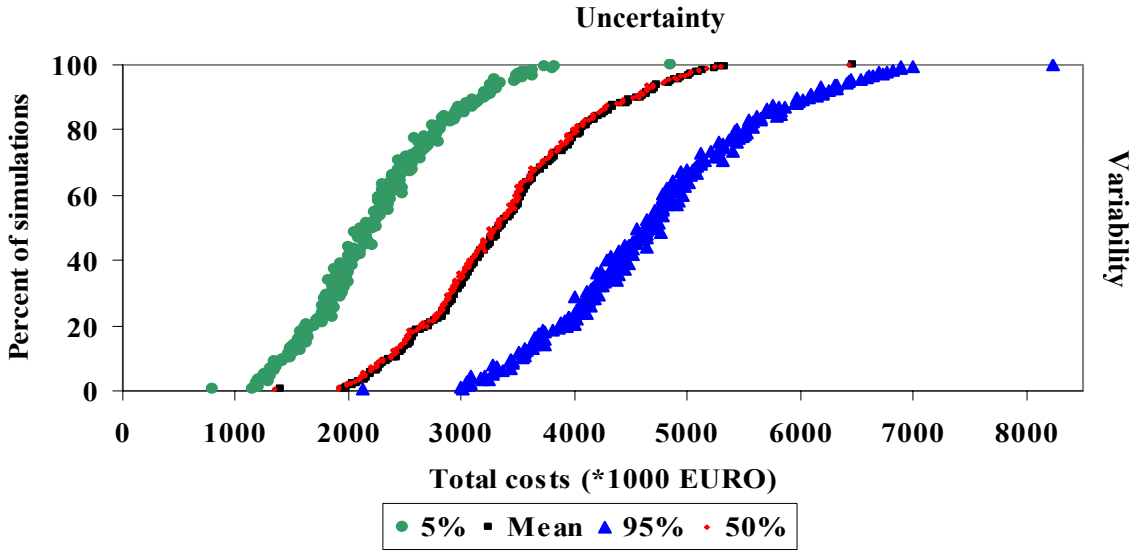


Figure 5.4. Estimated cumulative distribution of the mean,5th, 50th and 95th percentile of cost-of-illness related to Campylobacter-associated GBS cases for 2000, breaking down the total uncertainty into variability and uncertainty (undiscounted figures).

Table 5.10. Estimated mean and attendant uncertainty of discounted and undiscounted direct health care costs, direct non-health care costs, indirect non-health care costs and total costs respectively, due to Campylobacter-associated GBS cases (2000).

	Estimated costs (*million €)							
	Not discounted				Discounted at 4%			
	5%	Mean	50%	95%	5%	Mean	50%	95%
Direct health care costs	2.0	3.1	3.1	4.5	2.0	3.1	3.0	4.4
Direct non-health care costs	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Indirect non-health care costs	0.2	0.3	0.3	0.4	0.2	0.3	0.3	0.4
Total costs	2.2	3.4	3.3	4.9	2.1	3.3	3.3	4.8

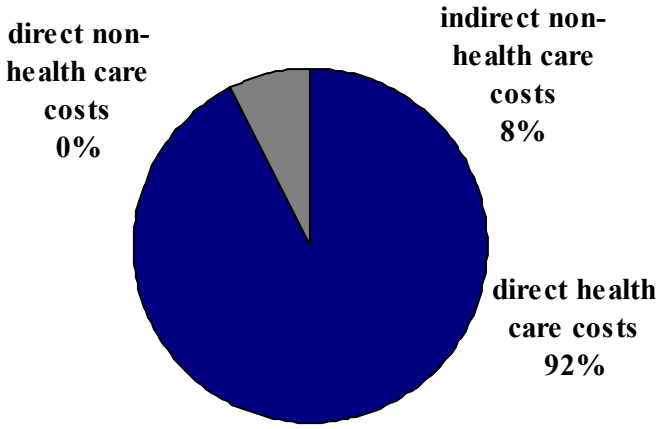


Figure 5.5. Breakdown of the estimated mean of the total costs due to Campylobacter-associated GBS cases into direct health care costs, direct non-health care costs and indirect non-health care costs (undiscounted figures).

Table 5.11. Breakdown of the average estimated direct health care costs for hospitalization and rehabilitation of mildly affected GBS patients and severely affected GBS patients for 2000 (undiscounted figures).

escription	Average estimated direct health care costs			
	Hospitalisation costs		Rehabilitation costs	
	Absolute (*1000 €)	Relative %	Absolute (*1000 €)	Relative %
Mildly affected GBS cases	68	94	4	6
Severely affected GBS cases	1,423	46	1,678	54

The average cost-of-illness per average Campylobacter-associated GBS case was estimated in this study to be nearly € 60,000 /case for the year 2000. The average costs for an average mildly affected GBS patient were estimated to be approximately € 10,000, whereas for an average severely affected GBS patients the average costs were estimated to be approximately € 70,000 (see Table 5.12).

Table 5.12. The average estimated cost-of-illness per average Campylobacter-associated GBS case, mildly affected GBS case and severely affected GBS case for the year 2000 (undiscounted figures).

Description	Average estimated costs (*1000 €/case)		
	Direct health care costs	Indirect non-health care costs	Total costs
GBS case	53.8	4.4	58.2
Mild GBS case	7.2	3.0	10.1
Sever GBS case	63.3	4.7	68.0

5.5.4 Sensitivity analysis

Given that running the model requires considerable time, we considered uncertain parameters as 'given' when doing sensitivity analysis. The 'average' value of the distributions describing uncertain parameters were considered as being 'best guesses'.

In our base scenario, we modelled the length of sickness leave of mildly affected GBS patients as an uniform distribution with as a minimum the length of hospitalisation and as a maximum the friction period, which is 123 days. No data were available here. In order to determine the impact of this assumption, sensitivity analysis was applied by assuming a) that all mildly affected GBS patients would stay off work only during hospitalisation and b) that the sickness leave of all mildly affected GBS patients would last at least the 123 days of the friction period. The average estimated indirect non-health care costs due to all GBS cases, approximately € 260,000, would a) decrease by € 21,200 and b) increase by € 26,000, respectively. And although changes of the assumed length of sickness leave of mildly affected GBS patients increase or decrease the average estimated indirect non-health care cost by ~ 10%, this is less than 1% of the total cost-of-illness of GBS cases. Therefore the assumptions made on the length of sickness leave of mildly affected GBS patients will have no major effect on our conclusions.

In our base scenario, we assumed that severely affected GBS patients who returned home after hospital discharge would need outpatient rehabilitation in 10-15% of cases. An earlier suggestion made by the GBS group from Rotterdam was that 40-45% of these GBS patients might need outpatient rehabilitation (our alternative scenario). This resulted in an increase of the direct non-health care costs and the total costs by more than 10%, or € 400,000.

5.6 Discussion

The estimated disease burden due to Campylobacter-associated GBS cases was, at an average of 299 DALYs, considerable, with a large uncertainty range of 199 DALYs (5^{th} Percentile) and 413 DALYs (95^{th} Percentile). And although we made the same assumptions about incidence and disability weights as Havelaar et al. (2000b), our estimate was slightly lower. The difference was partly due to the life expectancy used. For this study we used the Dutch standard life expectancy, which is slightly lower than the WHO/World Bank recommended standard life expectancy used by Havelaar et al. (2000b). Further, we used another more representative data set that included more patients from a larger geographical area. Hereby it turned out that especially elderly GBS patients are on average older at disease onset than assumed in the earlier study.

However, unlike Havelaar et al. (2000b) and other studies, within this study also we estimated the cost-of-illness due to GBS cases. The estimated average costs per average GBS case with Campylobacter as a previous infection are, at € 60,000 /case, quite considerable, although not all costs were and could be considered due to the non-availability of data.

Within this study we did not consider the costs for informal care of GBS patients, which would be required mainly by severely affected GBS patients when returning home after discharge from hospital or rehabilitation. Furthermore, we did not consider the costs for additional tools and aids or remodelling of housing required for severely affected GBS patients with a relatively bad outcome after discharge from hospital or rehabilitation, which can lead to considerable costs. But due to the lack of data, an estimate of these costs could not be made. Therefore the cost-of-illness due to GBS cases estimated here is an underestimation

of the real costs. To our knowledge there are also no previously published studies that estimate these costs. In order to come up with a more appropriate estimate of the cost-of-illness related to GBS cases, whether associated with Campylobacter infections or not, more data need be collected.

By applying the friction cost method, direct health care costs turned out to account for the majority of the total cost-of-illness due to GBS cases. Whereas in other studies that did not apply the friction cost method, e.g. Buzby et al. (1997a, b), indirect non-health care costs were for the most part more significant than the direct health care costs. By applying the friction cost method, we do consider only productivity losses for a maximum of 123 days for cases with long-lasting sickness leave, cases declared disabled due to the illness and fatal cases. By using the human capital approach, productivity losses would have been considered either until the patient returns to work or, for patients declared disabled and fatal cases, until their age of retirement. Therefore the estimated indirect non-health care costs per GBS case within other cost-of-illness studies are generally higher than the indirect non-health care costs estimated in our study.

Unlike Anonymous (2001), Buzby et al. (1997a, b), Lake et al. (2000) and Scott et al. (2000), we did consider rehabilitation costs separately from the hospitalisation costs. Particularly for severely affected GBS cases, rehabilitation costs seemed to be a significant cost category and accounted in our study for more than half of the total direct health care costs. By not considering the rehabilitation costs, however, all previously published studies omitted a considerable cost category.

Anonymous (2001), Buzby et al. (1997a, b), Lake et al. (2000), Scott et al. (2000) and (Withington and Chambers, 1997) were other studies that estimated the hospitalisation costs of Campylobacter-associated GBS cases. However, apart from the study of Buzby et al. (1997a, b) and Anonymous (2001), each study provided only little data, making a comparison of the estimated direct health care costs due to GBS cases seemingly impossible. Given that Anonymous (2001) is mainly an update of Buzby et al. (1997a, b), in order to estimate the costs for the year 2000, we will concentrate our comparison mainly on Buzby et al. (1997a, b). In his study Buzby et al. (1997a, b) did consider only severely affected GBS cases, separating the GBS patients into two age/ventilation categories. For the first age/ventilation category the authors considered a 30-year-old individual as representative of patients with GBS who were not mechanically ventilated, whereas for the second age/ventilation category they considered a 47-year-old individual as representative of patients with GBS who were mechanically ventilated. Mildly affected GBS cases were not considered at all in either study.

Although we consider additional costs for rehabilitation, something that Buzby et al. (1997a, b) and Anonymous (2001) had not considered, their estimated direct health care costs per severely affected GBS patients are much higher than ours. For example, Buzby et al. (1997b) estimated that the medical charge for severely affected GBS patients would be approximately $110,000/case (in 1995 dollars). However, in the study applied for the year 2000 the medical charges for GBS patients were estimated to be only ~$81,000/severly affected GBS case. However, an explication as to why the updated estimate of the direct health care costs related to GBS cases turned out to be lower was not given. Nevertheless, both studies came up with a higher estimate than the estimated approximately € 63,000 direct health care costs per average severely affected GBS case in our study. And the difference is even larger than that implies, as we also included costs for rehabilitation in the estimated average direct health care costs/average severely affected GBS case. The mean difference between our study and that of

Buzby et al. (1997b) lies partly in the assumptions made and partly in the higher costs/unit used by Buzby et al. (1997b). The assumptions made on the use of ICU and the length of stay in the ICU vary particularly significantly between our study and Buzby et al. (1997b). We assumed that only ventilated patients would be treated in an ICU, which was confirmed by practising neurologists, whereas Buzby et al. (1997b) assumed that non-ventilated GBS patients would also be treated for an average of 6 days in an ICU. Further, we assumed an average stay in the ICU of only 41 days for ventilated patients, whereas Buzby et al. (1997b) assumed that this would be on average 68 days. Although in Buzby et al. (1997b) the costs/medical unit used are expressed in 1995 dollars (US), the costs assumed for an ICU room/day and hospital room are double and triple, respectively, of the costs/unit assumed in our study (year 2000). This is to be expected. The direct health care costs in the US are among the highest in the world.

Despite all assumptions made as well as the fact that the costs estimated here are probably an underestimation, the estimated cost-of-illness due to Campylobacter-associated GBS cases are, at an average of € 3.4 million/year, considerable costs for Dutch society. Furthermore, although the incidence is on average only ~60 GBS cases with a wide range of uncertainty, the disease burden associated with these cases are, at an average of 300 DALYs/year, non-negligible.

6 Campylobacter-associated inflammatory bowel disease cases*

6.1 Background information

Crohn's disease and ulcerative colitis are collectively classified as inflammatory bowel disease (IBD). IBD is characterised as chronic intestinal disorders of unknown aetiology that can spread over many decades. Both diseases can occur at any age (Ward et al., 1999). However, the peak age of disease onset is early in the third decade of life (Bodger, 2002; Rosch et al., 2002b; Ward et al., 1999). Once diagnosed, a patient's course of illness often fluctuates, varying among mild, moderate, and severe disease states, or remission (Feagan et al., 2000). Although the disorder is heterogeneous, patients with Crohn's disease can be categorised by disease location, severity, and behaviour (inflammatory, fibrostenotic, fistulizing) (Marshall et al., 2002). Since patients with IBD have a near-normal life expectancy, the focus of treatment is on controlling symptoms and improving quality of life (Feagan et al., 2000). Management strategies can broadly dichotomise to those that treat acute, active disease and those that prevent relapse among patients in remission. None of the available medical therapies is uniformly effective and many, like systemic corticosteroids, can cause serious side effects. Severely ill patients may require hospitalisation, surgery, or both. This last group of individuals is likely responsible for most of the treatment costs (Feagan et al., 2000).

6.2 Estimating annual incidence of Campylobacter-associated IBD cases

Shivananda et al. (1996) estimated the incidence of IBD in Europe to be approximately 5.6 (95% CI: 2.8 to 8.3) Crohn's disease patients and 10.4 (95% CI: 7.6 to 13.1) ulcerative colitis patients per 100,000 population. In the Netherlands, the annual incidence for Crohn's disease is estimated to be 6.9 per 100,000 population and for ulcerative colitis the estimated annual incidence is 10 per 100,000, resulting in an incidence for IBD of 17 per 100,000 population per year (Van Hogezand, 2002).

Based on a registry-based, matched cohort study, Helms et al. (2003) estimated the excess mortality associated with infections with *Campylobacter* spp., *Salmonella* spp., *Yersinia enterocoliticica*, and *Shigella* spp.(see section 3.1.3.4 for details). However, in a separate study the authors also estimated the relative risk of developing IBD for laboratory-confirmed Campylobacter infections within the first year after symptom onset (results not yet published). The estimated additional risk to develop IBD after a laboratory-confirmed Campylobacter infection was, according to their findings, 11.46 (Helms, M., Statens Serum Institut, Copenhagen, Denmark, 2003, Unpublished data). With an average of 5650 laboratory-confirmed Campylobacter cases in the Netherlands, the estimated average annually Campylobacter-associated IBD incidence would be eleven cases. According to the Danish findings, the majority of these eleven IBD cases would develop ulcerative colitis. In the Danish study, ulcerative colitis was actually diagnosed in 70.5% of the cases, whereas Crohn's disease was diagnosed in 29.5% of the cases (Helms, pers. communication (2003)).

* Special thanks goes to Morten Helms from the Statens Serum Institute and his colleagues for sharing and letting us use their data.

The uncertainty of the probability that IBD patients had ulcerative colitis was considered by using a Beta distribution.

6.3 Estimating disease burden due to Campylobacter associated IBD cases

6.3.1 Symptom length and symptom severity

As already stated earlier, IBD is characterised as a chronic intestinal disorder of unknown aetiology. Crohn's disease, as one of the two diseases classed as IBD, is characterised by ulceration, stricturing and fistula formation (Bodger, 2002). 'Anatomically, Crohn's disease typically affects the distal small bowel (terminal ileum) and/or colon though it may involve any region of the intestinal tract and give rise to lesions at multiple sites in a discontinuous distribution' (Bodger, 2002). IBD is relatively uncommon and only in rare cases fatal. The major therapeutic goal for most patients with chronic illness is not a cure of the disease, but rather an improvement in function and life quality resulting from an alleviation of the illness or from a limitation of the progression of the disease (Ward et al., 1999). IBD patients mostly experience chronic relapsing episodes with intermittent acute clinical episodes, and this over decades (Bodger, 2002). Despite some periods of sometimes severe disease, the largest part of the clinical course of IBD is spent in remission (Bodger, 2002). This can be a spontaneous remission episode, a drug-induced remission episode or a post-surgery remission episode. Based on 174 diagnosed Crohn's disease patients, Silverstein et al. (1999) estimated for an average IBD patient, who would be 28.1 years old at disease onset, that the clinical course of a typical Crohn's disease patients would involve: 11.1 years in medical 'remission' (no drugs); 18.9 years in surgically-induced remission; 12.7 years taking an aminosalicylate drug; and 3.2 years taking oral corticosteroids or immuno-suppressants. The underlying assumption was that estimated life expectancy of Crohn's patients would not differ from those in the general population. According to Hay and Hay (1992b), the excess mortality for ulcerative colitis patients is also negligible. Therefore we assumed in this study that IBD patients have the same life expectancy as the general population. Further, we will base our assumptions on the clinical course of IBD for average IBD patients on the estimates of Silverstein et al. (1999).

6.3.2 Disability weights

Assuming for an average IBD patient the clinical course of IBD as estimated by Silverstein et al. (1999), we had to define a disease disability weight for each of these stages. The disability weights for each model health state were obtained from Stouthard et al. (1997). However, Stouthard et al. (1997) distinguished only two health stages of IBD. Theses were a disability weight of 0.18 (95% C.I.: 0.075 – 0.278) for IBD patients in remission with an EQ 5D+ classification of 111111 (80%) and 111221 (20%), and a disability weight of 0.40 (95% C.I.: 0.305 – 0.495) for IBD patients in active exacerbation. IBD patients in remission with a disability weight of 0.18 were equated with the 'medical remission' and the 'surgically-induced remission' of Silverstein et al. (1999). And IBD patients in active exacerbation with a disability weight of 0.40 were equated with the model health states of 'taking an aminosalicylate drug' and 'taking oral corticosteroids or immuno-suppressants' (see Table 6.1). Adding up the disease burden of the different health states, and dividing the total disease burden of an *average* IBD patient by the *average* life-expectancy as estimated by Silverstein et al. (1999), we obtained the *average* disability weight of an *average* IBD patient per year, as well as the variability range (see Table 6.1). In order to consider the variability of disease severity, we estimated the disease burden by using a uniform distribution with the range around the calculated *average* disability weight of average IBD patients per year.

Table 6.1. Average disability weights and range of an average IBD patient, and for different stages within the clinical course of an average IBD patient

Different stages within the clinical course of an average IBD patients[1)]	Years	Disability weight/ year/case
Medical ' remission' (no drugs)	11.1[1)]	0.18 (0.08-0.28)
Surgically-induced remission	18.9[1)]	0.18 (0.08-0.28)
Taking an aminosalicylate drug	12.7[1)]	0.40 (0.31-0.50)
Taking oral corticosteroids or immuno-suppressants	3.2[1)]	0.40 (0.31-0.50)
Average disability weight/year/case		0.26 (0.22-0.29)

[1)] According to Silverstein et al. (1999)

6.4 Estimating cost-of-illness due to Campylobacter-associated IBD cases

According to Hay and Hay (1992b), the prevalence approach is preferable to the incidence approach in order to estimate disease cost of long-term chronic disease such as IBD. And when aggregated across all patients and time periods, according to Hay and Hay (1992b), the prevalence approach should return the same result as an incidence approach. For all other illnesses, however, we have so far used the incidence approach. We therefore wanted to estimate the cost-of-illness due to Campylobacter-associated IBD cases by also using the incidence approach. However, the data available forced us to opt for a *kind* of prevalence approach. In a first step we defined the annual incidence of IBD cases and calculated for each patient the costs related to the diagnostic of the illness. We further determined for each IBD case individually the patient's life-expectancy, assuming that IBD would not result in earlier mortality. However, for direct health care and direct non-health care costs, as well as for indirect non-health care costs made during the patient's life-time, we had to use 'average' cost-of-illness, considering, in accordance with the prevalence approach, the proportion of patients in each disease state during that specific time period.

6.4.1 Diagnostic costs and other related costs

According to Dubinsky et al. (2002), symptoms reported by IBD patients are mainly non-specific gastro-intestinal symptoms, e.g. abdominal pain and/or diarrhoea. Within the Dutch system, where the GP is the 'gatekeeper' to further medical services, IBD patients would need to visit first their GP, who then refers the patient to a specialist. Physical examinations, stool panel, routine laboratory testing, as well as some further diagnostic minor procedures, e.g. colonoscopy, upper gastro-intestinal tract and small bowel follow-through, are needed in order to make a correct diagnostic (Dubinsky et al., 2002). Following Dubinsky et al. (2002), we therefore assumed that for a correct diagnosis, the following steps would occur for each IBD patient:

- Consultation with a gastro-enterologist, whereby a complete history and physical examination, stool panel, and routine laboratory testing are applied;
- Further a colonoscopy with biopsies, whereby a one-day admission to the hospital is required;
- And also an upper gastro-intestinal tract or small bowel follow-through.

Using Dutch cost estimates, where available, we estimated that the total diagnostic costs per patient would have been in 2000 approximately € 620. Details are shown in Table 6.2. But Dubinsky et al. (2002) and Ebinger et al. (2002), both reported that the sensitivity of testing is less than 100%. Therefore some of the IBD patients would have to come back for at least a

second time in order to diagnose IBD. In this study we therefore assumed that the test performance would have a sensitivity (p) of 0.85 (range 0.66-1.0), according to the test sensitivity assumed in the study of Ebinger et al. (2002). The uncertainty of the assumed test sensitivity (p) was considered by using a uniform distribution. The variability that IBD patients might have to go through one or two diagnostic procedures was modelled by using a Bernoulli(p) distribution. The direct health care costs for the second diagnostic procedure was assumed to be approximately € 530 per patient, given that no GP consultation is needed and only an additional subscription fee for a gastro-enterologist has to be billed.

Table 6.2. Assumed medical services and costs for diagnostic IBD (year 2000)

Medical service	Costs/unit (in €)	Source
GP-visit	17.8	Oostenbrink et al. (2000)
Gastro-enterologist consultation[1)]	48.5	Oostenbrink et al. (2000)
Short subscription (gastro-enteriologist)	92.12	Anonymous (2000b)
Colonoscopies plus 1 day hospital admission[1)]	356.5	Oostenbrink et al. (2000) and Anonymous (2000b)
Small bowel analysis	30.2	Anonymous (2000b)
Laboratory testing	72.3	Based on (Rösch et al., 2002b)
First diagnosis	~620	
Additional subscription fee for gastro-enterologist	22.7	(Anonymous, 2000b)
Second diagnosis [2)]	~530	

[1)] Assuming that 14% would go to a university hospital and 86% would go to a general hospital (Oostenbrink et al., 2000).
[2)] No GP consultation needed; further, the short subscription will be replaced by an additional subscription fee.

Apart from the direct health care costs IBD patients incur some travel costs as well as some productivity losses in visiting their GP and the specialist. When calculating travel costs and productivity losses, we made the same assumptions as for GE, ReA and GBS patients. In short, the assumptions were that patients travelling to/from hospital will always use either a car or public transport. Patients visiting their GP will take a car or public transport in only 50% of the cases (range 10% to 90%). For IBD patients in the working life age, age-specific salary wages for an average person in that specific age group are considered for the time spent off work, assuming that a GP consultation and a specialist visit/outpatient hospital visit would result in a loss of 0-0.25 days and 0.25-1 days/consultation, respectively. Furthermore, an additional day off work was assumed when admitted to the hospital in order to undergo a colonoscopy.

Symptoms of IBD are variable, which is why patients are likely to undergo a relatively large battery of tests prior to establishment of diagnosis (Hay and Hay, 1992b). But once the disease is diagnosed treatment will occur. We therefore assume that for each patient, apart from the diagnostic costs, an additional 50% of the estimated annually occurring ‘average’ direct and indirect non-health care costs would be made within the first year. These will be described in the following paragraphs.

6.4.2 Direct health care costs

The therapeutic options for a patient with IBD depend on the extent, site and severity of the disease (Ward et al., 1999). These include treatment with d-amino salicylic acid (5-ASA) derivatives, corticosteroids, immunosuppressive agents and surgery. Several therapeutic options to treat patients with IBD are, according to Ward et al. (1999), available. Details on

therapeutic options or medical management of IBD are given by Ward et al. (1999), Lombardi et al. (2002) and others.

Bodger (2002) reviewed the English published literature for cost-of-illness studies on Crohn's disease and/or IBD. Most of these studies focus on the costs of therapies and/or hospitalisations. Hay and Hay (1992b) and Feagan et al. (2000), for example, estimate the annual costs of care of Crohn's disease patients, based on insurance claims, whereas Cohen et al. (2000) and Bernstein et al. (2000) estimate only the direct health care costs of hospitalized IBD patients. Only Pinchbeck et al. (1988) and Blomqvist and Ekbom (1997) look at the direct health care costs, as well as direct and indirect non-health care costs of IBD patients. Another, but non-English study, and therefore not considered in the study of Bodger (2002), which considers direct and indirect costs of IBD patients, is the study of Rosch et al. (2002b). In another study Rosch et al. (2002a) analysed the resources used for outpatient treatment of 272 IBD patients in the year 2000 in a German hospital. Based on hospital and physician records, as well as a patient questionnaire (1015 respondents) of 1981, Pinchbeck et al. (1988) estimated the economic impact of IBD for Alberta, considering IBD patients within all categories within the clinical course. However, direct health care costs included only physician's fee and the costs of hospitalisation; drug costs or outpatient laboratory or radiological fees were not considered in this study. Using cross-sectional observational data, which were obtained from national registers and surveys on ambulatory care, hospital admissions, medication, sickness leave and early retirement, Blomqvist and Ekbom (1997) estimated the direct health care costs and indirect non-health care costs associated with IBD in Sweden during 1994. Rosch et al. (2002b) measured the cost of 95 IBD patients in Germany, using a cost diary over a 4 week follow-up period. They were asked to report weekly their use of health care and costs related to their illness. Within this study we will base our assumptions mainly on Blomqvist and Ekbom (1997), Rosch et al. (2002a) and Rosch et al. (2002b).

According to Blomqvist and Ekbom (1997) Sweden has one of the highest incidences of IBD world-wide. For Crohn's disease the incidence is 6 and the prevalence 150 per 100,000, and for ulcerative colitis the incidence is 15 and the prevalence 300 per 100,000, which is equal to an IBD incidence of 21 and prevalence of 450 per 100,000 (Blomqvist and Ekbom, 1997). Blomqvist and Ekbom (1997) counted 329 ambulant consultations for IBD per 100,000 population for Sweden in the year 1994. This is equal to 0.73 ambulant visits per IBD patient per year, of which 10% would consult their GP and 90% would consult a specialist. An ambulant hospital visit always includes a physical examination by a physician, and in laboratory testing, endoscope or sonographic services and radiology procedures would be required in a further 87%, 37% and 14% of the visits, respectively (Rösch et al., 2002b). Medication was prescribed in 93.6% of IBD outpatient visits (Rösch et al., 2002b). Where available, we used Dutch cost estimates for the year 2000. However, for laboratory testing, endoscopic or sonographic services and radiology procedures we used the estimated German cost estimates for the year 2000. According to the Dutch system we additionally considered a 'yearly subscription' fee for a gastro-enterologist. The average estimated costs for IBD patients for outpatient hospital care are summarised in Table 6.3. By using beta distributions the uncertainty on the probability of outpatient consultations/patient and the probability of the different medical services applied/consultation are considered (see Appendix V).

Table 6.3. Estimated annual costs for IBD patient's ambulant care

Medical services	Visits/patient (mean)	Service/visit (mean)	Costs/unit
GP visit	0.07 [1]		17.8 [2]
Outpatient visit	0.65 [1]		
Physical examination		1.00 [4]	48.5 [2, 3]
Laboratory testing		0.87 [4]	66.5 [4]
Endoscopic or sonographic services		0.37 [4]	107.0 [4]
Radiologic procedures		0.14 [4]	122.8 [4]
Medication		0.93 [4]	2687 [4]
Yearly subscription		1.00	115 [5]

[1)] Based on Blomqvist and Ekbom (1997)
[2)] Based on Oostenbrink et al. (2000)
[3)] Assuming that 14% would go to a university hospital and 86% would go to a general hospital outpatient care unit, according to Oostenbrink et al. (2000)
[4)] Based on Rösch et al. (2002b).
[5)] Based on Anonymous (2000b)

A total of 39 Crohn's disease patients and a total of 38 ulcerative colitis patients per 100,000 population per year were admitted in 1994 in hospital (Blomqvist and Ekbom, 1997). Taking into account that Helms et al. (pers. communication) found more ulcerative colitis patients than Crohn's disease patients within the Campylobacter-associated IBD group, we estimated that approximately 16% of the patients would be admitted to hospital. Similar findings were reported by Pinchbeck et al. (1988) and Feagan et al. (2000). Pinchbeck et al. (1988) found that approximately 75% of IBD sufferers had not been hospitalised at all during the analysed year. And Feagan et al. (2000) found that about 19% of patients who submitted a Crohn's disease-related medical claim during 1994 were hospitalised. Of the admitted IBD patients, in approximately 60% of cases a minor procedure (e.g. biopsies, colonoscopy or rectoscopy) or a surgery (e.g. colectomy) is applied (Blomqvist and Ekbom, 1997). Surgery is applied in 55% and minor procedures in 45% of the admissions with procedures/operations cases (Blomqvist and Ekbom, 1997). It was assumed that the average hospitalisation stay was 17.7 days, according to registered length of hospitalisations for IBD patients in 2000 in the Netherlands (Prismant, 2003). However, the registered hospitalisation stay in the Netherlands for IBD patients is much longer than what we found in the literature. Based on hospital and physician records, Pinchbeck et al. (1988) estimated that the mean number of days spent in hospital per year were 7.43 for Crohn's disease and 5.3 for ulcerative colitis. Cohen et al. (2000) reported a mean length of hospital stay of 8.7 days for 175 hospitalised Crohn's disease patients, whereas Bernstein et al. (2000) reported a mean length of 8 days for non-surgical treatment and 9.6 days for surgical treatment. We therefore will do here some sensitivity analysis about our assumption on the hospital stay. The costs/medical service unit used is summarised in Table 6.4. By using beta distributions, we considered the uncertainty of the probability of patients being hospitalized, as well as the probability of having a minor procedure or surgery. According to the Dutch system we additionally considered a 'yearly subscription' for a gastro-enterologist per hospitalisation.

Table 6.4. Estimated annual costs in € for IBD patients admitted to hospital

Medical services	Visits/patient (mean)	Service/visit (mean)	Costs (€)/unit
Hospital admissions	0.16 [1]		266.8 [2, 3]
Admission with minor procedures/surgery		0.60 [1]	
Minor procedures (e.g. endoscopy)		0.27 [1]	89.6 [5]
Surgery (e.g. colectomy)		0.33 [1]	775 [5]
Yearly subscription fee (gastro-enterologist)		1.00	115 [5]
Medical subscription fee (anaesthetist)		1.00	43.8[5]

For notes see Table 6.3.

Other health care costs, like various therapeutic consultations, special diets, stoma care visits and others were not considered in Blomqvist and Ekbom (1997). Rosch et al. (2002b), however, had questioned IBD patients on this type of medical services as well. According to the authors' findings, 3.3% of the IBD patients reported to have visited a therapist for stoma care once within a 4-week period on average, 4.3% went to a physiotherapist twice per week and about 2.2% consulted other therapists once within the four-week period. Approximately 31.5% of IBD patients needed special diets and 19.6% needed auxiliary aids, such as aids for stoma care. Further about 6.5% reported other additionally medical expenditures. The uncertainties of the different probabilities were considered by using beta distributions (see Appendix V). The average assumed costs per medical service unit for the various medical services used is summarised in Table 6.5. Where possible, Dutch cost estimates/unit were used. However, in some cases in which not enough data were available, we then used the German cost estimates. However, given that Rosch et al. (2002b) recruited subjects from the address list of an outpatient care unit, we assumed that only those patients would require such other services.

Table 6.5. Assumed average annual probability of outpatient IBD patients using other medical services; frequency of visits/year/patient and cost estimates/ medical unit in €.

Medical services	% of patients (mean)	Visits/year/patient (mean)	Costs /unit
Stoma therapist	3.3 [1]	13 [1]	19.4 [2]
Physiotherapist	4.3 [1]	104 [1]	19.4 [2]
Other therapists	2.2 [1]	13 [1]	19.4 [2]
Special diets	31.5 [1]	-	660 [1]
Auxiliary aids	1.96 [1]	-	645 [1]
Other medical expenditures	6.5 [1]	-	3966 [1]

[1)] Based on Rosch et al. (2002b).
[2)] Based on Oostenbrink et al. (2000)

6.4.3 Direct non-health care costs

Except for travel costs, only Rosch et al. (2002b) had published some information on other direct non-health care costs, such as informal care. According to Rosch et al. (2002b) approximately 5.4% of IBD patients would consult a healer. Given that within the Dutch sickness insurance scheme healer fees are not reimbursed, we considered these costs as direct non-health care costs, unlike Rosch et al. (2002b), who considered these costs as direct health care costs. Furthermore, Rosch et al. (2002b) had collected information of the use of informal care as well as on other non-medical activities, for example the member fee within an IBD patient's organisation, special books on the disease, and others. The details are summarised in

Table 6.6. Here, too, we assumed that only more severely affected IBD patients such as patients requiring outpatient treatment, would do something like consult a healer or would need informal care. Uncertainties around the different probabilities were considered by using beta distributions. When considering travel costs, we make the same assumptions as for GE, ReA and GBS. Travel costs were considered for GP visits, therapist visits and hospital visits, under the assumption that for a GP visits or a therapeutic visit on average 50% of the patients would use a car or public transport, whereas when travelling to and from hospital, patients would always use a car or public transport. For further details on these assumptions, see earlier chapters.

Table 6.6. Estimated annual direct non-health care costs, not considering travel costs for patients having outpatient care.

Medical services	% of patients (mean)	# per patient/year (mean)	Costs/unit
Healer	0.054 [1]	36 visits/year [1]	48.2 [2]
Informal care	0.141 [1]	231 hours/year [1]	8.5 [2]
Activities	0.261 [1]	-	135.5 [1]

[1)] Based on Rosch et al. (2002b).
[2)] Based on Oostenbrink et al. (2000)

6.4.4 Indirect non-health care costs

Although the disease burden of IBD is considerable, most patients are capable of full-time work. Ward et al. (1999) cited studies from Copenhagen, which found that the proportion of Crohn's disease and ulcerative colitis patients capable of full-time work was 75% and 90%, respectively. In a large Canadian study, over 50% of Crohn's disease and over 60% of ulcerative colitis patients did not lose any time from work outside the home due to IBD (Pinchbeck et al., 1988). Hay and Hay (1992b) reported that 5-10% of IBD patients experience work disability. Rosch et al. (2002b) falls in the range of these studies. Rosch et al. (2002b) reported that 30.4% (28 patients) were temporarily absent from their work, whereby paid and unpaid work were considered equivalent. In this study, absence from work might have been either because of disease severity or because of physician and therapeutic consultations. Only 13% of the IBD patients were absent from their work due to IBD for longer than three days, whereby the reported sickness leave for these patients was on average 14.7 working days with a standard deviation of 12 working days (Rosch et al., 2002b). However, this is lower as the reported mean number of days of work disability of Pinchbeck et al. (1988) of 26.1 days and 17.5 days per year for Crohn's patients and ulcerative colitis patients, respectively. Blomqvist and Ekbom (1997) also reported a longer sickness leave, with 44 days for Crohn's disease patients and 58 days for ulcerative colitis patients. Sickness leave was estimated for approximately 0.39 Crohn's disease patients per prevalent patient and 0.09 ulcerative colitis patients per prevalent patient in Blomqvist and Ekbom (1997). The total number of instances of sickness leave due to IBD was, with 86 per 100,000 population, slightly higher than the total number of hospital admissions due to IBD (77 per 100,000). Nevertheless, we decided to model only for hospitalized IBD patients within the working life age (15 to 64 years) a longer sickness leave. The length of sickness leave of hospitalised IBD patients was based on the findings of Blomqvist and Ekbom (1997). Given our uncertainty, we applied a uniform distribution in order to estimate the time spent off work, ranging from 0 to 0.25 days/consultation of a GP, therapist and/or healer, and 0.25 to 1 days/consultation for a specialist/outpatient hospital visit, as was done for the calculation of indirect non-health care costs related to GE, ReA and GBS.

In the study of Rosch et al. (2002b) about 65.2% of the interviewed patients had a regular job and only 14.1% were granted early retirement due to IBD. Blomqvist and Ekbom (1997) reported that in 1994 1.6 Crohn's patients and 0.9 ulcerative colitis patients per 100,000 population were granted early retirement due to the disease. The expected duration of early retirement was, according to Blomqvist and Ekbom (1997), fourteen years. In the Dutch working population in 2000, however, approximately 13.8% were considered as work disabled. Given that this percentage is close to the percentage reported by Blomqvist and Ekbom (1997) and Rosch et al. (2002b) for the IBD patients, we assumed that the pattern of earlier retirement due to IBD would be comparable to the pattern of earlier retirement observed in the general population. Or, according to Oostenbrink et al. (2000) the pattern of earlier retirement of the general population was considered in the estimated age-specific salary per person within the working-life population.

6.5 Results

6.5.1 Estimated annual incidence of Campylobacter-associated IBD cases

In Figure 6.1 we have summarised the estimated cumulative distribution of annual incidences of Campylobacter-associated IBD cases, breaking down the total uncertainty into a variability component and an uncertainty component. The estimated mean was eleven IBD cases/year, with the attendant uncertainty ranging from ten IBD cases/year (5th Percentile) to thirteen IBD cases/year (95th Percentile).

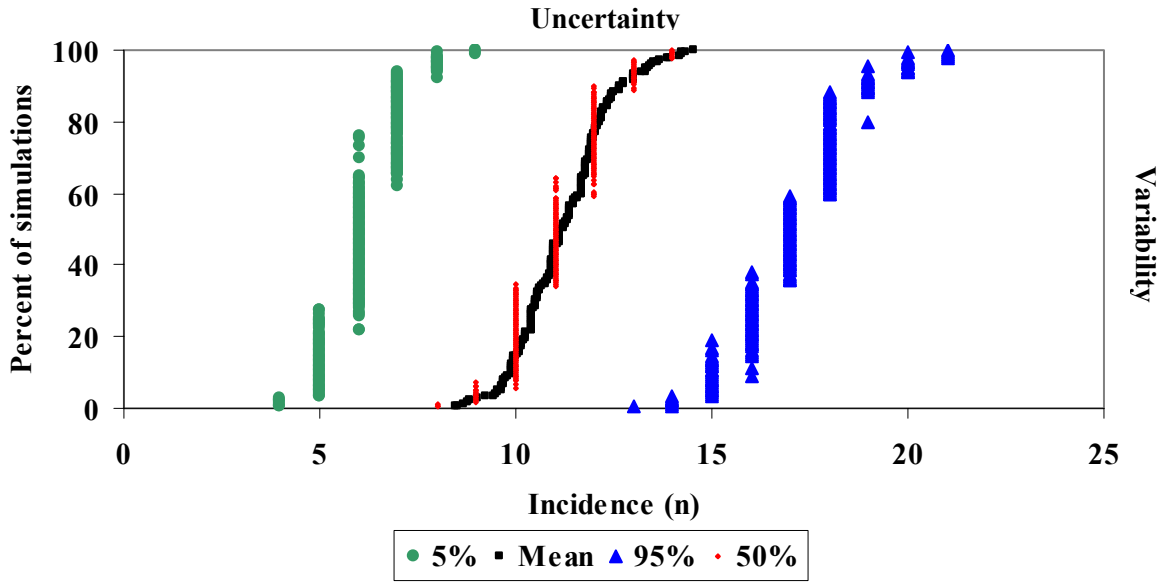


Figure 6.1. Estimated cumulative distribution of annual incidence of Campylobacter-associated IBD cases in the Netherlands, breaking down the total uncertainty into variability and uncertainty.

6.5.2 Estimated disease burden due to Campylobacter-associated IBD cases

Given that IBD is a chronic disease and most IBD patients are in their twenties or thirties at disease onset, the estimated disease burden per IBD case is, with an average of approximately

11 DALYs per average IBD case, quite considerable. Although only a few IBD cases/year are linked to a previous Campylobacter infection, the resulting total estimated disease burden should not be disregarded. The estimated cumulative distribution of the total disease burden due to the estimated number of Campylobacter-associated IBD cases in the Netherlands is summarised in Figure 6.2. Here the total uncertainty is broken down into a variability component and an uncertainty component. In Table 6.7 we summarised the mean and the attendant uncertainty of the estimated disease burden, discounted (4%) and not discounted. Given the long duration of the illness, discounting has an effect on the estimated disease burden. Furthermore, the DALYs estimated here are equal to the estimated YLD, because we made the previous assumption that IBD would not lead to earlier mortality.

Table 6.7. Estimated mean and the attendant uncertainty [1] of disease burden due to Campylobacter-associated IBD cases, undiscounted and discounted at 4%.

	Disease burden							
	Not discounted				Discounted at 4%			
	5%	Mean	50%	95%	5%	Mean	50%	95%
DALY	109	127	126	151	47	55	55	66

[1)] The model parameters used in this study are often uncertain or are variable or both. We therefore not only show for example the average annual incidence but also the 5th, 50th and 95th percentile, representing the uncertainty in the estimated average.

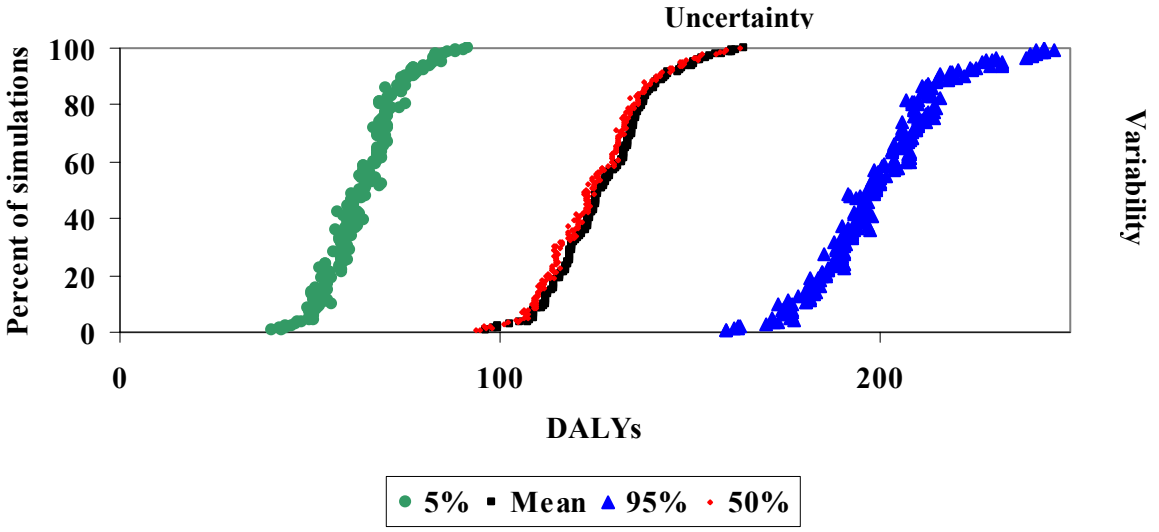


Figure 6.2. Estimated cumulative distribution of the disease burden due to Campylobacter-associated IBD cases in the Netherlands, breaking down the total uncertainty into variability and uncertainty (undiscounted figures).

6.5.3 Estimated cost-of-illness due to Campylobacter-associated IBD cases

The cumulative distribution of the estimated cost-of-illness related to Campylobacter-associated IBD cases in the Netherlands is summarised in Figure 6.3. Here we split up total uncertainty into a variability component and an uncertainty component. The estimated mean and the attendant uncertainty of the estimated cost-of-illness due to IBD cases is shown in Table 6.8, discounted (4%) and not discounted. Given the long duration of the illness, discounting has not only an effect on the estimated disease burden as was shown earlier, but also on the estimated cost-of-illness. Direct health care costs are by far the largest part of the total cost-of-illness related to IBD, see Figure 6.4.

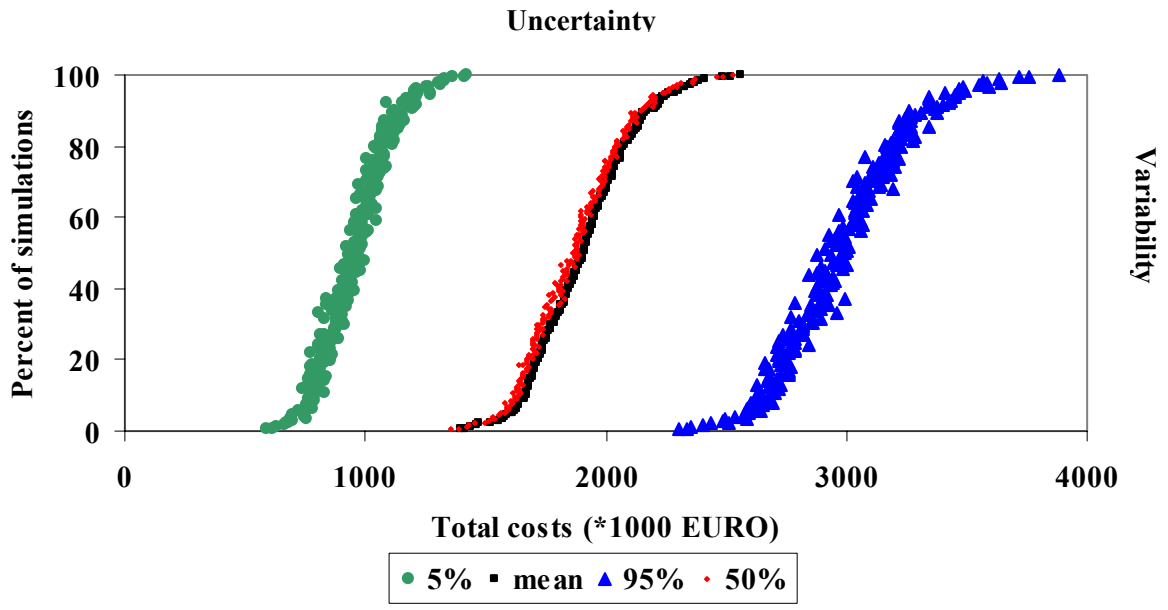


*Figure 6.3. Estimated cumulative distribution of the cost-of-illness (*1000 €) due to Campylobacter-associated IBD cases in the Netherlands for 2000, breaking down the total uncertainty into variability and uncertainty.*

Table 6.8. Estimated mean and attendant uncertainty of direct health care costs, direct non-health care costs, indirect non-health care costs and total cost respectively, due to Campylobacter-associated IBD cases, not discounted and discounted (year 2000).

	Estimated costs (*million €)							
	Not discounted				Discounted at 4%			
	5%	Mean	50%	95%	5%	Mean	50%	95%
Direct health care costs	1.4	1.7	1.7	2.0	0.6	0.7	0.7	0.9
Direct non-health care costs	0.02	0.04	0.04	0.07	0.01	0.02	0.02	0.03
Indirect non-health care costs	0.2	0.2	0.2	0.2	0.1	0.1	0.1	0.1
Total costs	1.6	1.9	1.9	2.3	0.7	0.9	0.9	1.0

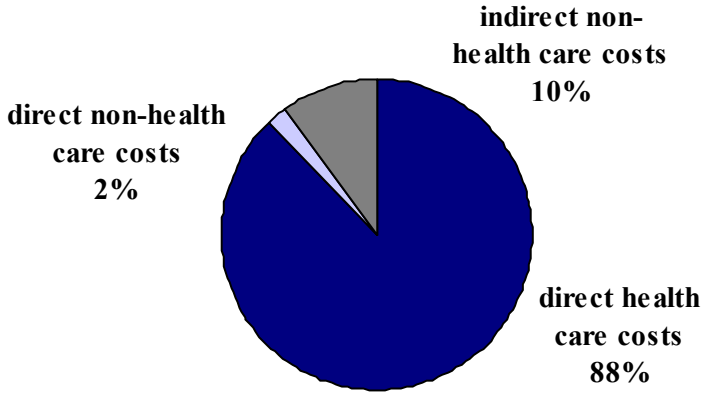


Figure 6.4. Distribution of the estimated average and not discounted total cost-of-illness due to Campylobacter-associated IBD cases in the Netherlands, into direct health care costs, direct non-health care costs and indirect non-health care costs (year 2000).

6.5.4 Sensitivity analysis

Given that running the model required a good deal of time, we considered uncertain parameters as 'given' when doing sensitivity analysis. The 'average' value of the distributions describing uncertain parameters were considered as being 'best guesses'.

In Figure 6.5 we have summarised the estimated differences in direct health care costs associated with IBD for the various sensitivity analyses applied. Sensitivity analysis was applied because the hospital stay of IBD patients reported in the literature was much shorter than the hospital stay for IBD patients registered for 2000 in Prismant (*base*). A reduction of the hospital stay to half of the length (*shorter hospital stay*) has only little impact on the direct health care costs. The assumption made about the use and the costs of drugs in order to control IBD has a much more significant impact (see Figure 6.5). In the studies of Rösch et al. (2002a) and Rösch et al. (2002b), 91.3% and 93.6% of IBD patients received medical therapy. However, in the study of Blomqvist and Ekbom (1997) only in 216 visits of the 295 outpatient's visits per 100,000 population was medical therapy given, which is equal to approximately 73%. Sensitivity analysis was applied. Further, sensitivity analysis was applied on the assumed annual drug costs per user. Especially the assumed annual drug costs per user is an important factor. An increase or a decrease of the drug costs by € 1000/year/user would increase or decrease the estimated average direct health care costs by approximately € 300,000, or 18% of the total direct health care costs.

In Figure 6.5 we have summarised the estimated differences in direct health care costs associated with IBD for the various sensitivity analyses applied.

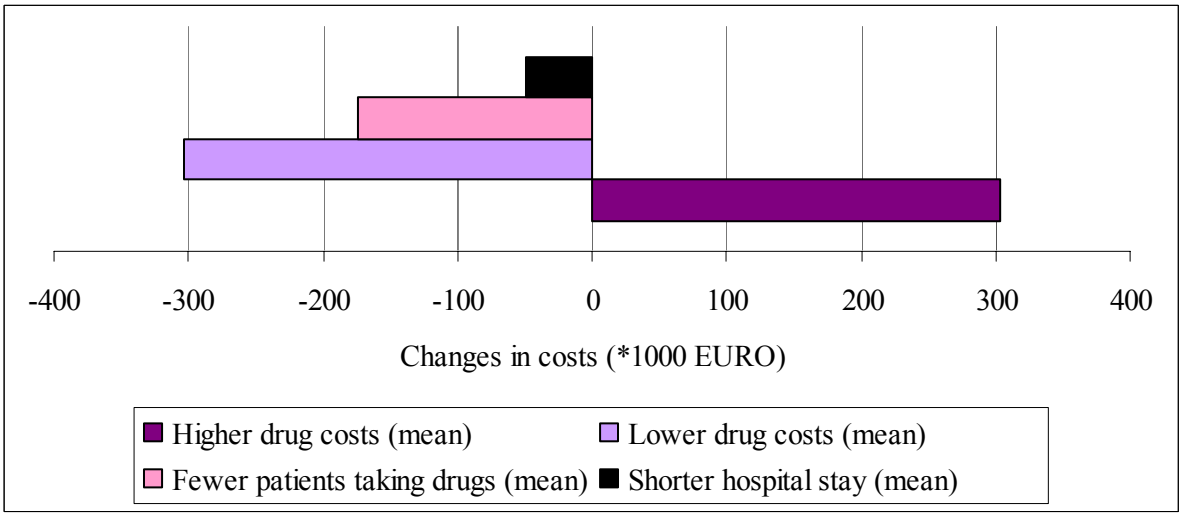


Figure 6.5. Calculated difference of the average estimated direct health care costs due to Campylobacter-associated IBD cases for various sensitivity analyses.

6.6 Discussion

When estimating the disease burden and/or the cost-of-illness associated with Campylobacter infections and sequelae, no study known to us considered IBD as being a complication of a previous Campylobacter infection. Consequently, this study is one of the first studies estimating the disease burden and the cost-of-illness related to Campylobacter-associated IBD cases.

The annual incidence of Campylobacter-associated IBD cases was based on the Danish study of Helms et al. (unpublished), which looked mainly at the IBD diagnostic within 1 year after laboratory-confirmed positive Campylobacter infections. This study was only a statistical assertion of IBD, but controlled for underlying diseases. There is no mechanistic support yet. The diagnosis for ulcerative colitis and Crohn's disease are substantially different (Hay and Hay, 1992b). According to Iversen et al. (1968), only 40% of ulcerative colitis patients would be detected within the first year after onset of symptoms. In the Danish studies, approximately 70% of the Danish Campylobacter-associated IBD cases observed were ulcerative colitis patients (Helms (2003), pers. communication). Therefore, if the detection of ulcerative colitis patients could not be improved since the study of Iversen et al. (1968), we largely underestimated the incidence, the disease burden and the cost-of-illness related to IBD cases. If these 40% are still correct at present, then we might have to double the estimated incidence, the estimated disease burden and the estimated costs in order to get closer to reality. But this is only speculation and more research is needed in order to come up with an appropriate estimate.

Given the relatively low incidence number of annual Campylobacter-associated IBD cases and given the available data on the illness itself, we opt to base our calculations on 'average' IBD cases, knowing that this is a strong simplification of the reality. Most cost-of-illness studies highlight the fact that in actuality 2% to 5% of the IBD cases are responsible for more than 25% of all health care costs, see, for example, Bernstein et al. (2000), Cohen et al. (2000) and Hay and Hay (1992a).

Furthermore, Crohn's disease patients and ulcerative colitis patients might not necessarily use the same amount of medical services. Bernstein et al. (2000) found that medical therapy admission costs for Crohn's disease and ulcerative colitis patients were similar. However, in the same study the authors acknowledge that surgical therapy admissions were costlier among ulcerative colitis patients than for Crohn's disease patients. When making assumptions about the use of medical services of an 'average' IBD patient, we tried to correct, wherever possible and where data were available, for the difference between Crohn's disease and ulcerative colitis patients. Nevertheless, we recognise the fact that this too is only a simplification.

Given that IBD is a chronic disease from which patients will never recover, it is not surprising that the direct health care costs account for more than 85% of all estimated costs. From the sensitivity analysis we know that two assumptions in particular, namely a) the percentage of patients assumed to use drugs, and b) the costs for the drugs itself, have the highest impact on the estimate of the direct health care costs. Therefore in order to improve the estimate of the cost-of-illness associated with IBD, future studies should elaborate in more detail on these last two points.

Despite the simplifications and the necessary assumptions made, this study could give a first estimate about the disease burden and the cost-of-illness of Campylobacter-associated IBD cases.

References

Adak, G.K., Long, S.M., and O'Brien, S.J. Trends in indigenous foodborne disease and deaths, England and Wales: 1992 to 2000. Gut 2002; 51 (6):832-841.

Allos, B.M. Association between Campylobacter infection and Guillain-Barre syndrome. J Infect Dis 1997; 176 Suppl 2:S125-S128.

Allos, B.M. Campylobacter jejuni infections: update on emerging issues and trends. Clin Infect Dis 2001; 32 (8):1201-1206.

Anonymous. Farmacotherapeutisch kompas 2000/2001. Amstelveen, the Netherlands: College Tarieven Gezondheidszorg 2000a.

Anonymous. Tariefboek medisch specialisten - jaar 2000. Amstelveen, the Netherlands: College Tarieven Gezondheidszorg 2000b.

Anonymous. A report of the study of infectious intestinal disease in England. London, UK: The Stationery Office 2000c.

Anonymous. Economics of foodborne disease: other pathogens. Washington, USA: Economic Research Service, USDA, 2001. http://ers.usda.gov/briefing/FoodborneDisease/otherpathogens.htm accessed on January 8, 2003.

Berden, J.H., Muytjens, H.L. and Van De Putte, L.B. Reactive arthritis associated with *Campylobacter jejuni* enteritis. Br Med J 1979; 1 (6160):380-381.

Bernsen, R.A., Jacobs, H.M., De Jager, A.E. and Van Der Meché, F.G.A. Residual health status after Guillain-Barré syndrome. J Neurol Neurosurg Psychiatry 1997; 62:637-640.

Bernsen, R.A., Jager, A.E., Schmitz, P.I. and Van Der Meche, F.G. Long-term sensory deficit after Guillain-Barre syndrome. J Neurol 2001; 248(6):483-486.

Bernsen, R.A., De Jager, A.E., Schmitz, P.I. and Van Der Meche, F.G. Long-term impact on work and private life after Guillain-Barre syndrome. J Neurol Sci 2002; 201(1-2):13-17.

Bernstein, C.N., Papineau, N., Zajaczkowski, J., Rawsthorne, P., Okrusko, G. and Blanchard, J.F. Direct hospital costs for patients with inflammatory bowel disease in a Canadian tertiary care university hospital. Am J Gastroenterol 2000; 95(3):677-683 .

Blaser, M.J. Epidemiologic and clinical features of *Campylobacter jejuni* infections. J. Infect. Dis. 1997; 176 (Suppl 2):S103-S105.

Blomqvist, P. and Ekbom, A. Inflammatory bowel diseases: health care and costs in Sweden in 1994. Scand J Gastroenterol 1997; 32(11):1134-1139 .

Bodger, K. Cost of illness of Crohn's disease. Pharmacoeconomics 2002; 20(10):639-652.

Bourke, B., Chan, V.L. and Sherman, P. *Campylobacter upsaliensis*: waiting in the wings. Clin Microbiol Rev 1998; 11(3):440-449.

Bremell, T., Bjelle, A. and Svedhem, A. Rheumatic symptoms following an outbreak of Campylobacter enteritis: a five year follow up. Ann Rheum Dis 1991; 50:934-938. Cited in Hannu et al. (2002).

Bunning, V.K., Raybourne, R.B. and Archer, D.L. Foodborne enterobacterial pathogens and rheumatoid disease. Soc Appl Bacteriol Symp Ser 1988; 17:87S-107S.

Bunte, F.H.J., Wolbrink, M., Van Rie, J.P. and Burgers, S. Kiplekker, een kosten-baten analyse van een reductie in de besmetting van pluimveevlees met Salmonella en Campylobacter. The Hague, the Netherlands: Agricultural Economics Institute, 2001.

Buzby, J.C., Roberts, T., Lin, J.C.T. and MacDonald, J.M. Bacterial Foodborne Disease - Health care costs & Productivity Losses. Washington, USA: Economic Research Service, USDA 1996. Agricultural Economic Report No 741.

Buzby, J.C., Allos, B.M. and Roberts, T. The economic burden of Campylobacter-associated Guillain-Barre syndrome. The Journal of Infectious Diseases 1997a: 176 Suppl 2:S192-S197.

Buzby, J.C., Roberts, T and Allos, B.M. Estimated Annual Costs of Campylobacter-associated Guillain-Barré Syndrome. Washington, USA: Economic Research Service, USDA 1997b. Agricultural Economic Report No. 756.

Chorus, A.M.J. Reuma in Nederland: de cijfers - Actualisiering 2000. Leiden, the Netherlands: TNO Preventie en Gezondheid 2001.

Cohen, R.D., Larson, L.R., Roth, J.M., Becker, R.V. and Mummert, L.L. The cost of hospitalization in Crohn's disease. Am J Gastroenterol 2000; 95(2):524-530. Cited in Bodger (2002).

De Pedro-Cuesta, J., Abraira, V., Jiang, G.X., Solders, G. and Fredrikson, S. Guillain-Barre syndrome in South-West Stockholm 1973-1991 - 3. Clinicoepidemiological subgroups. Acta Neurol Scand 1996; 93(2-3):175-183.

De Wit, M.A., Koopmans, M.P., Kortbeek, L.M., Van Leeuwen, N.J., Bartelds, A.I. and Van Duynhoven, Y.T. Gastroenteritis in sentinel general practices, the Netherlands. Emerg Infect Dis 2001a; 7(1):82-91.

De Wit, M.A., Koopmans, M.P., Kortbeek, L.M., Van Leeuwen, N.J., Vinje, J., and Van Duynhoven, Y.T. Etiology of gastroenteritis in sentinel general practices in the Netherlands. Clin Infect Dis 2001b; 33(3):280-288.

De Wit, M.A.S., Koopmans, M.P.G., Kortbeek, L.M., Wannet, W.J.B., Vinje, J., Van Leusden, F., Bartelds, A.I.M. and Van Duynhoven Y.T. Sensor, a population-based cohort study on gastroenteritis in the Netherlands: incidence and etiology. American-journal-of-epidemiology 2001c; 154(7):666-674.

De Wit, M.A.S. Epidemiology of gastroenteritis in The Netherlands. Amsterdam, the Netherlands: University of Amsterdam 2002. PhD-thesis.

Drummond, M.F., O'Brien, B., Stoddart, G.L. and Torrance, G. . Methods for the Economic Evaluation of Health Care Programmes. Oxford, UK: Oxford University Press 1997.

Dubinsky, M.C., Johanson, J.F., Seidman, E.G. and Ofman, J.J. Suspected inflammatory bowel disease - the clinical and economic impact of competing diagnostic strategies. Am J Gastroenterol 2002; 97(9):2333-2342.

Eastmond, C.J., Rennie, J.A. and Reid, T.M. An outbreak of Campylobacter enteritis--a rheumatological followup survey. J Rheumatol 1983; 10(1):107-108.

Ebinger, M., Rieber, A. and Leidl, R. Cost-effectiveness of magnetic resonance imaging and enteroclysis in the diagnostic imaging of Crohn's disease. Int J Technol Assess Health Care 2002; 18(3):711-717.

Feagan, B.G., Vreeland, M.G., Larson, L.R. and Bala, M.V. Annual cost of care for Crohn's disease: a payor perspective. Am J Gastroenterol 2000; 95(8):1955-1960. Cited in Bodger (2002).

Gillespie, I.A., O'Brien, S.J., Frost, J.A., Adak, G.K., Horby, P., Swan, A.V., Painter, M.J. and Neal, K.R.. A case-case comparison of *Campylobacter coli* and *Campylobacter jejuni* infection: a tool for generating hypotheses. Emerg Infect Dis 2002; 8(9):937-942.

Goosen, E.S.M., Hoogenboom-Verdegaal, A.M.M., Bartelds, A.I.M., Sprenger, M.J.W. and Borgdorff, M.W. Incidentie van gastro-enteritis in huisartsenpeilstations in Nederland, 1992-1993. Infectieziekten Bulletin 1996; 7(4):72-78.

Gregor, J.C., McDonald, J.W.D., Klar, N., Wall, W., Atkinson, K. and Lamba, B. An evaluation of utility measurement in Crohn's disuse. Inflamm Bowel Dis 1997; 3(4):265-276.

Hannu, T., Mattila, L., Rautelin, H., Pelkonen, P., Lahdenne, P., Siitonen, A. and Leirisalo-Repo, M. Campylobacter-triggered reactive arthritis: a population-based study. Rheumatology 2002; 41(3):312-318.

Havelaar, A.H., De Wit, M.A.S. and Van Koningsveld, R. Health burden in the Netherlands (1990-1995) due to infection with thermophilic Campylobacter species. Bilthoven, the Netherlands: Rijksinstituut voor Volksgezondheid en Milieu 2000a. RIVM report no. 284550 004.

Havelaar, A.H., De Wit, M.A.S., Van Koningsveld, R. and Van Kempen, E. Health burden in the Netherlands due to infection with thermophilic Campylobacter spp. Epidemiology-and-Infection 2000b; 125(3):505-522.

Havelaar, A.H. Campylobacteriose in Nederland – Risico's en interventiemogelijkheden. Bilthoven, the Netherlands: Rijksinstituut voor Volksgezondheid en Milieu 2002. RIVM report 250911001.

Havelaar, A.H., Van Duynhoven, Y.T.H.P, Nauta, M.J., Bouwknegt, M., Heuvelink, A.E., De Wit, G.A., Nieuwenhuizen, M.G.M. and Van De Kar, N.C.A.J. Disease burden in the Netherlands due to infections with Shiga-toxin producing *Escherichia coli* O157. Bilthoven, the Netherlands: Rijksinstituut voor Volksgezondheid en Milieu 2003. RIVM report No. 284550008/2003.

Havelaar, A.H. and Melse, J.M. Quantifying public health risks in the WHO guidelines for drinking-water quality. Bilthoven, the Netherlands: Rijksinstituut voor Volksgezondheid en Milieu 2003. RIVM report No. 734301022/2003.

Hay, A.R. and Hay, J.W. Inflammatory bowel disease: health care cost algorithms. J Clin Gastroenterol 1992a; 14(4):318-327. Cited in Ward et al. (1999).

Hay, J.W. and Hay, A.R. Inflammatory bowel disease: costs-of-illness. J Clin Gastroenterol 1992b; 14(4):309-317.

Helms, M., Vastrup, P., Gerner-Smidt, P. and Molbak, K. Short and long term mortality associated with foodborne bacterial gastrointestinal infections: registry based study. BMJ 2003; 326(7385):357.

Hoogenboom-Verdegaal, A.M., De Jong, J.C., During, M., Hoogenveen, R. and Hoekstra, J.A. Community-based study of the incidence of gastrointestinal diseases in The Netherlands. Epidemiol Infect 1994; 112(3):481-487.

Hughes, R.A.C. and Rees, J.H. Clinical and epidemiologic features of Guillain-Barre Syndrome. Journal-of-infectious-diseases 1997; 176 (suppl. 2):S92-S98.

Iversen, E., Bonnevie, O., Anthonisen, P. and Riis, P. An epidemiological model of ulcerative colitis. Scan. J. Gastroenterol. 1968; 3(6): 593-610. Cited in Hay and Hay (1992b)

Jacobs, B.C., Rothbarth, P.H., Van Der Meche, F.G., Herbrink, P., Schmitz, P.I., De Klerk, M.A. and Van Doorn, P.A. The spectrum of antecedent infections in Guillain-Barre syndrome: a case-control study. Neurology 1998; 51(4):1110-1115.

Johnsen, K., Ostensen, M., Melbye, A.C. and Melby, K. HLA-B27-negative arthritis related to *Campylobacter jejuni* enteritis in three children and two adults. Acta Med Scand 1983; 214(2):165-168.

Kapperud, G., Lassen, J., Ostroff, S.M., and Aasen, S. Clinical features of sporadic Campylobacter infections in Norway. Scand J Infect Dis 1992; 24(6):741-749.

Keat, A. Reiter's syndrome and reactive arthritis in perspective. N Engl J Med 1983; 309(26):1606-1615.

Kist, M. Food-borne Campylobacter infections. Bundesgesundheitsblatt-Gesundheitsforschung-Gesundheitsschutz 2002; 45(6):497-506.

Koopmanschap, M.A. and Van Ineveld, B.M. Towards a new approach for estimating indirect non-health care costs of disease. Soc Sci Med. 1992; 34(9):1005-1010.

Koopmanschap, M.A., Rutten, F.F., Van Ineveld, B.M. and Van Roijen, L. The friction cost method for measuring indirect non-health care costs of disease. J Health Econ. 1995; 14(2):171-189.

Kosunen, T.U., Kauranen, O., Martio, J., Pitkanen, T., Ponka, A., Hortling, L., Aittoniemi, S., Mutru, O., Penttila, O. and Koskimies, S. Reactive arthritis after *Campylobacter jejuni* enteritis in patients with HLA-B27. Lancet 1980; 1(8181):1312-1313.

Kosunen, T.U., Ponka, A., Kauranen, O., Martio, J., Pitkanen, T., Hortling, L., Aittoniemi, S., Penttila, O. and Koskimies, S. Arthritis associated with *Campylobacter jejuni* enteritis. Scand J Rheumatol 1981; 10(2):77-80.

Lake, R.J., Baker, M.G., Garrett, N., Scott, W.G. and Scott, H.M. Estimated number of cases of foodborne infectious disease in New Zealand. N Z Med J 2000; 113(1113):278-281.

Locht, H. and Krogfelt, K.A. Comparison of rheumatological and gastrointestinal symptoms after infection with *Campylobacter jejuni/coli* and enterotoxigenic *Escherichia coli*. Ann Rheum Dis 2002; 61(5):448-452.

Lombardi, D.A., Feller, E.R., and Shah, S.A. Medical management of inflammatory bowel disease in the new millennium. Compr Ther 2002; 28(1):39-49.

Lyttkens, C.H. Time to disable DALYs? On the use of disability-adjusted life years in health policy. Eur. J. Health Econom 2003; 4:195-202.

Marshall, J.K., Blackhouse, G., Goeree, R., Brazier, N., Irvine, E.J. and O'Brien, B.J. Clinical and economic assessment: infliximab for the treatment of Crohn's disease. Ottawa, Canada: Canadian Coordinating Office for Health Technology Assessment, 2002.

McCarthy, N. and Giesecke, J. Case-case comparisons to study causation of common infectious diseases. International Journal of Epidemiology 1999; 28(4):764-768.

McCarthy, N. and Giesecke, J. Incidence of Guillain-Barre syndrome following infection with *Campylobacter jejuni*. Am J Epidemiol 2001; 153(6):610-614.

McDowell, R.M. and McElvaine, M. D. Long-term sequelae to foodborne disease. Rev Sci Tech 1997; 16(2):337-341.

Mead, P.S., Slutsker, L., Dietz, V., McCaig, L.F., Bresee, J.S., Shapiro, C., Griffin, P.M., and Tauxe, R.V. Food-related illness and death in the United States. Emerg Infect Dis 1999; 5(5):607-625.

Melby, K.K., Svendby, J.G., Eggebo, T., Holmen, L.A., Andersen, B.M., Lind, L., Sjogren, E. and Kaijser, B. Outbreak of Campylobacter infection in a subartic community. Eur J Clin Microbiol Infect Dis 2000; 19(7):542-544.

Meythaler, J.M. Rehabilitation of Guillain-Barré Syndrome. Arch Phys Med Rehabil 1997; 78:872-879.

Meythaler, J.M., DeVivo, M.J. and Braswell, W.C. Rehabilitation outcomes of patients who have developed Guillain-Barré Syndrome. American Journal of Physical Medicine and Rehabilitation 1997; 14:411-419.

Mishu, B., Ilyas, A.A., Koski, C.L., Vriesendorp, F., Cook, S.D., Mithen, F.A. and Blaser, M.J. Serologic evidence of previous *Campylobacter jejuni* infection in patients with the Guillain-Barre syndrome. Ann-Intern-Med 1993; 118(12):947-953.

Nachamkin, I. Microbiologic approaches for studying Campylobacter species in patients with Guillain-Barre syndrome. J Infect Dis 1997; 176 Suppl 2:S106-S114.

Nachamkin, I., Allos, B.M., and Ho, T. Campylobacter species and Guillain-Barre syndrome. Clin Microbiol Rev 1998; 11(3):555-567.

Nagpal, S., Benstead, T., Shumak, K., Rock, G., Brown, M. and Anderson, D.R. Treatment of Guillain-Barre syndrome: a cost-effectiveness analysis. J Clin Apheresis 1999; 14(3):107-113.

Oostenbrink, J.B., Koopmanschap, M.A. and Rutten, F.F.H. Handleiding voor kostenonderzoek, methoden en richtlijnprijzen voor economische evaluaties in de gezondheidszorg. Amstelveen, the Netherlands: College voor zorgverzekeringen 2000.

Palmer, S., Houston, H., Lervy, B., Ribeiro, D. and Thomas, P. Problems in the diagnosis of foodborne infection in general practice. Epidemiol Infect 1996; 117(3):479-484.

Pearson, A.D. and Healing, T.D. The surveillance and control of Campylobacter infection. Commun Dis Rep CDR Rev 1992; 2(12):R133-R139.

Peterson, M.C. Clinical aspects of *Campylobacter jejuni* infections in adults. West J Med 1994a; 161(2):148-152.

Peterson, M.C. Rheumatic manifestations of *Campylobacter jejuni* and *C. fetus* infections in adults. Scand J Rheumatol 1994b; 23(4):167-170.

Pinchbeck, B.R., Kirdeikis, J. and Thomson, A.B. Inflammatory bowel disease in northern Alberta. An epidemiologic study. J Clin Gastroenterol 1988; 10(5):505-515.

Prismant. Ziektenhuisstatistieken - Landelijk gemiddelde verpleegduur per diagnose. Utrecht, the Netherlands: Prismant 2003. http://www.prismant accessed on May 18, 2003..

Rautelin, H. and Hanninen, M.L. Campylobacters: the most common bacterial enteropathogens in the Nordic countries. Ann Med 2000; 32(7):440-445.

Raybourne, R.B., Roberts, T., Williams, K.M. and Arthritis Working Group. Food Poisoning (d) Economic Implications. (2003).

Rees, J.H., Thompson, R.D., Smeeton, N.C. and Hughes, R.A. Epidemiological study of Guillain-Barre syndrome in south east England. J Neurol Neurosurg Psychiatry 1998; 64(1):74-77.

Roberts, J.A., Cumberland, P., Sockett, P.N., Wheeler, J., Rodrigues, L.C., Sethi, D. and Roderick, P. J. on behalf of the IID Study Executive. The study of infectious intestinal disease in England: socio-economic impact. Epidemiology-and-Infection 2003; 130:1-11.

Rodrigues, L.C., Cowden, J.M., Wheeler, J.G., Sethi, D., Wall, P.G., Cumberland, P., Tompkins, D. S., Hudson, M.J., Roberts, J.A. and Roderick, P.J. The study of infectious intestinal disease in England: risk factors for cases of infectious intestinal disease with *Campylobacter jejuni* infection. Epidemiology-and-Infection 2001; 127(2):185-193.

Rosch, M., Leidl, R., Thomas, S., von Tirpitz, C., Reinshagen, M., Adler, G. and Konig, H.H. Messung der ambulanten Behandlungskosten von chronisch entzündlichen Darmerkrankungen an einer deutschen Universitätsklinik. Med Klin 2002a; 97(3):128-136.

Rosch, M., Leidl, R., Tirpitz, C., Reinshagen, M., Adler, G. and Konig, H.H. Kostenerfassung bei chronisch-entzündlichen Darmerkrankungen durch direkte Patientenbefragung mit einem Kostenwochenbuch. Z Gastroenterol 2002b; 40(4):217-228.

Ruward, D. and Kramers, P.G.N. (eds.). Volksgezondheid Toekomst Verkenning 1997 - De som der delen. Bilthoven, the Netherlands: Rijksinstituut voor Volksgezondheid en Milieu; Elsevier/De Tijdstroom 1997.

Schonheyder, H.C., Sogaard, P. and Frederiksen, W. A survey of Campylobacter bacteremia in three Danish counties, 1989 to 1994. Scand J Infect Dis 1995; 27(2):145-148.

Scott, W.G., Scott, H.M., Lake, R.J. and Baker, M.G. Economic cost to New Zealand of foodborne infectious disease. New Zealand Medical Journal 2000; 113(1113):281-284.

Sedano, M.J., Calleja, J., Canga, E. and Berciano, J. Guillain-Barre syndrome in Cantabria, Spain. An epidemiological and clinical study. Acta Neurol Scand 1994; 89(4):287-292.

Shivananda, S., Lennard-Jones, J., Logan, R., Fear, N., Price, A., Carpenter, L. and Van Blankenstein, M. Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). Gut 1996; 39(5):690-697. Cited in Rosch et al. 2002a.

Silverstein, M.D., Loftus, E.V., Sandborn, W.J., Tremaine, W.J., Feagan, B.G., Nietert, P.J., Harmsen, W.S. and Zinsmeister, A.R. Clinical course and costs of care for Crohn's disease: Markov model analysis of a population-based cohort. Gastroenterology 1999; 117(1):49-57 .

Skirrow, M.B., Jones, D.M., Sutcliffe, E. and Benjamin, J. Campylobacter bacteraemia in England and Wales, 1981-91. Epidemiology-and-Infection 1993; 110(3):567-573.

Smith, J.L. *Campylobacter jejuni* infection during pregnancy: long-term consequences of associated bacteremia, Guillain-Barre syndrome, and reactive arthritist. J Food Prot 2002; 65(4):696-708.

Soderlin, M.K., Kautiainen, H., Puolakkainen, M., Hedman, K., Soderlund-Venermo, M., Skogh, T. and Leirisalo-Repo, M. Infections preceding early arthritis in Southern Sweden: a prospective population-based study. J Rheumatol 2003; 30(3):459-464.

Stouthard, M.E.A., Essink-Bot, M.-L., Bonsel, G.J., Barendregt, J.J., Kramers, P.G.N., Van De Water, H.P.A., Gunning-Schepers, L.J. and Van Der Maas, P.J. Disability weights for diseases in the Netherlands. Rotterdam, the Netherlands: Departement of Public Health, Erasmus University Rotterdam 1997.

Tompkins, D.S., Hudson, M.J., Smith, H.R., Eglin, R.P., Wheeler, J.G., Brett, M.M., Owen, R.J., Brazier, J.S., Cumberland, P., King, V. and Cook, P.E. A study of infectious intestinal disease in England: microbiological findings in cases and controls. Commun Dis Public Health 1999; 2(2):108-113.

Van Den Brandhof , W.E., De Wit, G.A., De Wit, M.A.S. and Van Duijnhoven, Y.T.H.P. Costs of gastroenteritis in the Netherlands. Epidemiology and Infection 2004; *in press*.

Van Der Meché, F.G.A., Schmitz, P.I.M. and Dutch Guillain-Barré Study Group. A randomized trial comparing intravenous immune globulin and palsma exchange in Guillain-Barré syndrome. N Engl. J. Med 1992; 326:1123-1129.

Van Hogezand, R. A. (2002). Zijn er interantionale verschillen? Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid 22 maart 2002.Bilthoven: Rijksinstituut voor Volksgezondheid en Milieu 2002. http://www.rivm.nl/vtv/data/kompas/gezondheidstoestand/ziekte/Inflamdarm/inflamdarm_internationaal.htm accessed on September 26, 2003.

Van Koningsveld, R., Van Doorn, P.A., Schmitz, P.I.M., Ang, C.W. and Van Der Meché, F.G.A. Mild forms of Guillain-Barré syndrome in an epidemiological survey in the Netherlands. Neurology 2000; 54:620-625.

Van Koningsveld, R. Epidemiological and clinical aspects of the Guillain-Barré syndrome. Rotterdam, the Netherlands: Erasmus Universiteit Rotterdam 2001. PhD-Thesis.

Van Koningsveld, R., Schmitz, P.I.M., Ang, C.W., Van Der Meché, F.G.A. and Van Doorn, P.A. Infections and course of the disease in mild forms of Guillain-Barré syndrome. Neurology 2002; 58(4):610-614.

Van Pelt, W., De Wit, M.A.S., Wannet, W.J.B., Ligtvoet, E.J.J., Widdowson, M.A. and Van Duynhoven, Y.T.H.P. Laboratory surveillance of bacterial gastroenteric pathogens in the Netherlands, 1991-2001. Epidemiol Infect 2003; 130(2):1-11.

Visser, L.H. The Guillain Barré Syndrome: clinical subgroups, prognosis and treatment. Rotterdam, the Netherlands: Erasmus Universiteit, 1997. PhD-thesis.

Vose, D. Risk analysis: a quantitative guide. 2nd edition. Chichester: John Wiley & Sons, Ltd 2000.

Ward, F.M., Bodger, K., Daly, M.J. and Heatley, R.V. Clinical economics review: medical management of inflammatory bowel disease. Aliment Pharmacol Ther 1999; 13(1):15-25.

Wheeler, J.G., Sethi, D., Cowden, J.M., Wall, P.G., Rodrigues, L.C., Tompkins, D.S., Hudson, M.J. and Roderick, P.J. 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. BMJ 1999; 318(7190):1046-1050.

William, C.S.Jr. Anklylosing spondylitis. Webster's New World Medical Dictonary. John Wiley & Sons, Inc. 2003a. http://www.medicinenet.com/Ankylosing_Spondylitis/index.htm accessed on March 6, 2003.

William, C.S.Jr. (2003b). Reactive arthritis. Webster's New World Medical Dictonary. John Wiley & Sons, Inc. 2003b. http://www.medicinenet.com/reactive_arthritis/index.htm accessed on March 6, 2003.

Williams, R.B. A compartmentalised model for the estimation of the cost of coccidiosis to the world's chicken production industry. International Journal for Parasitology 1999, 29:1209-1229.

Withington, S.G. and Chambers, S.T. The cost of campylobacteriosis in New Zealand in 1995. New Zealand Medical Journal 1997; 110(1046):222-224.

Wittenbrink, M.M. Campylobacter: Vorkommen und pathogene Bedeutung bei Mensch und Tier. Mitt. Lebensm. Hyg. 2002; 93:4-8.

World Health Organisation (WHO). Food safety - a world wide public health issue. Geneva: FAO 2003. http://www.who.int/fsf/fctshtfs.htm accessed on April 15, 2003.

Yu, D.T.Y. and Thomson, G.T.D. Clinical, epidemiological and pathogentic aspects of reactive arthritis. Food-Microbiology 1994; 11(2):97-108.

Yu, D. and Kuipers, J.G. Role of bacteria and HLA-B27 in the pathogenesis of reactive arthritis. Rheum Dis Clin North Am 2003; 29(1):21-36, v-vi.

Appendix I - Re-estimation of the SENSOR data

Within this study we standardised only for age and not for cohort and sex, as in De Wit et al. (2001c). This was done in order to avoid having subgroups with no observed Campylobacter-associated GE cases. The estimated percentage of positive Campylobacter as the triggering agent of GE, using 24, 6 and 4 subgroups, is summarised in Table A. A detailed description of the re-estimation of the raw SENSOR data of De Wit et al. (2001c) for STEC O157 associated gastrointestinal illness in the Netherlands is given in Havelaar et al. (2003). The same approach was used in this study to estimate Campylobacter associated GE cases in the Netherlands. The results of the re-standardisation are summarised in Table B.

Table A. Observed and estimated percentage of positive Campylobacter as the triggering agent of gastro-enteritis illness in the Netherlands.

Organism	raw	24 subgroups		6 subgroups		4 subgroups	
	% pos.	% pos.	incidence	% pos.	incidence	% pos.	Incidence
Campylobacter	1.3	2.4	107.000	1.7	78.500	1.3	56.500

Table B. Results of the re-standardised Campylobacter-associated GE cases in the Netherlands

De Wit ea, Am J Epidemiol 2001;154:666-74 SENSOR-study

Enumeration study

Crude incidence of GE
1050 cases observed in **2229** pyr

Prior for % (dist) a **0.15**
b **4**

Standardisation of incidence of gastroenteritis for age group (De Wit, pers. comm)

Age group	N	pyr	GE	IR	IR x N
0	**199728**	**311**	**237**	0.762	152204
1-4	**776447**	**419**	**372**	0.888	689352
5-11	**1379686**	**444**	**224**	0.505	696058
12-17	**1106685**	**307**	**49**	0.160	176637
18-64	**10166745**	**420**	**104**	0.248	2517480
65+	**2130934**	**328**	**64**	0.195	415792
Crude	*15760225*	*2229*	*1050*	0.471	7424063
Standardised				**0.295**	**4.65E+06**

Case control study — Campylobacter

cases	+ves	% (mean)	% (dist)	Inc. path
197	**1**	*0.5%*	0.6%	**870**
267	**4**	*1.5%*	1.5%	**10551**
128	**3**	*2.3%*	2.4%	**16592**
19	**0**	*0.0%*	0.6%	**1145**
57	**1**	*1.8%*	1.9%	**47344**
31	**0**	*0.0%*	0.4%	**1774**
699	*9*	*1.3%*		
		1.7%		**78276**

Legend

N	Number of persons in the Netherlands, 1999 (CBS)	-
pyr	Observation time	person years
GE	Observed cases of gastroenteritis	-
IR	Incidence rate gastroenteritis	per person year
IR x N	Number of gastroenteritis cases in the Dutch population	per population year
+ves	Number of isolates in case control study	
cases	Number of GE patients in case control study	
% (mean)	Fraction of positives (expected value)	
% (dist)	Uncertainty distribution of fraction of positives	
Inc. path	Incidence of gastroenteritis per pathogen	

Appendix II - Effect of illness due to a Campylobacter infection on the person who was ill

Table A. The effect of illness due to a Campylobacter infection on the person who was ill in the Community component and the GP case control component in the English IDD study (Source: Anonymous (2000c); pages 410-414)

Severity of symptoms with respect to human activities (in days)	Community component				GP case control component			
	Overall mean (n=23)		Responders		Overall mean (n=192)		Responders	
	Mean	range	mean	N	mean	range	mean	N
Overall effect of illness	6.52[1]	0-28	-	-	9.34[2]	0-56	-	-
In hospital:								
- confined to bed	-		-		0.18[3]	0-2	1.17	3
- able to get up	0.30	7	7	1	0.04	0-4	3.5	2
At home:								
- confined to bed	0.46	0-3	1.5	7	1.88	0-17	3.65	99
- able to get up, but not able to do most normal activities	2.5	0-13	3.83	15	3.59	0-20	4.75	145
- able to get up and do most normal activities	2.13	0-19	3.5	14	2.45	0-42	4.05	116
Feeling ill but able to go to work/school/shops etc.	0.91	0-5	3.5	6	1.80	0-24	5.09	68

[1] When adding up all the subtotals the overall mean is only 6.30 and not 6.52. Within this study we will work with the subtotals.
[2] When adding up all the subtotals the overall mean is 9.94 and not only 9.34. Within this study we will work with the subtotals.
[3] When multiplying the mean of the responders (1.17) with the number of responders (n=2) in order to obtain the total number of days, we obtain a total of 3.5 days (this was also the result reported). However, when dividing the 3.5 by 192 we would obtain an overall mean for 'in hospital and confined to bed' of 0.02 days rather than the reported 0.18 days. These 0.02 days would result in an overall mean of 9.77 days rather than the 9.94 days (see 2).

Table B. Estimating the effect of illness due to a Campylobacter infection on the person who was ill for patients visiting only a GP and for hospitalised patients.

	Visit GP only	Hospitalised
In hospital and confined to bed (in days)	-	1.17[1]
In hospital but able to get up (in days)	-	3.5[1]
At home and confined to bed (in days)	1.88[2]	1.88[2]
At home and able to get up but not able to do most normal activities (in days)	3.59[2]	3.59[2]
At home, but able to get up and do most normal activities (in days)	2.45[2]	2.45[2]
Feeling ill but able to go to work/school/shops etc. (in days)	1.80[2]	1.80[2]
Total (as used in this study)	9.72	14.39

[1] The average of responders as given in the English IDD study in the GP case control component (see Table A).
[2] The overall mean as found in the English IDD study in the GP case control component (see Table B).

Table C. Estimating the effect of illness due to a Campylobacter infection on the person who was ill for patients and not visiting a GP:

	Effect of illness due to a C. infection on person in cohort study (overall mean)	*100
-	Effect of illness due to a C. infection on person visiting GP only	*47
=	Effect of illness due to a C. infection on person not visiting GP	*53

Appendix III - Productivity losses

Productivity losses per day and per friction period in the year 2000 for an average 'person' and an average 'working person', depending on the age group of the patients[1].

Life years / 'average'	Per day (€)		Whole friction period (123 days) (* 1000 €)	
	Person	Working person	Person	Working person
15-19	9.8	30.2	1.2	3.7
20-24	43.9	72.5	5.4	8.9
25-29	60.8	98.8	7.5	12.2
30-34	65.5	107.8	8.1	13.3
35-39	70.6	116.0	8.7	14.3
40-44	75.3	120.7	9.3	14.9
45-49	72.9	133.3	9.0	16.4
50-54	63.9	130.1	7.9	16.0
55-59	49.0	124.3	6.0	15.3
60-64	19.2	121.9	2.4	15.0
'average'	56.2	107.6	6.9	13.2

[1)] Updated from Oostenbrink et al. (2000) for the year 2000.

Appendix IV - Campylobacter-associated ReA incidence – summaries of earlier studies

Table A - Estimated Campylobacter-associated ReA incidence, based on Campylobacter outbreaks.

Source	Study	Incidence; symptoms; duration; HLA-B27
Eastmond et al. (1983) United Kingdom	Controlling GP-records for rheumatological complaints presented within 3 months after an outbreak of Campylobacter (in 1979) of 130 persons. Group A: 88 persons had enteritis and had a positive stool sample; Group B: 42 persons had no symptom but had a positive stool sample (group B)	Group A: 2 patients had visited their GP due to rheumatological complaints. But in only one patient could the signs be clearly linked to the previous Campylobacter infection, resulting in an incidence of 1,1% (95% C.I. 0.03-5.43). • Patient had pain, swelling and stiffness in his elbow (2 weeks) • Mild cases might not have been reported to the general practitioners. Group B: No rheumatological symptoms were reported.
Bremell et al. (1991) Sweden	86 party guests were interviewed 2 years after an outbreak of a Campylobacter infection (in 1981). Group A: 35 guests (33%) had diarrhoea and were positive for *C. jejuni* (positive stool sample and/or increased antibody level); Group B: 31 guests (29%) were positive (increased antibody level) but had no symptoms; and Group C:20 guests (19%) were negative and remained healthy.	Group A: 7 patients (20%) reported symptoms from joints, muscles or spine • 6 patients had symptoms for less than 1 month • 1 patient (HLA-B27 positive) had symptoms for 2 to 3 months with a subsequent 2 month absence from work Group B: 4 patients (all HLA-B27 negative) reported long-term rheumatic disorders starting 3 to 8 months after the party: • 2 of the 4 patients reported absent from work for 4 months and 6-12 months, respectively. • 1 of the 4 patients had symptoms for 9 months. Group C: No long-term rheumatic disorders reported
Melby et al. (2000) Norway	Questionnaires were sent to the inhabitants of a community with a waterborne Campylobacter outbreak in 1988. 77 persons of the 520 respondents were ill, allowing the assumption that 330 persons got ill during the epidemic. For a part of the community faecal and sera samples of ill and control persons were taken.	21% and 9% of the ill respondents reported joint swelling and joint pain respectively. 2 reactive arthritis cases (2/330 = 0.6%) were reported [1,2)]

[1)] Apart from the fact that the two reactive cases were either IgA or IgB seropositive, no further data are given in this paper. There are also no data on what they based these two ReA cases.

[2)] The authors highlight the fact that there was only a low number of campylobacters in the water. According to the authors this might have contributed to the low attack rate.

Appendix IV - Campylobacter-associated ReA incidence (suite)

Table B Estimated Campylobacter-associated ReA incidence, based on sporadic campylobacteriosis cases

Source	Study	Incidence; symptoms; duration; HLA-B27
Kosunen et al. (1980) Kosunen et al. (1981) Finland	Study group of 342 hospitalised patients which were positive for *C. jejuni* (July 1978 to December 1979); Primarily cultivated from stools and in some cases confirmed by agglutinating antibodies in the sera	8 patients were found to have developed arthritis (2,3%), 5 of 7 were tested HLA-B27 positive: • 3 had migratory polyarthritis (7-17 weeks); 2 had polyarthritis and 3 had monoarthritis (1-3 weeks)
Johnsen et al. (1983) Norway	52 cases of *C. jejuni* infections (June 1980 – Sept. 1981) diagnosed at the University of Tromsö; 37 patients resubmitted their questionnaire. Patients that reported rheumatoid symptoms were clinical examined 7-8 months after disease onset; Additional information was obtained from patient records (GP or hospital)	7 (19%) reported joint or back symptoms; 5 (13.5%) had developed ReA symptoms. • All 5 patients had short-lasting acute synovitis, which resolved spontaneously within 3-7 days; treatment was usually unnecessary; 2 patients were hospitalised
Locht and Krogfeld (2002) Denmark	In a retrospective study 210 adult patients with a laboratory-confirmed Campylobacter infection (1997-1999) from all parts of Denmark were contacted in June 2000 to fill in a questionnaire on enteric and extra-intestinal symptoms (173 respondents); Case-controls were patients with *E-coli* infection proved by stool culture. Serum samples were collected 2 weeks, 3 months, 6 months and 2 years after disease onset	37 patients reported joint symptoms, of whom 27 (16%) were considered to probably have ReA • Median duration of joint symptoms was 60 days (interquartile range 29-180 days); 5 patients claimed to have symptoms for > than 1 year 48% had consulted their doctor[2)] ; 67% took analgesics[2)] and 26% stayed at home from work because of joint tenderness [2)]
Hannu et al. (2002) Finland	A questionnaire on enteric and extra-intestinal symptoms was sent to 870 laboratory-confirmed campylobacteriosis cases with a positive stool culture (610 respondents) and to an equal number of controls (April 1997 – September 1998); 220 of the 582 campylobacteriosis patients (38%) and 185 of the 758 controls (24%) reported recent joint or other musculo-skeletal symptoms. 11 weeks after disease onset (range 3-37), a clinical examination, together with measurement of the erythrocyte sedimentation; C-reactive protein and rheumatoid factor and HLA-B27 antigen analysis was done for 113 (51%) and 31 (17%) of campylobacteriosis patients and controls, respectively, that had reported rheumatoid symptoms.	7% patients (45/609) fulfilled the criteria for ReA[1)] and another 1% patients for reactive tendinitis, enthesopathy or bursitis (ReTEB), thus a total of 9% showed reactive musculoskeletal symptoms (10% of adults vs 0% of children). • 9 (20%) ReA patients had inflammatory lower back pain; 9%, 31% and 40% had a monoarticular, oligoarticular (2 to 4 joints) and a polyarticular peripheral arthritis, respectively. • Most were mild cases; 20% of the ReA cases (9/45) had visited a physician; and 2% (1/45) of the ReA patients were hospitalized. • Duration: 44% (20/45) had fully recovered within ≤ 6 months; of which 50%, 15%, 5%, 25% and 5% in ≤ 1, 1-2, 2-3, 3-4 and 4-6 months, respectively after onset of ReA symptoms [3)]

[1)] 'ReA was defined as the development of synovitis (either swelling or limitation of joint movement, and pain) in a previously asymptotic joint, or as inflammatory low back pain (low back pain that was worse at night) within the first 2 months after a gastrointestinal infection' (Hannu et al., 2002)

[2)] The follow-up of the patients stopped 6 months after disease onset. Therefore no information is available for the 25 ReA patients (56%) with symptoms longer than 6 months (Hannu (2003); personal communication).

[3)] The authors highlight the fact that there 'might have been some overlap regarding, for example, absence from work because of either gastrointestinal discomfort or joint tenderness'.

Appendix V - Distribution functions

Distribution functions of parameters used to estimate the disease burden and the cost-of-illness associated with Campylobacter infections and sequelae.

Model parameters	Input distribution	5%	Mean	50%	95%
All illnesses					
Cost-of-illness					
Proportion of patients travelling to GP, using a car or public transport	RiskPert(0.1,0.5,0.9)	0.23	0.50	0.50	0.75
Length of sickness leave per GP, healer or physiotherapy consultation (days)	Uniform(0, 0.25)	0.013	0.125	0.125	0.237
Length of sickness leave per specialist or outpatient hospital consultation (days)	Uniform(0.25,1)	0.29	0.625	0.625	0.96
Gastro-enteritis (GE)					
Annual incidence					
GE cases (population)	Simulation [1]	27,924	78,785	69,298	162,219
Proportion of GE cases visiting GP	Indirect	0.23	0.24	0.24	0.25
Laboratory confirmed GE cases	Custom	5,527	5,655	5,658	5,777
Proportion of laboratory confirmed GE cases being hospitalised	Indirect	0.08	0.09	0.09	0.10
Fatal GE cases	Simulation	20	28	27	37
Severity and duration					
Average life expectancy of fatal cases (years)	Custom	17.5	22.7	22.3	31.9
Cost-of-illness					
*Proportion of GE patients **not** visiting a GP and taking over-the counter medicine*					
Prop. of GE cases taking pain killers	Beta(183, 404)	0.28	0.31	0.31	0.34
Prop. of GE cases taking ORS	Beta(29, 558)	0.04	0.05	0.05	0.06
Prop. of GE cases taking anti-diarrhoea	Beta(27, 560)	0.03	0.05	0.05	0.06
Proportion of GE patients visiting a GP and taking medicine (on prescription and over-the counter medicine)					
Prop. of GE cases taking pain killers	Beta(37,26)	0.49	0.59	0.59	0.69
Prop. of GE cases taking ORS	Beta(21, 42)	0.24	0.33	0.33	0.43
Prop. of GE cases taking anti-diarrhoea	Beta(3, 60)	0.01	0.05	0.04	0.10
Prop. of GE cases taking antibiotics	Beta(17, 46)	0.18	0.27	0.27	0.36
Prop. of GE cases taking other medicines on prescription	Beta(9, 54)	0.08	0.14	0.14	0.22
Proportion of GE patients for which a third person was absent from work (age-dependant)					
For GE cases of 0-4 years	Beta(57, 382)	0.10	0.13	0.13	0.16
For GE cases of 5-9 years	Beta(23, 98)	0.13	0.19	0.19	0.25
For GE cases of 10-14 years	Beta(2, 15)	0.02	0.12	0.10	0.26
For GE cases ≥ 15 years	Beta(4, 73)	0.02	0.05	0.05	0.10
Reactive arthritis (ReA)					
Annual incidence					
Prop. of GE cases[2] at risk to develop ReA	Beta(46,565)	0.06	0.07	0.07	0.09
Prop. of ReA cases visiting GP	Beta(10, 37)	0.11	0.20	0.20	0.30
Prop. of ReA cases being hospitalised	Beta(2,45)	0.00	0.02	0.02	0.06
Duration and severity					
ReA duration (in years)	Expon(0.608)	0.04	0.61	0.42	1.78
Cost-of-illness [3]					

[1)] For details see Appendix I.

[2)] It was assumed that only GE cases that visit a GP, hospitalised or not, were at risk to develop ReA.

[3)] When estimating the ReA associated costs-of-illness, we modelled the uncertainty, using a distribution, for 'general' parameters, but for 'ReA specific' cost-of-illness parameters only average values were used.

Appendix V - Distribution functions (continued I)

Model parameters	Input distribution	5%	Mean	50%	95%
Guillain Barré Syndrome					
Annual incidence					
Incidence rate (per 100,000 pyr)	Normal(1.18, 0.05)	1.10	1.18	1.81	1.26
Attr. Proportion *C. jejuni* mild cases	Bootstrapping [4]	0.03	0.15	0.15	0.37
Attr. Proportion *C. jejuni* severe cases	Bootstrapping [4]	0.17	0.28	0.27	0.37
Sensitivity serology	Bootstrapping [4]	0.63	0.74	0.74	0.85
Specificity serology	Fixed	-	0.97	-	-
Proportion of mild cases < 50 years	Bootstrapping [4]	0.63	0.69	0.74	0.85
Proportion of severe cases < 50 years	Bootstrapping [4]	0.63	0.69	0.74	0.85
Case-fatality ratio	BetaPert(0.01, 0.02, 0.05)	0.013	0.023	0.023	0.036
Severity and duration					
Disability weights in the 1st year after disease onset for					
Mild cases	Beta(1.49, 15.29)+0.001 [4]	0.012	0.080	0.073	0.223
Severe cases < 50 years	Beta(3.47, 22.18)+0.130 [4]	0.175	0.244	0.256	0.389
Severe cases ≥ 50 years	Beta(5.83, 32.74)+0.190 [4]	0.259	0.316	0.335	0.444
Disability weights in the 2nd and following years after disease onset for					
Mild cases	Beta(0.87, 29.67) [4]	0.001	0.027	0.019	0.088
Severe cases < 50 years	Beta(2.50, 18.36)+0.041 [4]	0.074	0.161	0.147	0.294
Severe cases ≥ 50 years	Beta(3.54, 22.34)+0.074 [4]	0.124	0.211	0.200	0.334
Average duration of symptoms (years)					
Mild cases < 50 years	Custom	0	35.2	45.5	66.7
Mild cases ≥ 50 years	Custom	0	10.7	14.3	30.7
Severe cases < 50 years	Custom	37.6	45.7	45.7	54.3
Severe cases ≥ 50 years	Custom	11.7	16.4	16.4	21.5
Average life expectancy of fatal cases (years)	Custom	0	14.8	11.2	53.1
Cost-of-illness					
Mild GBS cases					
Prop. of cases getting an IVIg treatment	Uniform(0.3, 0.5)	0.31	0.40	0.40	0.49
Hospital stay (> 50 years); in days	Exponential(14)	1	14	10	41
Hospital stay (≥ 50 years); in days	Exponential(20)	1	20	14	60
Prop. of cases needing physiotherapy	Uniform(0.6, 0.75)	0.61	0.68	0.68	0.74
Severe GBS cases					
Prop. of cases needing 2nd IVIg treatment	Uniform(0.0, 0.1)	0.01	0.05	0.05	0.09
Prop. needing ventilation: < 50 years	Beta(35, 126)	0.17	0.22	0.22	0.27
Prop. needing ventilation: ≥ 50 years	Beta(33, 123)	0.16	0.22	0.21	0.27
Length of ICU stay (< 50 years) in days	Exponential(41)	2	41	28	122
Length of ICU stay (≥ 50 years) in days	Exponential(41)	2	41	28	122
Stay (days) in regular room of ventilated GBS patients (< 50 years)	ICU length * 1.05 fixed factor	-	1.05	-	-
Stay (days) in regular room of ventilated GBS patients (≥ 50 years)	ICU length * 1.20 fixed factor	-	1.20	-	-
Length of hospital stay (in days) of not ventilated GBS patients (only regular rooms)					
GBS cases < 50 years	Exponential(33)	2	33	23	97
GBS cases ≥ 50 years	Exponential(37)	2	37	26	109
Proportion of severe GBS cases admitted to rehabilitation centre					
Not ventilated GBS cases < 50 years	Beta(5, 22)	0.08	0.19	0.18	0.32
Not ventilated GBS cases ≥ 50 years	Beta(12, 28)	0.20	0.32	0.31	0.44
Ventilated GBS cases < 50 years	Beta(7, 18)	0.15	0.28	0.27	0.42
Ventilated GBS cases ≥ 50 years	Beta(12, 14)	0.31	0.46	0.46	0.62
Proportion of severe GBS cases, who returned home after hospital discharge, needing ambulant rehabilitation					
All GBS cases	Uniform(0.1, 0.15)	0.1	0.12	0.13	0.15
Length of rehabilitation (in days): inpatient and outpatient rehabilitation					
GBS cases < 50 years	Exponential(116)	6	116	80	346
GBS cases ≥ 50 years	Exponential(225)	12	228	156	671

[4] For more details see Havelaar et al. (2000a, b)

Appendix V - Distribution functions (continued II)

Model parameters	Input distribution	5%	Mean	50%	95%
Guillain Barré Syndrome (suite)					
Proportion of severe GBS cases that had fully recovered from the disease 3 to 6 years after disease onset (final F-score were 0,1 or 2)					
GBS cases admitted in reha. Centre	Beta(4, 31)	0.04	0.11	0.11	0.21
GBS cases returned home	Beta(43, 36)	0.45	0.54	0.54	0.64
*Proportion of **not** fully recovered severe GBS cases that had a final F-score of 0,1 or 2 at 3-6 years after disease onset*					
GBS cases admitted in reha. centre	Beta(20, 12)	0.48	0.63	0.63	0.76
GBS cases returned home	Beta(34, 3)	0.84	0.92	0.93	0.98
Prop. of invalid declared severe GBS cases with patients that had a 'good' outcome	Beta(17, 67)	0.14	0.20	0.20	0.28
Years of physiotherapy after rehabilitation discharge, and if not applicable, after hospital discharge for GBS cases with an F-score of 0, 1 or 2. [5]					
GBS cases < 50 years	Discrete((0.5, 1), (40, 9))	0.5	0.59	0.5	1
GBS cases ≥ 50 years	Discrete((0.5, 1), (44, 15))	0.5	0.63	0.5	1
Length of sickness leave of fully recovered GBS patients	Exponential(161) [6]	9	161	112	479
Length of sickness leave of *not* fully recovered GBS patients	Exponential(317) [6]	17	317	219	934
Fatal GBS cases					
Time period between hospital admission and death (in days)	Exponential(63)	3	63	44	188
Inflammatory bowel disease (IBD)					
Annual incidence					
Relative risk to develop IBD for laboratory confirmed GE cases	10^Normal(2.5225,0.0898)	9.76	11.51	11.45	13.44
Prop. of ulcerative colitis cases of IBD cases	Beta(89, 211)	0.25	0.30	0.30	0.34
Prop. IBD cases needing a second diagnostic procedure	Uniform(0, 0.34)	0.02	0.17	0.17	0.32
Prop. IBD cases having a GP visit/year	Beta(35, 417)	0.07	0.08	0.08	0.08
Prop. IBD cases having an outpatient visit/year	Beta(296, 156)	0.65	0.65	0.65	0.69
Proportion of IBD cases that have an outpatient visit/year:					
have laboratory tests conducted	Beta(238, 36)	0.83	0.87	0.87	0.90
have an endoscopie applied	Beta(101, 173)	0.32	0.37	0.37	0.42
have radiology analysis applied	Beta(39, 235)	0.11	0.14	0.14	0.18
have drugs prescript	Beta(256, 18)	0.91	0.93	0.93	0.95
need stoma therapy	Beta(4, 90)	0.01	0.04	0.04	0.08
need physiotherapy	Beta(5, 89)	0.02	0.05	0.05	0.10
need other therapy	Beta(3, 91)	0.01	0.03	0.03	0.07
need special diets	Beta(30, 64)	0.24	0.32	0.32	0.40
need other aids/tools	Beta(19, 75)	0.14	0.20	0.20	0.27
need stoma care	Beta(5, 89)	0.02	0.05	0.05	0.10
have other health care expenditure	Beta(7, 87)	0.04	0.07	0.07	0.12
go to a healer	Beta(6, 88)	0.03	0.06	0.06	0.11
need informal care	Beta(14, 80)	0.09	0.15	0.15	0.21
have other non-health care activities	Beta(25, 69)	0.19	0.27	0.26	0.34
Proportion of ulcerative colitis patients being hospitalised annually	Beta(39, 263)	0.10	0.13	0.13	0.16
Proportion of Crohn's disease patients being hospitalised annually	Beta(40, 112)	0.21	0.26	0.26	0.32

[5] Severe GBS patients with a final F-score of 3 or 4 were assumed to have during 2 years once a week physiotherapy (fixed).

[6] The maximum length considered in our calculation is 123 days, which is the assumed friction period.