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Health burden in the Netherlands (1990-1995) due to infections with thermophilic *Campylobacter* species

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Abstract

Infection with thermophilic *Campylobacter* spp. (mainly *C. jejuni*) usually leads to an episode of acute gastro-enteritis, which resolves within a few days to a few weeks. Occasionally, more severe and prolonged diseases may be induced, notably Guillain-Barré syndrome, reactive arthritis or bacteraemia. For some patients, the disease may even be fatal. This report describes the epidemiology of illness associated with thermophilic *Campylobacter* spp. in the Netherlands in the period 1990-1995 and attempts to integrate the available information in one public health measure, the Disability Adjusted Life Year (DALY). DALYs are the sum of Years of Life Lost by premature mortality and Years Lived with Disability, weighed with a factor between 0 and 1 for the severity of the illness. There is considerable uncertainty and variability in the epidemiological information underlying the estimated health burden, which is explicitly taken into account in the analysis. The estimated health burden of illness associated with thermophilic *Campylobacter* spp. in the Dutch population is estimated by simulation as 1400 DALY per year (90% confidence interval 900-2000 DALY per year). The main determinants of health burden are acute gastro-enteritis in the general population (310,000 cases, 290 DALY), gastro-enteritis related mortality (30 cases, 410 DALY) and residual symptoms of Guillain-Barré syndrome (60 cases, 340 DALY). The influence of uncertain assumptions in the above calculations is evaluated by sensitivity analysis. In all scenarios, the estimated health burden was within the above-mentioned range.

Preface

This report was built on the work of many. The data on gastro-enteritis were based on the work of Adrie Hoogenboom, who laid the foundations for surveillance at the population and general practice level. Martien Borgdorff and Yvonne van Duynhoven further developed this line of work, with important contributions by Simone Goosen and Wilfrid van Pelt. The data on Guillain-Barré syndrome were based on the research team headed by Frans van der Meché and the Dutch Guillain-Barré syndrome Study group. In particular the studies of Leendert Visser and Bart Jacobs provided crucial input in our work. Guus de Hollander and Elise van Kempen made an essential contribution by generating severity weights for the most important end-points of infection with thermophilic *Campylobacter* spp. The input of Maarten Nauta and Peter Teunis was instrumental in developing the modelling approaches for uncertainty analysis. Eric Evers and André Henken critically read and improved a draft version of the report.

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Samenvatting

Infectie met thermofiele *Campylobacter* spp. (met name *C. jejuni*) leidt meestal tot een episode van acute gastro-enteritis, welke binnen enkele dagen tot enkele weken spontaan geneest. Soms treden ernstiger en langduriger ziekteverschijnselen op, zoals Guillain-Barré syndroom, reactieve artritis of sepsis. Voor sommige patiënten heeft de ziekte een fatale afloop. Dit rapport beschrijft de epidemiologie van met thermofiele *Campylobacter* spp. geassocieerde ziekte in Nederland in de periode 1990-1995 en poogt deze informatie te integreren in één gemeenschappelijke volksgezondheidsmaat, de Disability Adjusted Life Year (DALY). DALYs zijn de som van het aantal verloren levensjaren ten gevolge van voortijdige sterfte, en het aantal jaren dat met ziekte wordt doorgebracht, gewogen met een factor tussen 0 en 1 voor de ernst van die ziekte.
De jaarlijkse incidentie van met *Campylobacter* geassocieerde enteritis, zoals gemeten in een populatieonderzoek, is 310.000 gevallen per jaar. Ongeveer 18.000 patiënten bezoeken hun huisarts (behoudens telefonische consulten). Van 6.800 patiënten wordt uit een voor laboratoriumonderzoek ingezonden fecesmonster *Campylobacter* geïsoleerd. Slechts een klein gedeelte van alle gevallen wordt herkend in een voedselgerelateerde explosie. Het aantal sterfgevallen is erg onzeker, de meest waarschijnlijke waarde is 30 gevallen per jaar, met name onder ouderen. De incidentie van Guillain-Barré syndroom in Nederland is ongeveer 180 gevallen per jaar, waarvan 60 worden geïnduceerd door infectie met *C. jejuni*. Daarvan hebben 50 gevallen een ernstig beloop (d.w.z. zijn niet in staat zelfstandig te lopen). De sterfte is laag (1 geval per jaar) maar er zijn restverschijnselen; circa 30% van de patiënten herstelt niet volledig maar ondervindt blijvend functionele beperkingen. De incidentie van met *C. jejuni* geassocieerde reactieve artritis is eveneens onzeker, met een meest waarschijnlijke waarde van 6.000 gevallen per jaar.
Weegfactoren voor acute enteritis en de verschillende stadia van Guillain-Barré syndroom werden bepaald met behulp van protocols gebaseerd op die van de Volksgezondheid Toekomst Verkenning 1997 (VTV). De duur van ziekte en levensverwachting van fatale gevallen werden uit verschillende epidemiologische onderzoekingen afgeleid.
Combinatie van bovengenoemde informatie leidt tot een schatting van de gezondheidslast door thermofiele *Campylobacter* in de Nederlandse bevolking. Onzekerheid en variabiliteit in de epidemiologische informatie zijn expliciet bij de analyse betrokken door middel van Monte Carlo simulatie en gevoeligheidsanalyse. De geschatte gezondheidslast bedraagt ca. 1400 (90% betrouwbaarheidsinterval 900-2000 DALY per jaar). De belangrijkste bijdragen worden geleverd door acute gastro-enteritis in de algemene bevolking (290 DALY), aan gastro-enteritis gerelateerde sterfte (410 DALY) en restverschijnselen van het Guillain-Barré syndroom (340 DALY). De gezondheidslast van maag-darmpathogenen kan derhalve worden onderschat wanneer uitsluitend gastro-enteritis wordt beschouwd.
De belangrijkste oorzaken van gezondheidslast betreffen patiënten die niet in een klinische omgeving worden gezien. De meest gedetailleerde gegevens zijn echter beschikbaar uit klinische onderzoekingen, maar deze betreffen ziektebeelden of –stadia die weinig bijdragen aan de totale gezondheidslast. Actieve surveillance van maag-darmaandoeningen op populatiebasis is dan ook te verkiezen boven passieve surveillance gebaseerd op klinische rapportages. Vergelijking van de resultaten met VTV toont dat de gezondheidslast door *Campylobacter* vergelijkbaar is met ziekten als meningitis, sepsis, bovenste luchtweg infecties, maag- en darmkanker, het Down syndroom, geweld en toevallige verdrinking.

Summary

Infection with thermophilic *Campylobacter* spp. (mainly *C. jejuni*) usually leads to an episode of acute gastro-enteritis. Occasionally, more severe and prolonged diseases may be induced, notably Guillain-Barré syndrome and reactive arthritis. For some patients, the disease may be fatal. We describe the epidemiology of illness associated with thermophilic *Campylobacter* spp. in the Netherlands in the period 1990-1995 and integrate the available information in one public health metric, the Disability Adjusted Life Year (DALY). DALYs are the sum of Years of Life Lost by premature mortality and Years Lived with Disability, weighed with a factor between 0 and 1 for the severity of the illness.
The annual incidence of *Campylobacter* associated enteritis, as measured in a community-based study, is 310,000 cases per year. Approximately 18,000 patients visit their general practitioner (excluding consultations by telephone). A faecal sample is sent to a laboratory and tested positive for *Campylobacter* for 6,800 patients. Only a small fraction of all cases is involved in recognised foodborne outbreaks. The number of fatal cases is highly uncertain, with a most likely value of 30 per year, mainly among the elderly. The incidence of Guillain-Barré syndrome in the Netherlands is approximately 180 cases per year, of which 60 are induced by infection with *C. jejuni*. Of these, 50 are severely affected (i.e. not able to walk independently). Mortality is low (1 case per year) but there is considerable residual disability; approximately 30% of the severely affected patients did not fully recover but continue to suffer from functional limitations. The incidence of *C. jejuni* related reactive arthritis in the Netherlands is also highly uncertain, with a most likely value of 6000 cases per year.
Severity weights for acute enteritis and the different stages of Guillain-Barré syndrome were obtained by panel elicitation, using protocols based on those developed for the Dutch Public Health Status and Forecast Study (PHSF). Duration of disease and life expectancy of fatal cases were obtained form different epidemiological studies.
Combining this information, the health burden of illness associated with thermophilic *Campylobacter* spp. in the Dutch population can be estimated. Uncertainty and variability in the epidemiological information are explicitly taken into account in the analysis by Monte Carlo simulation, and by sensitivity analysis. The mean health burden is 1400 (90% confidence interval 900-2000) DALY per year. The main determinants are acute gastro-enteritis in the general population (290 DALY), gastro-enteritis related mortality (410 DALY) and residual symptoms of Guillain-Barré syndrome (340 DALY). Thus, the health burden associated with gastro-intestinal pathogens may be underestimated if only diarrhoeal illness is accounted for.
The most important causes of health burden affect patients that are not usually seen in clinical settings. Most detailed data are available from clinical studies, but these relate to diseases or disease stages that only have a small contribution to the overall health burden. Thus, active surveillance for gastro-intestinal pathogens, based on population studies is preferred above passive surveillance based on clinical reports. Comparison with results from the PHSF study shows that the health burden of *Campylobacter* infection is similar to diseases such as meningitis, sepsis, upper respiratory infections, stomach and duodenal ulcers, Down syndrome, violence and accidental drowning.

List of abbreviations and symbols

Abbreviations

CFR	Case-fatality ratio
ELISA	Enzyme Linked Immuno Sorbent Assay
F-score	Functional status of Guillain-Barré syndrome patients
GBD	Global Burden of Disease study
GBS	Guillain-Barré syndrome
GE	Gastro-enteritis
GP	General practitioner
HC	Healthy control
HLA	Human Leucocyte Antigen
HospC	Hospital control
ICD	International Classification of Diseases
IgA,G,M	Immunoglobulin subclasses
IVIg	Intravenous immunoglobulin treatment
ReA	Reactive arthritis
NDC	Neurological disease control
NINCDS	National Institute of Neurological and Communicative Diseases and Stroke
NIVEL	Netherlands Institute for Research in Health Care
NSAIDs	Non-steroid anti-inflammatory drugs
PE	Plasma exchange treatment
PTO	Person Trade-Off protocol
TTO	Time Trade-Off protocol
VAS	Visual Analog Scale
VTV	Dutch Public Health Forecast study
WHO	World Health Organization

Symbols

a	Age
AP	Attributable proportion
CV	Coefficient of variation
d	Number of fatal cases
DALY	Disability Adjusted Life Year
$e^{*}(a')$	Mean standardised life expectancy in a 5-year age interval
IR	Incidence rate of disease
k	Dispersion factor
L	Duration of disease
ln	Natural logarithm
M	Median value
N	Incidence of disease
OR	Odds ratio
P_{app}	Apparent prevalence
P_{true}	True prevalence
Prob{.}	Probability
r	Discount rate
S	Sensitivity of model results
SE	Sensitivity of a diagnostic test
SLE	Standard Life Expectancy
SP	Specificity of a diagnostic test
W	Severity weight of disease
yld_i	Health burden of an individual case
YLD	Years Lived with Disability
YLL	Years of Life Lost
Δp	Change in parameter value
Δo	Change in output value
μ	Mean
σ	Standard deviation

1. Introduction

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

Risks of gastro-intestinal pathogens are usually expressed as the probability of infection, resulting from consumption of a product. However, for public health policy it is of more interest to estimate the probability of disease. Moreover, the spectrum of disease by intestinal pathogens may vary from a short, self-limiting episode of nausea and vomiting to life-long sequelae or even death. It is therefore necessary to integrate the different health effects of gastro-intestinal infection into a common measure. Economic analyses, which identify all costs to society, including a monetary equivalent of life years lost, are frequently used for this purpose. However, the economical approach does not take into account the effects of disease on the quality of life, which is an important objective of public health policy.

In this report, a methodology is presented to estimate the health burden of gastro-intestinal disease. The methodology is illustrated by a case study of the health burden of infection with thermophilic *Campylobacter* species in the Netherlands. To reach this aim, the available epidemiological and clinical literature is summarised, and quantitative estimates are made of the incidence of important disease end-points, their duration and severity. The data are primarily selected to reflect the situation in the Netherlands in the period 1985-1995, with an emphasis on the second half of this decade. Where necessary and appropriate, international data are also used. The available data are integrated in the public health indicator “Disability Adjusted Life Years”, which combines the effects of morbidity and mortality in one estimate of health burden to the population. Uncertainty and variability are explicitly taken into account by using statistical distribution functions for the model parameters, by analysing the data by Monte Carlo simulations and by sensitivity analysis.

2. Conceptual model

This Chapter describes a general chain model for analysing the effects of oral exposure to pathogenic microorganisms, see Figure 2.1. Specific application to thermophilic *Campylobacter* species will be described in the following Chapters.

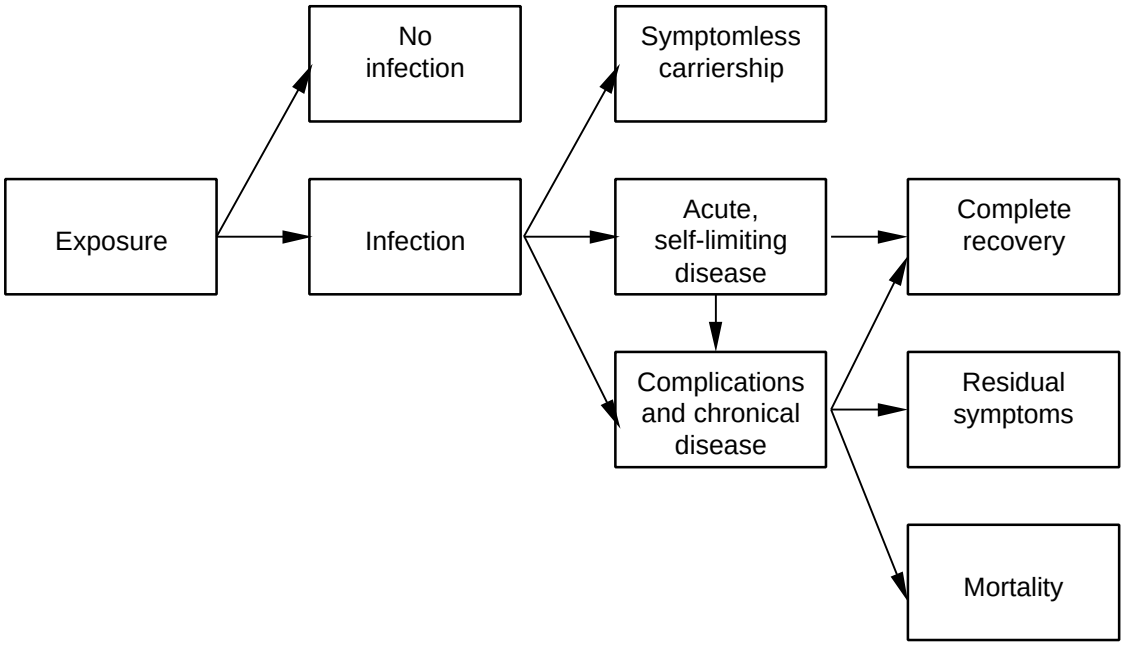


Fig. 2.1. Chain model of infectious gastro-intestinal disease.

The host can be in any of a number of possible health states, and the transitions between these states can be described by a set of conditional probabilities, i.e. the chance of moving to a health state, given the present health state.
The probability of *infection*, that is the ability of the pathogen to establish and multiply within the host, depends on the exposure to gastro-intestinal pathogens in food, water or other environmental factors. Based on data from human feeding studies, statistical dose-response models have been developed to quantify the relationship between the number of ingested organisms and the probability of infection (Teunis *et al*., 1996; Havelaar and Teunis, 1998). These models are empirical and do not explicitly identify the factors that may influence the process of infection. Such factors are the physiological status of the pathogen, the matrix in which it is presented to the host, the microbial dynamics in the host, the aspecific (e.g. gastric acid, enzymes, bile, peristalsis) and the specific (cellular and humoral immunity) host resistance. Thus, generalisation of dose-response models is only possible to a limited extent.
There are also experimental data on the probability of *acute, gastro-intestinal disease* after infection. In most human feeding studies, clinical symptoms were also described, but the relationship with the ingested dose is less uniform than for infection (Teunis *et al*., 1997). Additional data may be derived from epidemiological studies, such as outbreak investigations or prospective cohort studies.
Usually, gastro-enteritis is a self-limiting disease and the host will *recover* within a few days to a few weeks without any residual symptoms. In most cases, symptomatic or asymptomatic infection confers immunity that may protect from infection and/or disease upon subsequent

exposure. Usually, immunity against enteric pathogens is short-lived and the host will enter again a susceptible state within a period of months to years. In a small fraction of infected persons (with or without acute gastro-enteritis), *chronical infection or complications* may occur. Some pathogens, such as salmonellae are invasive and may cause bacteraemia and generalised infections. Other pathogens produce toxins that may be transported by the blood to susceptible organs, where severe damage may arise. An example is the haemolytic uremic syndrome, caused by damage to the kidneys from Shiga-like toxins of some *E. coli* strains. Complications may also arise by autoimmune reactions: the immune response to the pathogens is then also directed against the host tissues. Reactive arthritis (including Reiters'syndrome) and Guillain-Barré syndrome are well-known examples of such diseases. The complications from enteritis normally require medical care, and frequently result in hospitalisation. There may be a substantial risk of *mortality*, and not all patients may recover fully, but may suffer from *residual symptoms*, which may last life-long. Therefore, despite the low probability of complications, the public health burden may be significant.

3. Epidemiology of *Campylobacter* infections

3.1 General

Infection with *Campylobacter* bacteria may lead to a great diversity of outcomes, many of which are extremely rare. Butzler *et al*. (1992) have divided the symptoms of *Campylobacter* enteritis in four different phases: prodromal, diarrhoeic, recovery and complications. For the purpose of this report, this classification is modified as indicated in Table 3.1.

Table 3.1. Outcomes of Campylobacter enteritis[1].

Disease phase	Symptoms
PRODROMAL	anorexia, arthralgia, dizziness, fever (>37.5 °C), malaise, myalgia, nausea, vomiting
DIARRHOEIC	abdominal cramps, abdominal pain[2], profuse diarrhea, watery or slimy stool containing inflammatory exudate, leukocytes and fresh blood
ABDOMINAL COMPLICATIONS	appendicular syndrome, cholecystitis, colitis, gastrointestinal bleeding, mesenteric adenitis, pancreatitis, peritonitis, pseudomembranous colitis, rectal bleeding, splenic rupture, toxic megacolon
EXTRAINTESTINAL COMPLICATIONS	abortion, bacteremia (particularly in HIV-infected), haemolytic anaemia, encephalopathy, meningitis, neonatal infection, osteomyelitis, urinary tract infections,
POSTINFECTIOUS COMPLICATIONS	Guillain-Barré syndrome, Miller Fisher syndrome infectious arthritis, reactive arthritis, Reiter's syndrome, carditis, endocarditis, myopericarditis erysipelas-like lesions, erythema nodosum hemolytic uremic syndrome, purpura abdominalis (Henoch-Schoenlein syndrome), liver abcess, nephropathy

In the prodromal phase, which usually lasts a few hours to a few days, general, non-specific symptoms predominate. Some of these symptoms may also continue in later phases. For the purpose of characterising disease burden, this phase is not very important because of its limited duration and mild symptoms. Furthermore, most literature sources do not specify this phase separately, but report symptoms of the prodromal phase as a part of the acute, diarrhoeal phase. In the diarrhoeal phase, symptoms of toxic diarrhoea usually predominate, but tissue invasion and resulting damage may also occur. The complications after *Campylobacter* infection are subdivided into three categories following Allos and Blaser (1995): abdominal, extraintestinal and postinfectious. The justification of this subdivision is that the mechanisms leading to these three types of complications differ. For the purpose of characterising the health burden, only complications that occur relatively frequently will be considered in this report: Guillain-Barré syndrome and Miller Fisher syndrome, bacteremia and reactive arthritis. The recovery phase combines transitions from different disease syndromes and is therefore highly diverse. In this report, it is not recognised as a separate

[1] After Butzler *et al.* (1992), Anonymous (1994), Allos and Blaser (1995), Mossel *et al*. (1995), Buzby *et al*. (1996)

[2] May be mistaken for acute inflammatory bowel disease or acute appendicitis, may lead to laparotomy or appendectomy

entity but is discussed as a part of the clinical course of each syndrome. The risk of death is also discussed as a possible outcome of different diseases.

3.2 Acute, diarrhoeal diseases

3.2.1 Incidence in the Netherlands

The incidence of acute *Campylobacter* enteritis can be estimated from different data sources: outbreak reports, laboratory reports, surveillance in general practices and population-based surveys. Each data source is biased (Borgdorff and Motarjemi, 1997), and consequently the data must be interpreted with care.

Foodborne outbreaks

Table 3.2 gives a summary of data from surveillance of foodborne outbreaks in the Netherlands (Hoogenboom-Verdegaal *et al*., 1992; Goosen *et al*., 1995[b], Van Duynhoven and De Wit, 1998; 1999).

Table 3.2. Total and Campylobacter-related foodborne disease incidents in the Netherlands, 1979-1997.

Years	Outbreaks		Patients in outbreaks		Single cases	
	Total[1]	*Camp.*[2]	*Total*	*Camp.*	*Total*	*Camp.*
1979-82	988	19 (1.9)	6717	360 (5.4)	174	9 (5.2)
1983-86	869	14 (1.6)	6026	88 (1.5)	20	3 (15.0)
1987-90	542	5 (1.0)	4093	32 (0.8)	101	2 (2.0)
1991-94	1534	3 (0.2)	6480	8 (0.1)	1087	9 (0.8)
1995-98	1722	4 (0.2)	9053	19 (0.2)	1315	2 (0.2)
Total	5655	45 (0.8)	32369	507 (1.6)	2697	25 (0.90)

[1] Total number of foodborne outbreaks (patients in outbreaks, single cases) per period

[2] Number of outbreaks (patients in outbreaks, single cases) for which *Campylobacter* was identified as the causative agent per period (percentage of total)

In the years 1979-1997, 45 outbreaks and 25 single cases of campylobacteriosis, together involving 532 patients were identified by Food Inspection Services in the Netherlands, i.e. an average annual incidence of 28 patients per year. There appears to be a decreasing trend in the number of *Campylobacter*-related outbreaks with time. In contrast, the annual number of reported outbreaks and patients has increased. The latter can be attributed to increased public awareness, by the introduction of a free telephone number and extensive publicity campaigns in 1991. The proportion of campylobacteriosis cases in reported outbreaks is very low, indicating that campylobacteriosis is not readily recognised as a foodborne disease from outbreak statistics.

Laboratory surveillance

Laboratory surveillance data are available since April 1995. In the 15 participating Regional Public Health Laboratories the annual average rate of *Campylobacter* isolations was 3.0% (2,871/94,598) in 1995 and 3.6% (3,748/10,4305) in 1996. It is estimated (W. van Pelt, personal communication) that for *Campylobacter* spp. these laboratories cover about 62% of the Dutch population, leading to an estimated annual incidence of laboratory-confirmed *Campylobacter* enteritis of approx. 5,800 cases per year (4 per 10,000 persons per year). Whereas the total number of submitted faecal specimens is relatively constant throughout the

year, there is a remarkable seasonal variation in the incidence of laboratory confirmed campylobacteriosis, as can be seen from Figure 3.1. The isolation rates peak in summer, when 6-7% of all samples are positive for *Campylobacter*.

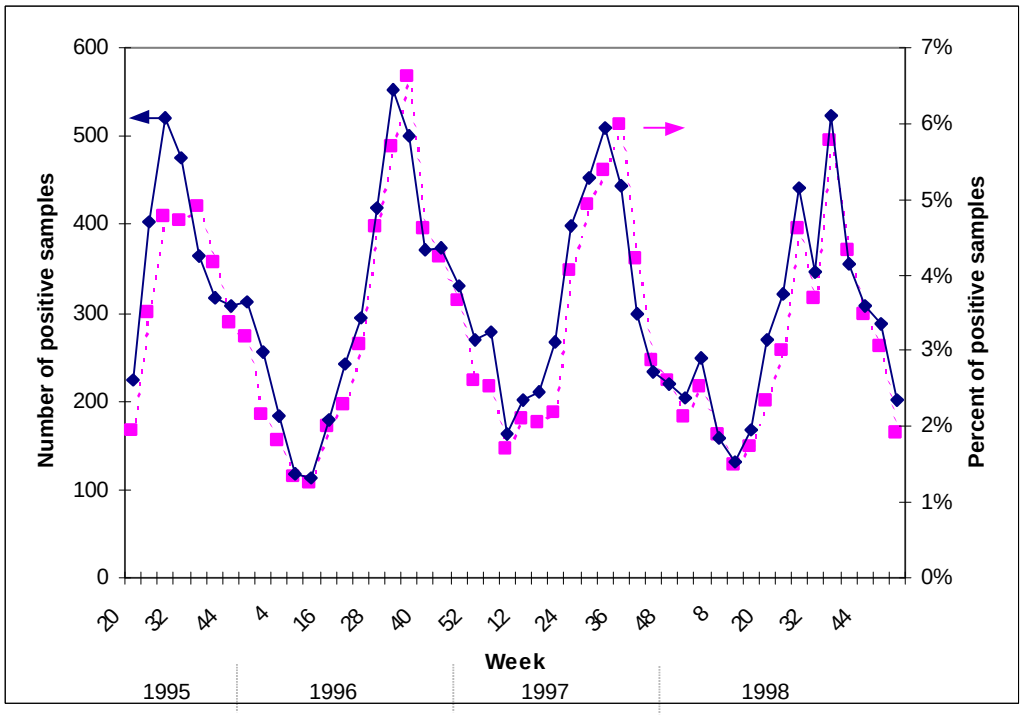


Fig. 3.1. Laboratory surveillance for Campylobacter in the Netherlands: absolute number of faecal samples from which the organism was isolated and percentage of all samples, per 4-week period.

Talsma *et al*. (1999) have evaluated data from the Regional Public Health Laboratory in Arnhem and found an isolation rate of 5.4%, which was constant throughout 1994-1996, and also peaked in the summer months. In this region, the average incidence was 3.5 cases per 10,000 person years, which is slightly lower than the above-mentioned national estimate. After correction for an estimated coverage of 67%, the incidence would be 5.2 per 10,000 person years. Among males, incidence was higher in infants, young children and the elderly, while in the young adult age group (20-29 years) the higher incidence was among females.

Sentinel surveillance in general practices

In the years 1987-1991, a sentinel study was carried out in general practices in the cities of Amsterdam and Helmond to estimate the incidence of acute gastro-enteritis and the major etiologic factors (Hoogenboom-Verdegaal *et al.*, 1994[a]). The average crude incidence of gastro-enteritis was 15 episodes per 1000 person-years[3], the peak incidence was in the age-class 0-4 years (40-80 episodes per 1000 person-years) and was relatively constant in all other age-classes. *Campylobacter* could be cultured from 14% of all faecal samples (as compared to 5% for *Salmonella*). This percentage varied between 11 and 21% with no

[3] The case-definition used was acute diarrhoea with 2 or more times per day loose stools, different from normal consistency and at least two of the following symptoms: vomiting, nausea, abdominal pain or cramps, fever, blood or mucus in faeces

obvious trend over the years. There was little difference between isolation rates in the two cities (13% in Amsterdam vs. 15% in Helmond). There was no trend in the age-specific isolation percentage in Amsterdam, whereas in Helmond, the isolation percentage was only 5% in the 0-4 year old, and peaked to approximately 30% in the age-classes 10-14 and 15-19. Hence, in these two cities, the incidence of *Campylobacter* enteritis, leading to consultation of a general practitioner, was estimated as 21 episodes per 10,000 person-years.
The sentinel studies were repeated in the years 1992-93, using the established NIVEL[4] sentinel surveillance system, which is a representative selection of practices throughout the country (Bartelds, 1993; 1994; Goosen *et al*., 1995[a]). In this study, the age- and sex standardized incidence of acute gastro-enteritis[5] was 55.3 per 10,000 person-years; after correction for non-response the incidence was 89.9 per 10,000 person-years. In 1993, the incidence was significantly lower than in 1992: 59.6 vs. 46.6 per 10,000 person-years. The incidence was not different between men and women, and was highest in the summer months. Also, there were differences between regions of the country and related to urbanisation. As in the 1987-91 studies, the incidence peaked in the younger age classes (420 resp. 182 per 10,000 person-years in the 0 and 1-4 year old). *Campylobacter* could be cultured from 14.6% of all faecal samples (4.4% yielded *Salmonella*). The isolation percentage was lowest (≤ 5% in the very young (0 years) and in the old (65+), and peaked in the 15-19 age-class (33%). The estimated standardized incidence of *Campylobacter* enteritis was 6.9 per 10,000 person-years. If a correction for non-response were applied, this estimate would be 11.7 per 10,000 person years. It is likely, however that the non-response was biased towards the less severe cases so that the corrected incidence could be an overestimation because infection with thermophilic *Campylobacter* spp. usually leads to a relatively severe form of enteritis. The incidence was highest below 5 years of age, but this conclusion is based on small numbers.
The incidence of *Campylobacter* enteritis in this study was considerably lower than in the earlier study, which may be related to several factors. The cities of Amsterdam and Helmond may not be representative for the Netherlands as a whole. This might have resulted in overestimation of the incidence in the first study. There were indications that the motivation of the general practitioners in the NIVEL study was lower, which may have influenced their response and their decision whether a patient's symptoms met the case-definition; this might have resulted in underestimation of the incidence of gastro-enteritis in the NIVEL study. Note that the isolation rates of *Campylobacter* spp. in both studies were similar.
From the sentinel surveillance studies, it is concluded that in the years 1987-1993 the incidence of *Campylobacter* enteritis, leading to consultation of a general practitioner in the Netherlands, is 7-21 per 10,000 person-years. There are differences related to age, season and place of residence, but the available data do not allow definitive conclusions to be made. Taking all sources of possible bias into account, we have selected the corrected incidence of campylobacteriosis from the NIVEL study in 1992-3 as the basis for estimation of the health burden. The impact of other possible choices will be evaluated in a sensitivity analysis (see Chapter 4.4.3).
The sentinel study, using the NIVEL network, is being repeated in the years 1996-1999. Interim results for the first two years (De Wit *et al*., 1999) indicate that the incidence of gastro-enteritis (corrected for non-response) was 58 per 10,000 personyears (77 after correction for non-response). *Campylobacter* was isolated from 10% of faecal samples from

[4] Nederlands Instituut Voor Onderzoek in de Gezondheidszorg: Netherlands Institute for Research in Health Care, Utrecht, the Netherlands
[5] The case-definition used was 3 or more times per day loose stools, different from normal consistency ór loose stools and 2 or more of the following symptoms: fever, nausea, abdominal pain or cramps, , blood or slime in faeces ór vomiting and 2 or more of the abovementioned symptoms, preceeded by a complaint-free period of at least 14 days; only physical consultations were recorded but not consultations by telephone

cases, and 0.2% of controls. Thus, in the current study, the incidence of campylobacteriosis, leading to consultation of a general practitioner, is estimated at 7.7 per 10,000 person years. This is lower than in the 1992-93 study, mainly because of the lower isolation rate of *Campylobacter* from the faeces of patients.

Population-based surveillance
In 1991, a population-based surveillance study on the incidence of acute gastro-enteritis[6] was performed, leading to an age-standardised estimate of 447 episodes per 1000 person-years (Hoogenboom *et al*., 1994[b]; De Wit *et al*., 1996). *Campylobacter* was isolated from 4.5% of faecal samples (1.6% yielded *Salmonella*). The number of positive samples was too small to draw conclusions on the effect of sex, age or region. Thus, the standardised incidence of *Campylobacter* enteritis in the Dutch population is estimated at 20.1 per 1,000 person-years. A (voluntary) selection of the participants in this study submitted a weekly faecal sample for microbiological examination, independent of the presence of gastro-intestinal symptoms. From these data, which may be biased towards persons who experience gastro-intestinal problems more frequently, the standardised incidence of (symptomatic and asymptomatic) infections with *Campylobacter* is estimated at 85 per 1,000 person-years[7].

Summary
Table 3.3 summarises the information on incidence of *Campylobacter* infections in the Netherlands. Each year, an estimated 1.2 million persons are infected, and of these, approximately 25% or 300,000 persons experience symptoms of gastro-enteritis. 18,000 patients visit their general practitioner (excluding consultations by telephone). A faecal sample is sent to a laboratory and tested positive for *Campylobacter* for 6,800 patients. Only a small fraction of all cases is involved in recognised foodborne outbreaks.

Table 3.3. Incidence of Campylobacter infections and associated enteritis in the Netherlands, according to different surveillance systems (data collected in the period 1987-1993).

Surveillance system	Incidence of *Campylobacter* enteritis	
	Cases per 10,000 py	*Cases per year*
Population study (infection)	850	$1{,}2 \times 10^6$
Population study (enteritis)	200	$3{,}0 \times 10^5$
GP sentinel surveillance	12	$1{,}8 \times 10^4$
Laboratory surveillance	4.5	$6{,}8 \times 10^3$
Outbreak investigations	0.004	6

Uncertainty in estimates of the incidence of campylobacteriosis
The uncertainty distribution of the standardised incidence of gastro-enteritis is not known exactly, but can be deducted from the uncertainty in the unstandardised incidence. De Wit *et al*. (1996) used Poisson regression, resulting in a lognormal distribution of the estimate:

[6] A comprehensive case-definition was used: diarrhoea or vomiting with at least two other symptoms: diarrhoea, vomiting, fever, nausea, abdominal pain or cramps, , blood or slime in faeces in a period of 7 days

[7] From the population survey, the risk of becoming ill after infection with thermophilic *Campylobacter* spp. is thus estimated at 25%. This is somewhat lower than the results in the volunteer experiment of Black *et al*. (1988), who reported 29 ill / 89 infected (33%). Bremell *et al*. (1991) investigated an outbreak in which 35 cases had overt disease (16 with positive stools and 29 with antibody response) and 31 cases were infected but had no symptoms of disease; the ratio of ill : infected in this study was 35 : 66 = 53%.

median value M = 563 per 1000 pyr, 95% confidence interval 502-630. Defining the dispersion factor k by Prob{M/k<X<kM} = 0.95 (Slob, 1994), we can deduce that k = v(630/502) = 1.12. If we assume that the dispersion factor is not affected by age standardisation, then the standardised incidence follows a lognormal distribution with M = 447 and k = 1.12. On the (natural) log scale, this converts to $\mu = \ln(M) = 6.10$ and $s = \ln(k)/1.96 = 0.058$. From 245 faecal samples of patients with gastro-enteritis, 11 were positive for *Campylobacter* spp. Using Bayesian statistics with a non-informative Beta(1, 1) prior distribution, the fraction of *Campylobacter*-positive stools then follows a Beta(12, 235) posterior distribution (Vose, 1996). Note that the mean of this distribution is 4.9%, i.e., slightly higher than the simple estimate of 4.5% that was reported on the previous page. This will also result in a slightly higher estimate of the incidence of *Campylobacter*-associated gastro-enteritis in the general population.
Goosen *et al*. (1995) estimated the incidence of GP consultations for *Campylobacter*-associated gastro-enteritis at M = 6.9 per 10,000 pyr, 95% confidence interval 6.0-8.0; this is approximately a normal distribution with $s = (8.0-6.0)/(2 \times 1.96) = 0.51$. The incidence rate is then corrected for non-response by patients and doctors to yield an estimate of 11.7. Assuming that correction does not affect the uncertainty in the estimate, the standard deviation of the corrected incidence rate is $s = 0.51 \times (11.7/6.9) = 0.87$.

3.2.2 Symptoms, severity and duration

Data on symptoms and severity of *Campylobacter* enteritis can be obtained from the same sources as data on incidence, although in general the available information is less comprehensive. Outbreak reports are valuable sources of information because they may involve a wide representation of the general population, which is usually well characterised with regard to geographic location, age and sex. In the Netherlands, outbreaks of *Campylobacter* enteritis are rarely recognised, and if detected, the number of persons involved is low and the available clinical data are limited. Published outbreak reports from other industrialised countries provide additional information that may be relevant for the situation in the Netherlands. Laboratory surveillance as such does not produce useful information on clinical aspects, but some studies have sought specific information from patients by using questionnaires. In the Amsterdam-Helmond sentinel study (1987-91, 263 *Campylobacter* positive patients) and the NIVEL sentinel study (1992-93, 182 *Campylobacter* positive patients), data were collected on the symptoms at the moment of presentation to the GP, and the time interval between onset of symptoms and consultation, but not on the duration of symptoms after consultation. Also, data are available on medication and absence from school or work. An overview of the available data is given in Appendix 2; the data is summarised in Table 3.4.

Table 3.4. Frequently reported symptoms of Campylobacter enteritis.

Symptoms	Mean percentage of patients with symptoms	
	outbreaks	clinical studies[1]
Fever	74	64
Abdominal pain	88	74
Vomiting	39*	25*
Diarrhoea	94	95
Blood in stool	26	27

[1] General practitioner, laboratory surveillance and hospital-based studies

* Significantly different from each other (t-test, p = 2%)

It might be hypothesised that data obtained from clinical studies represent the more serious cases of disease, as these may be more likely to consult a doctor. However, as the data in Table 3.4 show, there was no significant difference between the percentage of patients in outbreaks or in clinical studies that reported fever, abdominal pain, diarrhoea or blood in stool. Outbreak patients reported significantly more often vomiting than clinical patients, which may be related to the time that has elapsed between onset of the symptoms and consultation of a doctor. Therefore, it might be concluded that the data in Table 3.4 represent the clinical course of all patients with *Campylobacter* enteritis. It is possible however, that outbreak associated strains of bacteria are more virulent than average. In the population survey (1991), data were collected on symptoms, medication, absence from school or work and duration of complaints. However, only 17 persons with *Campylobacter* infection were detected of which only 3 had concurrent diarrhoea. These data are too limited to evaluate the representativeness of outbreak data for the severity of campylobacteriosis in the general population, and the possibility that many cases have a less severe clinical course cannot be excluded. To link data on incidence and severity of complaints in clinical and outbreak studies to the level of the general population, it may be useful to study the determinants for consultation of the GP for gastro-enteritis in general. Duration has already been identified as a determinant: 60% of patients with gastro-enteritis during 6 weeks or more consulted their GP vs. 11% with a duration of 1-2 weeks. Age has also been identified as a determinant of GP consultation; it is more frequent under 5 and above 45 (De Wit *et al*., 1996).
Rijntjes (1987) has published a detailed study on clinical aspects of acute diarrhoea in general practice. For most purposes, the population could be divided into two groups: children (0-10 years) and adults (11 years or older). The median time interval between onset of disease and consultation of the GP was 2-3 days for adults and 3-4 days for children. From the data of Rijntjes, it can be deduced that at the time of contact with the physician, the symptoms were at a maximum, or possibly already beyond. Rijntjes gives data on the percentage of patients who have suffered from specific symptoms in the premedical period, and on the total duration of symptoms. From his data, Figures 3.2[a,b] have been constructed.
It appears that in the majority of patients, who consult their general practitioner for acute gastro-enteritis, the symptoms are most prominent after 2 days, after one week most symptoms have disappeared, with the exception of diarrhoea, which may still be present in 40-60% of all patients. Note that these data are for all cases of gastro-enteritis, independent of the aetiology, and that the data were obtained in the period 1983-1984. Specific information on the duration of *Campylobacter* enteritis is given in Appendix 3. Data from Kapperud and Aasen (1992) confirm the observation of Rijntjes (1987) that diarrhoea generally persists longer than other symptoms. The Appendix also suggests that cases in clinical studies have a longer duration than cases in outbreak studies, although this is difficult to evaluate formally.

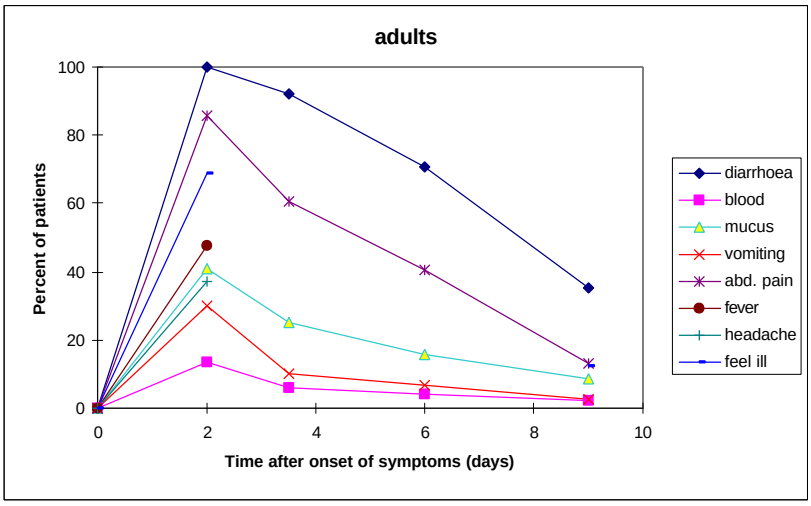


Fig. 3.2[a]. Duration of symptoms in patients who consult their general practitioner for gastro-enteritis (Rijntjes, 1987).

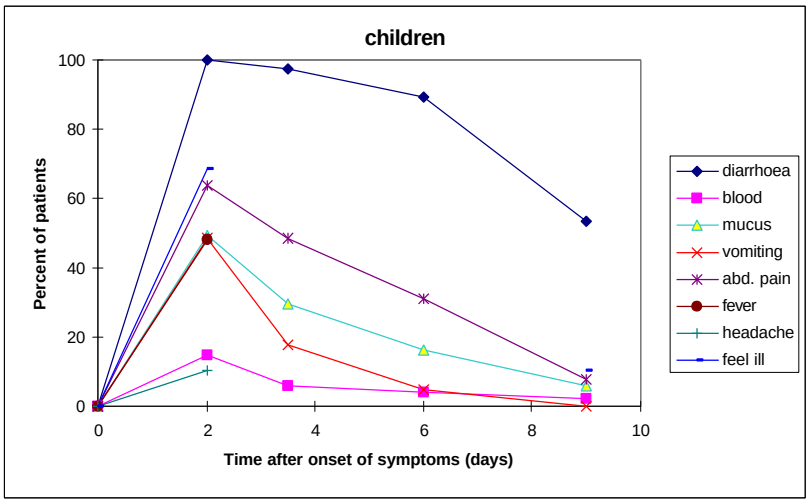


Fig. 3.2[b]. Duration of symptoms in patients who consult their general practitioner for gastro-enteritis (Rijntjes, 1987).

From the information in this paragraph, it may be concluded that *Campylobacter* enteritis is a relatively severe form of gastro-enteritis, with diarrhoea in the great majority of patients but which also frequently involves fever, severe abdominal pains, vomiting and blood in the stool. The median duration is estimated at 4-6 days, but follows a highly skewed distribution with a maximum up to a month or more. There are no adequate data to fit a statistical distribution. We therefore constructed a lognormal distribution for the duration of campylobacteriosis in the general population with parameters $\mu = 1.5$ and $s = 0.5$. This distribution (see Fig. 3.3) has a median of 4.5 days, a mean of 5.1 days, and a 95% range of 1.7-12 days.

The duration of gastro-enteritis in patients who consult their general practitioner is generally longer than in patients who do not. Again, there are few data and an approximation must be used. The data from Rijntjes (1987) can be fitted with a lognormal distribution with

parameters $\mu = 2.0$ and $s = 0.5$. This distribution (see Fig. 3.3) has a median of 7.4 days, a mean of 8.4 days, and a 95% range of 2.8-20 days.

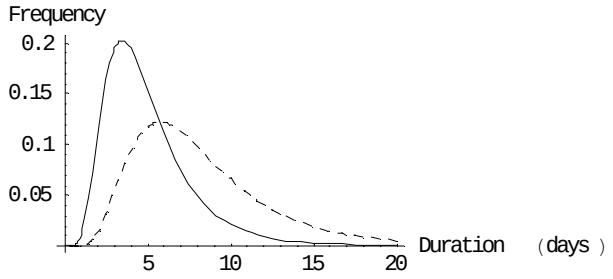


Fig. 3.3. Proposed probability density function for the duration of campylobacteriosis in the general population (solid line) and for patients consulting their GP (dashed line).

3.2.3 Recovery and mortality

Uncomplicated *Campylobacter* enteritis resolves without any residual symptoms. The most important complications will be discussed in later paragraphs. The mortality risk of *Campylobacter* enteritis is low, but important in respect to health burden. There is little information on *Campylobacter* associated mortality. Tauxe (1992) estimates the case-fatality ratio of campylobacteriosis as 3/10,000 outbreak related cases (2 deaths among 6,000 cases) and applies this rate to an estimate of all cases of *Campylobacter* enteritis in the USA (incidence 96-108 per 10,000 person-years, or 2.2-2.4 million cases per year) to arrive at an estimate of 680-730 *Campylobacter* associated deaths per year in the USA. A similar estimate for the Netherlands would be 90 deaths per year. Smith and Blaser (cited in Tauxe, 1992) have reported 2 deaths among 600 cases detected by laboratory surveillance in Colorado, USA, leading to an estimated 200 deaths per year for the USA and 23 deaths per year in the Netherlands. The CAST report on Foodborne pathogens (Anonymous, 1994) estimates the annual number of *Campylobacter* associated deaths in the USA as based on the work of Bennet *et al.* (1987) and Todd (1989) as 2,100 and 1, resp. The reported number of diarrhoeal deaths from all causes in the USA is approximately 3200 per year (Lew *et al.*, 1991). Hence, if the high estimates of Tauxe (1992) and Bennet *et al.* (1987) were realistic, it would be concluded that *Campylobacter* accounts for a major part of diarrhoeal deaths, or that there is considerable underreporting. Alternatively, these data overestimate the actual situation. Thus, there is major uncertainty in the estimated number of deaths related to *Campylobacter* enteritis. We will use a conservative estimate of 30 cases per year, with a range between a minimum of 3 and a maximum of 90. Hence, the most likely value of the case-fatality ratio is estimated at 1/10,000 with a range between minimum 1/100,000 and maximum 2/10,000. Having no distributional information, the uncertainty will be formalised in a Beta-Pert distribution (Vose, 1996).

The public health burden of *Campylobacter* associated deaths is also determined by the age at death and the life expectancy at that age. Lew *et al.* (1991) report that 51% of all diarrhoeal deaths in the USA occur among the elderly (75+) followed by adults between 55 and 74 years of age (27%) and children up to 5 years of age (11%). More detailed data can be found in national mortality statistics, as for example reported by the Statistics Netherlands and the Office for National Statistics (formerly Office of Population Censuses and Surveys) in the

UK. These statistics are subdivided by ICD code, and do not report *Campylobacter* related deaths separately. Therefore, in the following it will be assumed that the age-distribution of mortality from all infectious intestinal diseases (ICD codes 1-9) is representative of *Campylobacter* associated mortality. Figure 3.4 gives the frequency distribution of the number of deaths by age for England and Wales and the Netherlands. The patterns in these two countries are very similar, but the incidence of death between the ages of 5 and 45 appears to be somewhat higher in England and Wales. This is probably related to the larger number of cases, which increases the chance of finding a case in this age-range. Also, mortality risks in the very young (0 years) are higher in England and Wales. These differences result in a shift to higher ages in the data in the Netherlands, as can for example be seen from the median age at death: 75 years in England and Wales and 77 years in the Netherlands.

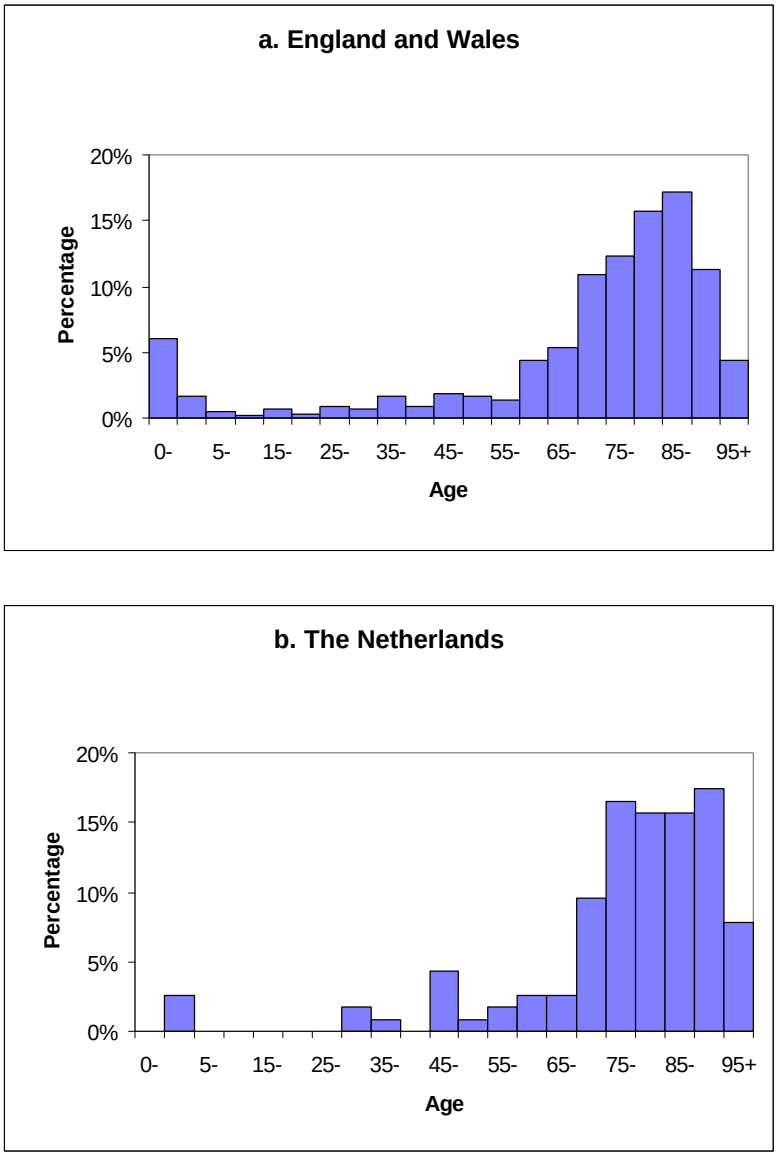


Figure 3.4. Age-distribution of deaths from infectious intestinal disease in (upper panel) England and Wales (1990-1992, 593 cases, Office of Population Censuses and Surveys) and (lower panel) the Netherlands (1993-1995, 115 cases, Statistics Netherlands).

3.3 Guillain-Barré syndrome

The Guillain-Barré syndrome is an acute immune-mediated disease of the peripheral nervous system. Since the eradication of poliomyelitis in most parts of the world, it has become the most common cause of acute flaccid paralysis. Because the pathogenesis is still largely unknown, it is defined by a set of clinical, laboratory and electrodiagnostic criteria (Asbury and Cornblath, 1990). The disease is characterised by areflexia, acute progressive and symmetrical motor weakness of more than one limb, ranging from minimal weakness of the legs to total paralysis of all extremities, and rapid progression (50% of patients reach their nadir in less than 2 weeks and 90% within 4 weeks). Respiratory muscles may also be affected and up to one-third of patients may need artificial ventilation.

Table 3.5. Scoring system for functional status of patients with Guillain-Barré syndrome (Hughes et al., 1978).

F-score	Functional status
0	healthy
1	having minor symptoms and signs, but fully capable of manual work
2	able to walk ≥ 10 m without assistance
3	able to walk ≥ 10 m with a walker or support
4	bedridden or chairbound (unable to walk 10 m with a walker or support)
5	requiring assisted ventilation for at least part of the day
6	dead

The functional status of patients with Guillain-Barré syndrome is scored on a seven-point disability scale, see Table 3.5. Recovery usually begins two to four weeks after progression stops and may take several months to years. Most patients recover functionally, but in more severe cases residual disability and death may occur. There is marked patient to patient variation in the clinical features of Guillain-Barré syndrome, and it is suggested that the disease is not a single entity. Recognised variants of Guillain-Barré syndrome include a pure motor and a sensory motor variant. Additionally, there are variants that primarily affect the cranial nerves, such as the Miller Fisher syndrome (oculo motor nerves) and the pharyngo-brachial variant (lower bulbar nerves). Different variants of Guillain-Barré syndrome may result from different pathogenic mechanisms.
Two-thirds of patients with Guillain-Barré syndrome suffer from a preceding gastro-intestinal, flu-like or respiratory infectious illness. The muscle weakness usually occurs one to three weeks after recovery, suggesting that not the infectious agent but the immune response is related to the onset of Guillain-Barré syndrome. Several studies have shown that particular infectious agents are strongly associated with the onset of Guillain-Barré syndrome. Jacobs *et al*. (1998) demonstrated a significant relation with antecedent infection by *Campylobacter jejuni*, cytomegalovirus and Epstein-Barr virus. Jacobs (1997) has studied the mechanism of Guillain-Barré syndrome and Miller Fisher syndrome related to antecedent *C. jejuni* infections. It is postulated that the lipopolysaccharide of *C. jejuni* harbours structures that mimic epitopes on human gangliosides (molecular mimicry). There is large variation between different strains of *C. jejuni*, both with respect to molecular structures and immunogenicity. Infection may lead to activation of T-cells, which in their turn stimulate antibody production by pre-existing B-cells against gangliosides, leading to the production of antibodies with cross-reactive anti-ganglioside activity. These antibodies may directly interfere with nerve function or may activate inflammatory reactions, leading to

heterogeneous responses. The heterogeneity may be further induced by presently poorly characterised host-factors.

3.3.1 Incidence and relation to *Campylobacter* infections

Van Koningsveld *et al*. (2000) give cite 13 studies on the incidence of Guillain-Barré syndrome, in which the criteria of the National Institute of Neurological and Communicative Disorders and Stroke (Asbury and Cornblath, 1990) were applied. The crude incidence varies between 0.8 and 2.0 per 100 000 persons per year; the variation in reported incidence can probably be attributed to differences in methodology rather than true differences in incidence. There appears to be no trend in the incidence of Guillain-Barré syndrome over the years, or in relation to factors such as race, standard of living, season or climate. Most studies report an increase of incidence with age, and sometimes also a peak incidence in young adults.

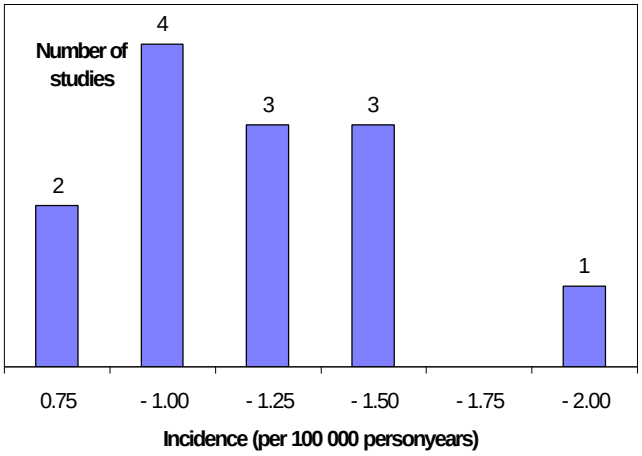


Figure 3.5. Incidence of Guillain-Barré syndrome in international studies conforming to the NINCDS criteria (references in Van Koningsveld et al., 2000).

Figure 3.5 gives a summary of these studies, the median incidence is 1.00-1.25 per 100,000 personyears. Nachamkin *et al*. (1998) quote a median incidence of 1.3 per 100,000 person years (range 0.4-4.0). It is noteworthy that recent estimates of the incidence of Guillain-Barré syndrome in the United States are considerably higher, e.g. 3.0 (Prevots and Sutter, 1997) to 3.64 (Buzby *et al*., 1997) per 100,000 person years. These estimates may indicate considerable underreporting in data based on passive surveillance systems or alternatively may overestimate the true incidence by applying less strict inclusion criteria or failing to exclude double registrations. Van Koningsveld *et al*. (2000) have reported a retrospective study on the incidence of Guillain-Barré syndrome in the southwest Netherlands in the years 1986-1997 and present an estimate of 1.18 (standard deviation 0.05) per 100,000 person years. This estimate will be used throughout this report, but the effect of higher incidence estimates will be investigated. Thus, in the Netherlands with a population of approximately 15 million, the incidence of Guillain-Barré syndrome is estimated at 177 cases per year. A prospective study covering the entire country has been initiated (Van der Meché, personal communication) and will ultimately yield a more precise estimate of the incidence. Patients with a severe course of the disease ($F > 2$ at nadir) are frequently included in clinical trials, and detailed information is available on this subgroup. On the contrary, very limited information is available on patients for which the disease takes a mild course ($F \leq 2$). In the retrospective study data were available for 436 patients of which 121 (28%) were mildly affected ($F = 2$) and 315 (72%) were severely affected ($F > 2$).

Different authors have studied the relationship between Guillain-Barré syndrome and antecedent infections with *C. jejuni*, see Appendix 4. In the first case reports the association was usually based on the isolation of the organisms from faeces, but the chance of finding a positive stool culture is usually small because several weeks pass between the acute enteritis and onset of Guillain-Barré syndrome. Later studies have relied on serology as a marker of recent infection with *C. jejuni*, and have used a case-control design to establish the strength of the relationship. A summary of the data is given in Table *3.6*. The Table shows that in all studies except the study by Vriesendorp *et al*. (1993), there was a significant association between positive serology for *C. jejuni* and Guillain-Barré syndrome[8]. The attributable proportion varied between 11 and 38% with a mean of 24%.
In the retrospective study, serological evidence for antecedent infection with *C. jejuni* was obtained for 38/114 (33%) of severe cases and 3/14 (21%) of mild cases. No serological data for controls are available in this study. However, the patients in the Dutch IvIg trial were recruited from the same cohort so that we can use data from the control group reported by Jacobs *et al*. (1998). Based on this information (which is also included in Table *3.6*), the attributable proportion of cases induced by *C. jejuni* is estimated to be 15% for mild cases of GBS and 28% for severe cases.

Table 3.6. Antibodies against C. jejuni in patients with Guillain-Barré syndrome and in controls.

Serological test	Cases[1]	Controls[2]	Odds ratio[3] (95% CI)	Attributable proportion[3,4]	Reference
ELISA (IgA, IgG, IgM)	21/56	NDC: 0/27 HC: 0/30	- -	0.38 0.38	Kaldor & Speed, 1984
Complement fixation test	14/99	HospC: 2/99	8.0 (1.8-36)	0.12	Winer *et al*., 1988
ELISA (IgA, IgG, IgM)	10/58	NDC: 3/42 HC: 2/29	2.7 (0.70-10) 2.8 (0.57-14)	0.11 0.11	Vriesendorp *et al*., 1993
Immunoblot (IgA)	15/38	NDC: 8/109 HC: 7/39	8.1 (3.1-21.3) 2.9 (1.05-8.5)	0.35 0.26	Enders *et al*., 1993
ELISA (IgA, IgG, IgM)	42/118	NDC: 5/56 HC: 5/47	5.6 (2.1-15) 4.6 (1.7-13)	0.29 0.28	Mishu *et al*., 1993
ELISA (IgA, IgG, IgM)	27/103	HospC: 1/81 HC: 2/85	28 (3.8-210) 15 (3.4-64)	0.25 0.24	Rees *et al*., 1995[a]
ELISA (IgA, IgG, IgM)	49/154	NDC: 18/154 HC: 4/50	3.5 (1.9-6.4) 5.8 (2.0-17)	0.23 0.26	Jacobs *et al*., 1998
ELISA mild cases	3/14	HC: 4/50[5]	3.14(0.61-16)	0.15	Van Koningsveld *et al*. (2000)
ELISA severe cases	38/114	HC: 4/50[5]	5.75 (1.93-17)	0.28	Van Koningsveld *et al*. (2000)

[1] Positive serology/total number
[2]:NDC: neurological disease control, HospC: hospital control, HC: healthy control; positive serology/total number
[3] Calculated with WinEpiscope 1.0a (de Blas *et al*., 1996)
[4] Calculated as (OR-1)/OR x prevalence of positive serology among cases
[5] Control group from Jacobs *et al*. (1998)

[8] Note that the prevalence of positive serology among healthy and hospital controls is relatively high with a mean of 6.7% and a range between 0 and 18%. Using incidence data from paragraph 3.2.1 (1.2 million infections per year in the Netherlands), assuming that all infections lead to a serological response and estimating the duration of a positive immune response of three months (Black *et al*., 1988), the estimated prevalence of a positive serological test would be 1,200,000 x (3 / 12) / 15,000,000 = 2.0%, which is considerably lower than the measured prevalence in controls

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. Several authors (Mishu *et al*., 1993; Herbrink *et al*., 1997) 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*-enteritis. These results could be explained by absence of seroconversion in a large proportion of enteritis patients, but is more commonly seen as a measure of test sensitivity. This is supported by Bremell *et al*. (1991) who observed seroconversion (to one or more immunoglobulin classes) in 29/35 (83%) of patients in a common source outbreak of *Campylobacter* enteritis. This indicates that the lower sensitivity of serological tests in the epidemiological investigations of Guillain-Barré syndrome may be related to the requirement for a positive response in two or three antibody classes. In Table 3.7, the results from the retrospective study are corrected for published performance characteristics of the serological tests applied in this study (Herbrink *et al*., 1997).

Table 3.7. Estimation of the true attributable proportion of C. jejuni associated cases of Guillain-Barré syndrome.

	Mild cases		Severe cases	
	Cases	*Controls*	*Cases*	*Controls*
ELISA (positive/total)	3/14	4/50	38/114	4/50
Apparent prevalence	0.214	0.080	0.333	0.080
Sensitivity			74%[1]	
Specificity			97%	
True prevalence[2]	0.260	0.070	0.427	0.070
C. jejuni infection (+ve/total)	4/14	4/50	49/114	4/50
True odds ratio (95% CI)	4.6 (1.04-22)		8.9 (2.9-26)	
True attributable proportion	0.20		0.38	

[1]34 positive results of 46 patients with culture confirmed *C. jejuni* gastro-enteritis
[2]calculated as $P_{true} = (P_{app} + SP - 1)/(SE + SP - 1)$,
with P_{app} = apparent prevalence, SP = specificity, SE = sensitivity (Henken *et al*., 1997)

Combining these estimates, it follows that the incidence of *C. jejuni* associated Guillain-Barré syndrome in the Netherlands can be estimated at 59 cases per year (10 mild cases and 49 severe cases). Combining with estimates of the incidence of *C. jejuni* infections[9] (1,200,000 cases per year) and associated enteritis (300,000 cases per year) this leads to the following conditional probabilities:
Risk of Guillain-Barré syndrome given infection with *C. jejuni*: 4.9×10^{-5} (1 per 20,000)
Risk of Guillain-Barré syndrome given *C. jejuni* enteritis: 2.0×10^{-4} (1 per 5,000).
Allos (1997) estimates that in the United States of America, one of every 1058 *Campylobacter* infections results in a case of Guillain-Barré syndrome. There is about a fivefold difference between this estimate and the estimate for the Netherlands. This is explained partly by a higher estimate of the incidence of Guillain-Barré syndrome in the USA (3 per 100,000 vs. 1 per 100,000 personyears) and partly by a lower estimate of the incidence of campylobacteriosis (1,000 per 100,000 vs 2,000 per 100,000 personyears). The surveillance data from the USA as well as from the Netherlands are subject to different sources of bias, making it difficult to further evaluate this difference. We will use the US

[9] Note that a small proportion of infections with thermophilic *Campylobacter* spp. are associated with other species, mainly *C. coli*. Because GBS is associated exclusively with *C. jejuni* the risks are slightly underestimated

estimate as an upper limit of the probability of developing Guillain-Barré syndrome after campylobacteriosis. McCarthy *et al*. (1999) have estimated the probability of Guillain-Barré syndrome following infection with *C. jejuni* in a follow-up study of three outbreaks of campylobacteriosis in Sweden, involving 8000 patients. No cases of Guillain-Barré syndrome were detected; so that the probability was 0 in 8000 (95% confidence interval 0-3). Hence, the Dutch estimate would fall in this range, whereas the US estimate would fall outside. It must be noted however that it is possible that the *Campylobacter* strains involved in the Swedish outbreaks were not causal agents of Guillain-Barré syndrome, which might result in underestimation of the probability in the general population.

3.3.2 Symptoms, severity, duration, recovery and mortality

The clinical course of Guillain-Barré syndrome is highly variable. In several studies, it has been shown that about 20-25% of clinical patients will have a mild course, remaining able to walk independently (F=2), whereas 20-35% will be severely affected and need artificial respiration (F= 5) (Van der Meché, 1994; Van der Meché *et al*., 1992). Treatment of patients consists of monitoring and supportive care, augmented with specific treatment. Plasmapheresis (PE) and intravenous immunoglobulin (IVIg) are established treatments, corticosteroids and combination therapies are still under study. Prognostic factors of a poor outcome of the disease are older age, need for ventilatory support, a rapidly progressive course and low compound muscle action potential after distal nerve stimulation. Several studies have demonstrated that an association with *C. jejuni* also adversely affects the clinical course of the disease (see Rees *et al*., 1995[b] and Appendix 5).
The IVIg clinical trial in the Netherlands compared treatment with PE with IVIg (Van der Meché *et al*, 1992). The age at hospitalisation had a mean of 47 years and a standard deviation of 19 years. The age-distribution (see Figure 3.6) appears to be somewhat bimodal and is skewed to the left. In the retrospective study, the mean age of patients was also 47 years (standard deviation 21 years); the incidence was more constant in the age range between 30 and 80 years.

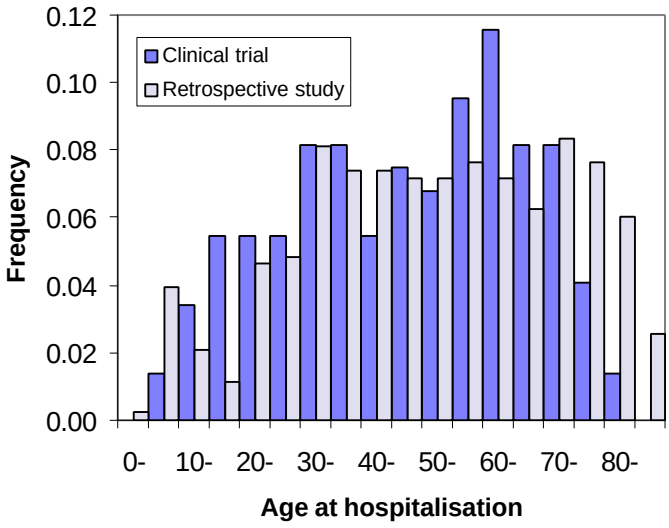


Figure 3.6. Age at hospitalisation of patients with Guillain-Barré syndrome in the Dutch IVIg trial (Van der Meché et al., 1992) and in the retrospective study in the southwest Netherlands (Van Koningsveld et al., 2000).

The age distribution of mild and severe cases is shown in Table 3.8, based on data from the retrospective study (note that here the total number of patients is 432 by lack of complete data for 4 patients). It follows that among the mild cases 69% is < 50 years, whereas among the severe cases 48% is < 50 years.

Table 3.8. Age distribution of mild and severe cases of Guillain-Barré syndrome in the retrospective study in the southwest Netherlands (Van Koningsveld et al., 2000).

Age	Mild	Severe	Total
<50 years	84	150	234
≥ 50 years	37	161	198
Total	121	311	432

Combining all previous information leads to the age- and severity distribution for *C. jejuni* associated cases of Guillain-Barré syndrome as shown in Table 3.9.

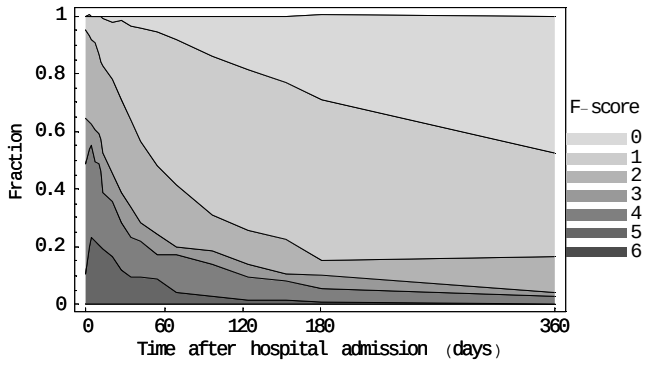
Table 3.9. Distribution of C. jejuni associated cases of Guillain-Barré syndrome.

Age	Mild	Severe	Total
<50 years	7	24	31
≥ 50 years	3	25	27
Total	10	49	59

Visser (1997) has shown that the probability of reaching the stage of independent locomotion after 6 months (F ≤ 2) is smaller for patients over 50 years of age. Other clinical studies also commonly report age as an important determinant of recovery, hence in the following the clinical course is separately described for patients younger or older than 50 years. Obviously, it is also necessary to distinguish the prognosis of mild and severe cases.
Very limited information is available for mildly affected atients. Clinical experience at the outpatient department of University Hospital Rotterdam suggests that after 6 months, 50% of the patients are fully recovered (F=0), whereas virtually all patients have reached F=1. From this information, a model for the clinical course of mildly affected patients was constructed, assuming simple exponential decrease of the number of patients in states F2 and F1, see Appendix 6. According to the model, 79% of patients have fully recovered after 1 year whereas 21% still suffer from minor symptoms (F = 1). The initial ratio of patients in F-scores 1 and 2 was independent of age. In the absence of further information, we assume that the time course of recovery is also similar for patients younger or older than 50 years.
The clinical heterogeneity of severely affected patients in relation to antecedent infections and treatment choice is described by Visser (1997), who analysed data of patients in the Dutch IVIg trial (Van der Meché *et al*., 1992). A summary of the data is given in Appendix 7. *C. jejuni* associated Guillain-Barré syndrome is clearly more severe in nature than other Guillain-Barré syndrome, as can be seen from the difference in functional score at nadir: a very high proportion of *C. jejuni* positive patients required assisted ventilation (F=5: 54% vs 20% for all patients). *C. jejuni* positive patients recovered significantly better when subjected to IVIg as compared to PE. For other patients, including those infected with cytomegalovirus, this difference was only apparent after 8 weeks of treatment, but not after 6 months. Using IVIg treatment, 75% of *C. jejuni* positive patients are able to walk independently after 6 months. This figure is in-between the values of 73 and 82%, which were found for all patients, treated with PE and IVIg, respectively. Hence it is assumed that the data on all

patients in the Dutch trial are representative for *C. jejuni* positive patients, provided they receive optimal treatment.
Information on the clinical course of severe cases was obtained from original data of the Dutch IVIg trial (Van der Meché *et al*., 1992). Directly after hospitalisation, 60% of the randomized patients have an F-score of 4. At nadir, approximately 20% of the patients are have an F-score of 5. Throughout the hospitalisation period, patients recover which is reflected by a gradual increase of the percentage of patients in F-scores 0-2. Virtually all patients recover from the need of intensive care treatment, but after ½ year (the end of follow-up in the clinical trial); a sizeable proportion still is severely affected (17% in F-scores 3 and 4). Bernsen *et al*. (1997) evaluated the residual health status of patients after a period of 31 months to 6 years after onset. Within this time period, there were no significant differences in residual functional health status related to the time since the acute phase. It is therefore assumed that the health status at follow-up in this study will persist life-long. This study showed that only 25% of all patients recovered functionally (F=0) but continued to report psychosocial impairment, whereas 44% of patients continued to suffer from minor symptoms (F-score = 1). As much as 31% of the severely affected patients did not fully recover but continued to suffer from functional limitations (F-scores 2-4).
Figure 3.7 shows the time-course of the functional status of Guillain-Barré syndrome patients, combining the information on mild and severe cases.

a. Age < 50 years



b. Age ≥ 50 years

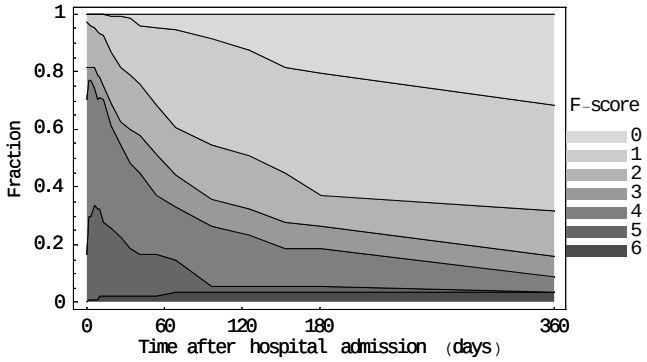


Figure 3.7. Functional status of patients with Guillain-Barré syndrome.

Mortality related to Guillain-Barré syndrome is usually low. In the Dutch clinical trial, a case-fatality ratio of only 2% was observed (Van der Meché *et al*., 1992), other studies report ratio's up to 5%. Van Koningsveld *et al*. (2000) report 16 fatal cases among 476 cases of Guillain-Barré syndrome in the southwest Netherlands (mortality ratio 3.4%). The mean age of the fatal cases was 71 years (range 30-86). The age distribution is shown in Fig. 3.8.

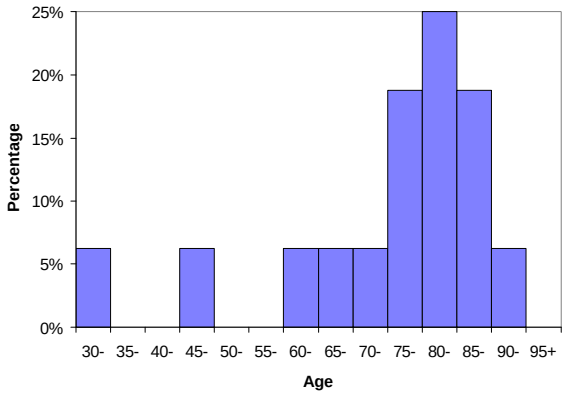


Figure 3.8. Age at death of 16 fatal cases of Guillain-Barré syndrome, southwest Netherlands, 1987-1996.

3.4 Reactive arthritis

Reactive arthritis is an immune-mediated inflammation of the joints, that is associated with recent infection at a distant site, usually the urogenital or gastro-intestinal tract. There may or may not be extra-articular features. Rheumatic symptoms develop between 3 and 30 days after infection, and are accompanied by an increase in specific antibodies. Although reactive arthritis is generally considered a sterile arthritis, bacterial cell wall fractions (possibly as immune complexes) as well as viable bacteria have been isolated from the affected joints (Beutler and Schumacher, 1997). The pathogenic mechanism is not completely clear, there is evidence of genetic predisposition because approximately 70% of patients with reactive arthritis are HLA-B27 positive whereas this is only 7% in the general population (Tak, 1995).

3.4.1 Incidence, duration and relation to *Campylobacter* infections

Berden *et al*. (1979) and Van de Putte *et al.* (1980) in the Netherlands first reported infection with *C. jejuni* as the triggering agent of reactive arthritis. The duration of symptoms in these six patients was 2, 2, 2, 3, 3 and 23 weeks, respectively and most were treated with NSAIDs. The incidence of reactive arthritis is difficult to estimate. The diagnosis depends on clinical or laboratory evidence of recent infection but subclinical precipitating infections are well known. Also, different studies have used different case-definitions, resulting in inclusion of cases with different degrees of severity and duration. Kvien *et al*. (1994) report a general practitioner based survey of the incidence of reactive arthritis in Oslo, Norway in the period March 1988 to March 1990. The incidence of reactive arthritis associated with gastro-enteritis was 2.9 per 100 000 person years for the total population and 5.0 per 100 000 person years for the population between 18 and 60 years of age. Of these, 11% (3/27 patients) were associated with *C. jejuni*, or 3.2 per 1 000 000 person years for the total population. Similar data are not available for the Netherlands. Extrapolation of the Oslo data may give a rough indication of the expected number of patients, but ignores differences in incidence of infection with *C. jejuni* and prevalence of the HLA-B27 gene (83% of all patients in Oslo carried this gene). These data would lead to an estimate of 50 GP consultations because of *C. jejuni* associated reactive arthritis per year. This relatively low estimate of the incidence of severe cases of reactive arthritis would be supported by the fact that a rheumatologist in the Netherlands sees only 7-10 patients per year.[10]

In a follow-up study, Glennås *et al*. (1994) reported the outcome of disease in the Oslo patient cohort to be independent of the triggering agent or the presence of the HLA-B27 gene. The medium duration of reactive arthritis, estimated by Kaplan-Meier analysis, was 25 weeks (25 and 75 percentiles were 14 and 53 weeks, respectively). After two years, none of the patients had persistent arthritic symptoms with the exception of one patient who had a history of back-pain and stiffness.

Eastmond *et al*. (1983) reported a follow-up study of 136 culture-positive individuals, who were infected with *C. jejuni* as a consequence of a power failure of a milk pasteurisation plant. Of this cohort, 88 had developed symptoms of gastro-enteritis and one patient developed reactive arthritis (1.1% of clinical, culture-positive cases or 0.74% of all culture-positive individuals). The duration of the symptoms was 2 weeks.

Bremell *et al*. (1991) conducted a follow-up study of 86 attendants at a banquet, 35 of whom developed gastro-enteritis and 31 of whom were asymptomatically infected. These authors found symptoms in joints, muscles or spine in seven subjects with enteritis (20%), vs. none of the asymptomatically infected persons. In six patients, the symptoms were restricted to pain in the muscles, joints or lower back that lasted less than a month. One patient was diagnosed

[10] B.A.C. Dijkmans, Free University Hospital, Amsterdam; personal communication.

as having incomplete reactive arthritis, this patient was HLA-B27 positive, had a familial history of arthritis and again developed classical reactive arthritis in association with a new episode of gastro-enteritis after seven years. None of the 31 patients without enteritis, but with serological evidence of infection with *C. jejuni* showed acute rheumatic symptoms, but four (13%) reported symptoms starting three to eight months after the party. Of these, three were possibly triggered by the infection whereas one patient, who developed systemic lupus erythematosus was considered unrelated. Thus, the probability of developing rheumatic symptoms was estimated as 2.9% after *C. jejuni* enteritis and symptoms may also occur after asymptomatic infection[11]. However, the time interval between the asymptomatic infection and development of rheumatic symptoms was relatively long, and no control group was included in this study. Hence, other causal mechanisms can not be ruled out.
Based on these outbreak studies, the risk of developing reactive arthritis after *C. jejuni* associated enteritis is estimated at 1-3% (mean 2%). On this basis, the estimated number of cases of *C. jejuni* related reactive arthritis in the Netherlands would be 3000-9000 per year. This is considerably higher than the number of 50 estimated above, which may possibly be explained by the fact that GP's or hospitals see only the more severe cases and/or of longer duration. To estimate the health burden of *C. jejuni* associated reactive arthritis on a population basis, the risk as derived from outbreak studies will be used. There is little information on the duration of unselected cases of *C. jejuni* associated reactive arthritis, because most published information refers to cases seen by GP's or in hospitals. A wide range of 2-10 weeks (mean 6 weeks) will be used.

[11] Outbreak studies with other enteropathogenic bacteria (in particular *Salmonella* spp.) have estimated the risk of developing reactive arthritis as 1-7% (Mäki-Ikola and Granfors, 1992), but risks as high as 15% have also been reported (e.g. Locht *et al*., 1993). In the study of Kvien *et al*. (1994), 63% (17/27) of patients with gastro-enteritis associated reactive arthritis were culture-positive for *Salmonella*. Bearing in mind that in most countries the incidence of salmonellosis is lower than that of campylobacteriosis, these results also indicate that the risk of developing reactive arthritis after infection with *Salmonella* is higher than after infection with thermophilic *Campylobacter* spp..

3.5 Bacteraemia

Two reports on the incidence of C*ampylobacter* bacteraemia were identified in the recent literature, see Table 3.10.

Table 3.10. Epidemiological features of bacteremia by C. jejuni and C. coli.

Country and reference	England and Wales (Skirrow *et al.*, 1993)	Denmark (Schønheyder *et al.*, 1995)
Population (x 10^6)	45	1.3
Study period (years)	1981-91 (11)	1989-94 (5)
Cases	350	12
Incidence (per 100000 pyr)	0.07	0.2
Number with underlying disease/total (%)	65/228 (29)	8/12 (67)
Number of deaths	7	0
Case-fatality ratio	0.02	-
Number of faecal cultures	267565	990 in 3 years
Ratio blood/faecal cultures	0.0013	0.008

These data show that *Campylobacter* bacteremia is a relatively rare event that occurs only in 1 out of every 77-125 laboratory confirmed cases. Applying this figure to data from the Netherlands gives an estimate of 9-54 cases per year. Extrapolating the incidence estimate gives an estimate of 10-30 cases per year in the Netherlands. Of these cases, ⅓ to ⅔ would occur in patients with underlying disease, and the mortality would be less than 1 case per year. Most cases of bacteremia are completely cured within a month by administration of antibiotic therapy and residual symptoms are rare. Hence, the public health burden of *Campylobacter* bacteremia is small compared to other health effects and will not be considered further.

4. Health burden of *Campylobacter* infections

4.1 Disability adjusted life years as an aggregate measure of public health

For the purpose of integrating the health burden of different outcomes of *Campylobacter* infection or to compare the effects of campylobacteriosis with other diseases, a common measure is necessary. Traditionally, public health policy has concentrated on mortality and the severity of disease was expressed in death rates or the number of life years lost by a certain cause. However, many diseases do not lead to premature mortality, but may be a significant cause of morbidity. Healthy life expectancy is increasingly becoming the focus of public health policy (Van der Maas and Kramers, 1997). Two important projects have developed a methodology to quantify healthy life expectancy or its opposite, loss of healthy life years, on a population level. Murray and Lopez (1996) have proposed the use of Disability Adjusted Life Years (DALYs) to assess the global burden of disease. This integrated measure combines years of life lost by premature mortality (YLL) with years lived with a disability, that are standardised by means of severity weights (YLD). Thus:

$$DALY = YLL + YLD$$

In the Dutch Public Health Forecasts study (VTV, Van der Maas and Kramers, 1997), the DALY methodology has been used to estimate the disease burden in the Netherlands. For this purpose, mortality and disability related to 52 diseases, subdivided into 175 disease stages, was estimated.

4.1.1 Years of life lost

To estimate YLL on a population basis, the average number of life years lost by death from gastro-intestinal disease, the age-specific mortality rates (Chapter 3.2.3) must be combined with the life expectancy of the fatal cases, had they not developed the disease. If mortality affects the population in a random fashion, the life expectancy can be derived from standard life tables. In this report, the table as proposed by Murray (1996) is used. This table is based on the highest observed national life expectancy (for Japanese women), but takes into account differences in life expectancy between men and women. The table is reproduced in Appendix 8. The standard life expectancy at birth is 82.5 years for women and 80.0 years for men. For comparison, the life expectancy in the Netherlands in 1994 was 74.6 years for men and 80.3 years for women (Van der Maas and Kramers, 1997). If mortality affects a susceptible subpopulation, the use of standard life expectancy would lead to a gross overestimation of YLL. In this case, disease-specific information is necessary to estimate the additional loss of life years by the disease under consideration.
The table in Murray (1996) gives the life expectancy at the beginning of each age-interval. The average life expectancy in 5-year age classes, assuming identical numbers of men and women, is then calculated as:

$$e^*(a') = \frac{SLE(a_i, f) + SLE(a_i, m) + SLE(a_{i+1}, f) + SLE(a_{i+1}, m)}{4}$$

where $e^*(a')$ is the mean life expectancy in the 5-year age interval a_i, a_{i+1}, a is age, f is female, m is male, $SLE(a_i, f)$ is the standard life expectancy for women at age a_i, etcetera.
Then, the total loss of life years is calculated as:

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

where *i* is an index for different age-classes, *j* is an index for different disease categories, and d_{ij} is the number of fatal cases per age-class and disease categorie.

4.1.2 Years lived with disability

To estimate YLD on a population basis, the number of cases must be multiplied by the average duration of the disease and a weight factor that reflects the severity of the disease on a scale from 0 (perfect health) to 1 (dead). If necessary, the disease process can be subdivided into several stages with different duration and/or severity. This is possible by dividing the patient cohort in subgroups, who develop different disease patterns, by dividing the time course of the disease in different stages, or a combination of both. Thus,

$$YLD = \sum_j N_j L_j W_j$$

where *j* is again an index for different disease categories, and N_j is the number of patients, L_j is the duration of disease and W_j is the severity weight per disease category.

4.2 Measuring health

Health is defined as a state of complete physical, mental and social well being, and not merely the absence of disease and infirmity (WHO, 1992). This classical definition implies that health needs to be assessed in three different domains: the physical, psychological and social domains. Each of these domains is an aggregate of a number of dimensions, which are usually measured by means of questionnaires. There are three main types of questionnaires for health status measurement: generic, disease-specific and domain-specific (Essink-Bot, 1995). Generic instruments cover the three domains of health in a non-disease specific way, assuming that different diseases can be characterised as patterns of physical, psychological and social disfunctioning. Several generic instruments have been developed, that differ in the emphasis that is placed on each domain. Disease-specific instruments are developed to study changes in health as a consequence of (treatment for) a specific disease. Domain-specific instruments concentrate on the consequences of disease in a specific domain of health or, more specifically, on a specific symptom.

The choice between these three types of instruments depends on the purpose and the perspective of the study. In our case, the objective of the study is to integrate and compare the health effects of very different diseases, which leads naturally to the choice for generic instruments. This choice is further supported by the societal perspective of the study: the objective is to evaluate the impact of disease on a public health level, which leads to the need of non-disease specific and comprehensive, i.e. generic measurements.

Information from questionniares gives a descriptive evaluation of health status, which must be valuated for further analysis. Different valuation methods are available, such as Standard Gamble (SG), Time Trade Off (TTO), Person Trade Off (PTO) and Visual Analog Scale (VAS) (Torrance, 1986; Murray, 1996; Brooks, 1996). For public health analyses the PTO and the TTO methods are the most natural approaches. The PTO protocol has two variants. In the PTO1-variant, respondents are asked to choose between an intervention that prolongs the life of 1000 individuals in perfect health and an intervention that prolongs the life of N individuals with less then perfect health. In the PTO2-variant, the alternative is to cure N individuals in less than perfect health. The value of N at which the respondent cannot make a choice (the indifference point) is used to calculate the disability weight of the health state under consideration. In the TTO protocol, respondents are asked to weigh the benefits of an immediate “cure” against possible later loss of health. Nord (1995) has outlined that the PTO protocol is by its nature most suitable for evaluation of health care programmes from a

societal perspective. Societal perspective also requires that the values used be based on public perception rather than on the opinion of patients or health professionals. However, in the GBD study and in the VTV study, the panels were composed of medical experts, because they were expected to be most able to compare a large number of diseases in an objective manner.
In the first version of the Global Burden of Disease study (GBD1, Murray, 1994), all possible health states were assigned to one of six classes, defined by the ability to perform activities in the fields of recreation, education, procreation and occupation. To assist the assignment of severity weights, a set of disabling sequelae was described for each class. This approach has been criticised and was subsequently replaced by a protocol that aimed at a more deliberate weighing process. In the next version of the GBD study (GBD2, Murray and Lopez, 1996), a set of 22 indicator conditions was described, representing different grades of disability in the dimensions physical functioning, neuro-psychological conditions, social functioning, pain and sexual/reproductive functions. In a formal procedure, using the Person Trade Off protocol (see above), these indicator conditions were assigned disability weights and classified into 7 disability classes which are reproduced in Appendix 9. In a next step, several hundred outcomes were evaluated with respect to the distribution of each condition across the seven disability classes. From these data, a composite disability weight for each condition was calculated.
In the framework of the Dutch VTV project (Ruwaard and Kramers, 1997), the burden of disease in the Dutch population was estimated. In this study Stouthard *et al*. (1997) selected 52 diagnostic groups of greatest public health importance. These were divided in 176 health states of different disease severity or stage. The weighing procedure consisted of two steps. First, in order to develop a calibrated scale, a panel of physicians evaluated 16 indicator conditions with different severity using the PTO1 and PTO2 protocols. The diseases were characterised by a short clinical description; a standardised classification using the dimensions from the EuroQol-5D+C questionnaire (see Appendix 9) was used to harmonise the mental image. Subsequently, the remaining health states were valued by means of interpolation, i.e ranking health states as similar to or in-between indicator conditions.

4.3 Severity weights for diseases induced by thermophilic *Campylobacter* spp.

4.3.1 Severity weight for *Campylobacter* enteritis

In the GBD (Murray and Lopez, 1996[b]), watery diarrhoea (further specified as five episodes a day without major pain or cramps) is one of the indicator conditions, and a mean disability weight of 0.066 is assigned (median 0.054). A Beta-distribution with parameter values (1.5, 21) has these characteristics and will be used to describe the variability in individual weights.
In the VTV project, infectious diseases of the gastro-intestinal tract are differentiated into two stages. Uncomplicated gastro-enteritis (duration 2 weeks, EuroQol-5D+C score 112211) is assigned a disability weight of 0.00 and complicated gastro-enteritis (duration 2-4 weeks, EuroQol-5D+C score 323311) is assigned a disability weight of 0.03. It must be noted that in order to fit into the PTO-protocol, all descriptions of health states were offered as an annual profile. Hence, gastro-intestinal disease was weighed as “one year with one episode of mean duration 2 weeks”. Because of the limited duration, this procedure leads to low disability weights in the annual profile, which may even disappear if the data are rounded to two significant digits. For example, if an episode with duration of 2 weeks and a severity weight of 0.09 as in the GBD is weighed on an annual basis, the result would be 0.003, which would be rounded to 0.00 (in fact, the score in the VTV exercise was 0.005, J. Melse, personal

communication). Hence, the weights from the GBD and VTV studies are not too dissimilar, even though they were derived on a different basis. To estimate the health burden of *Campylobacte*r-associated gastro-enteritis in the general population, the severity weight for watery diarrhoea from the GBD study will be used, see Figure 4.1.
De Hollander *et al*. (unpublished) have elicited severity weights for several health states related to environmental pollution from a panel of 24 physicians and 11 environmental epidemiologists, basically following the protocol described by Stouthard *et al*. (1997). In this study, a definition[12] of the more severe cases of bacterial gastro-enteritis was included as follows:

> Patients suffer from watery diarrhoea, with a defecation frequency of a few to more than ten times per day, sometimes preceded by a period of anorexia, nausea, vomiting and abdominal pain. A part of the patients suffer from severe abdominal cramps, fever, chills, headache and myalgia, nausea and malaise. Blood or mucus is often present in the faeces. In some cases, diarrhoea leads to dehydration. EuroQol 5D+C scores 113211, 213211, 113111 and 213311 (25% each).

In contrast to Stouthart *et al.* (1997), who valuated a year of life with one or more episodes of acute illness, De Hollander *et al*. valuated the acute condition as such, without reference to its duration. Duration is entered as one of the independent factors in the final calculations of health burden.The median severity weight for this health state was 0.37 (range 0.05-0.97). The individual scores could be fitted with a Beta (1.23, 1.90) distribution, see Figure 4.1. This weight is much higher than previously mentioned weights for uncomplicated diarrhoea, reflecting the importance of an accurate case-definition and instructions given to the panel. We will use this weight for patients who visit their general practitioner, because it is the more serious cases who seek medical attention.

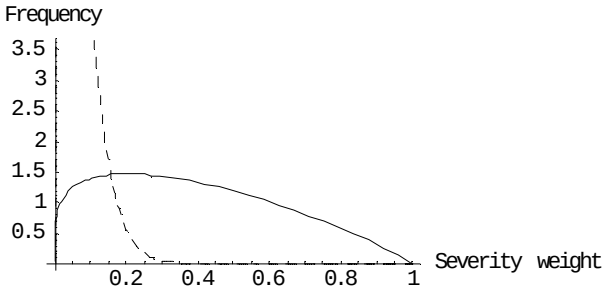


Figure 4.1. Probability density functions of the severity weight of campylobacteriosis in the general population (Beta(1.5,21), dashed) and in patients who visit their general practitioner (Beta(1.23,1.90), solid).

4.3.2 Severity weights for Guillain-Barré syndrome

The clinical heterogeneity of Guillain-Barré syndrome requires a differentiation in disability classes. De Hollander *et al*. (unpublished) have also valuated these different functional classes, see Table 4.1. The Table also shows fitted Beta distributions, which are graphed in Figure 4.2.

[12] This case-definition was developed by AH Havelaar in collaboration with (medical) microbiologists and epidemiologists at RIVM

Table 4.1. Severity weights of Guillain-Barré syndrome in different functional grades.

F-score	Case-definition[13]	EuroQol 5D score	Severity weight		
			Median	*Range*	*Beta-distr.*
1	Completely recovered from an episode of Guillain-Barré syndrome, but having problems of insomnia, fatigue and related emotional and social restraints	11211	0.10	0.00-0.61	0.66, 4.13
2	Muscle weakness in legs and arms, able to walk at least 10 m without a walking aid, but unable to run	21211	0.30	0.04-0.65	2.16, 5.62
3	Muscle weakness in legs and arms, and only able to walk at least 10 m with a walking aid	22321	0.44	0.20-0.80	5.50, 6.70
4	Severe muscle weakness in legs and arms, not able to walk, bedridden of in a wheelchair	33322	0.80	0.25-0.95	5.55, 1.53
5	Severe muscle weakness in legs and arms, not able to walk, bedridden and need artificial ventilation for at least part of the day	33332	0.94	0.75-0.99	18.35, 1.63

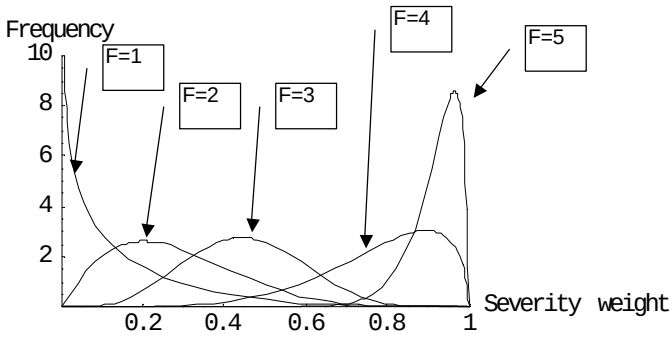


Figure 4.2. Probability density functions of severity weights of different functional classes of Guillain-Barré syndrome, see Table 4.1.

4.3.3 Severity weight of reactive arthritis

A severity weight for reactive arthritis is not available in the literature. The VTV study lists weights for three different grades of rheumatoid arthritis – mild: 0.21; moderate: 0.37 and severe: 0.94. Given the fact that most cases of reactive arthritis are relatively mild, a severity weight of 0.21 would be most appropriate. There is no information on the variability of this weight. A BetaPert distribution with most likely value 0.21, minimum 0.00 and maximum 0.42 (i.e. 2x most likely) will arbitrarily be used.

[13] Developed by AH Havelaar and R van Koningsveld in collaboration with clinical neurologists at Erasmus Medical Center

4.3.4 Modelling severity weights

An alternative for obtaining severity weights by direct panel elicitation is a model-based approach. For this purpose, health states are described by a generic, multiattribute classification system such as the EuroQol-5D system. The EuroQol-5D describes health in five dimensions with 3 levels each (see Appendix 9), resulting in $3^5 = 243$ possible health states. Different studies have evaluated a subset of these health states, using different valuation methods and different groups of respondents. A randomly selected sample of the general population in the UK was invited to evaluate 15 health states using Visual Analog Scale (VAS) and Time Trade Off (TTO) techniques. By varying the health states submitted to respondents, it was possible to obtain valuations for 42 EuroQol health states. Dolan (1997) constructed a regression model to interpolate the other 201 health states on this scale. Different models were tested and on the basis of goodness-of-fit to the (TTO) data, and interpretability. The following main effects model was selected.

$$V(\vec{x}) = a + b_1 MO + b_2 SC + b_3 UA + b_4 PD + b_5 AD + b_6 M2 + b_7 S2 + b_8 U2 + b_9 P2 + b_{10} A2 + b_{11} N3$$

Here, $V(\vec{x})$ is the value function of the health state with $\vec{x}$ the vector of the health state description, a is an intercept that represents the effects of any move away from full health, and the ß-values are regression coefficients. MO, SC, UA, PD and AD are dummy variables representing the score at the dimensions mobility, self-care, usual activities, pain/discomfort and anxiety/depression, respectively. These dummies take the value 0 if the level is 1, 1 if the level is 2 and 2 if level is 3. M2, S2, U2, P2 and A2 are additional dummy variables for the above dimensions, which take the value 1 if the level is 3 and 0 otherwise. N3 is a dummy variable that takes the value 1 if any dimension is at level 3 and 0 otherwise.

Table 4.2. Comparison of severity weights from the panel elicitation and from a regression model.

Health state	EuroQol score	Severity weight	
		Panel[1]	Model[2]
Gastro-enteritis			
General population	112211	0.07[3]	0.15
General practitioner	11321, 21321, 11311, 21331	0.39	0.40
Guillain-Barré syndrome			
F=1	11211	0.14	0.07
F=2	21211	0.28	0.12
F=3	22321	0.45	0.47
F=4	33322	0.78	0.73
F=5	33332	0.92	0.90

[1] De Hollander *et al.*, unpublished; mean from fitted Beta distributions
[2] Dolan (1997), rescaled[14] results from regression model
[3] Mean score from Global Burden of Disease Study

In general, there is good agreement between weights for relatively severe health states (see Table 4.2), but the panel weighs less severe states of Guillain-Barré syndrome considerably higher than the general public. When comparing the valuations obtained by applying this model with the direct panel elicitation, several factors must be taken into account.

[14] The model allows negative scores for health states that are considered worse than death. Actually, the predicted score for state 33333 is –0.59. In the panel elicitation, all health states were valuated on a scale between 0 (best imaginable health) to 1 (worst imaginable health). Therefore, the model predictions were divided by a factor of 1.59.

- The panel elicitation was based on the PTO protocol and the model on values obtained with the TTO protocol. In general, the TTO protocol assigns slightly higher severity weights than the PTO protocol.
- The general public (whose values were used to develop the model) assigns a higher severity weight to any health state than (medical) professionals (in the panel).
- Furthermore, the general public attaches more weight to severe health states as is explicitly demonstrated in the model structure.
- EuroQol-5D+C scores informed the panel elicitation. The model values were based on EuroQol-5D scores. Krabbe *et al*. (1999) have demonstrated that adding a score of 1 on the cognitive dimension (as was the case for all diseases considered here) does not result in significant differences of the valuation of several health states.

Therefore, it is not to be expected that the two sets of severity weights correspond exactly. The model values are another possible set of values, and the effect of using these values instead of the values from the panel will be evaluated in a sensitivity analysis (see 4.4.3).

4.4 Estimation of the health burden of *Campylobacter* infections in the Netherlands

4.4.1 Point estimates

The information in the preceding paragraphs can now be integrated into an estimate of the health burden of infection with thermophilic *Campylobacter* spp. in the Netherlands. Table 4.3[a] shows the total burden of morbidity. The annual morbidity burden of disease related to thermophilic *Campylobacter* spp. is estimated at approximately 960 YLD, of which 30% is attributed to the effects of acute gastro-enteritis and 35% to residual disability from Guillain-Barré syndrome.

Table 4.3 Health burden due to infection with thermophilic Campylobacter spp. in the Netherlands[1]

a. Morbidity

	Number of cases	Duration (years)	Severity weight	YLD
Gastro-enteritis				
General population	311,000	0.014	0.067	291
General practitioner	17,500	0.023	0.393	159
Guillain-Barré syndrome				
Clinical phase	58.3	1	0.281	16
Residual symptoms	57.0	37.1	0.158	334
Reactive arthritis	6570	0.115	0.210	159
Total				959

b. Mortality

Population	Number of cases	Life expectancy (years)	Severity weight	YLL
Gastro-enteritis	31.7	13.2	1.00	419
Guillain-Barré syndrome	1.3	18.7	1.00	25
Total				444

c. Health burden

Population	YLD	YLL	DALY
Gastro-enteritis			
General population	291	419	710
General practitioner	159		159
Guillain-Barré syndrome			
Clinical phase	16	25	41
Residual symptoms	334		334
Reactive arthritis	159		159
Total	959	444	1403

[1] Based on mean values of the estimated annual incidence, the severity weight and the duration

Mortality associated with acute gastro-enteritis accounts for only 32 cases per year, but adds a significant health burden to the total estimate of approximately 420 YLL, the mortality related to Guillain-Barré syndrome is of minor importance (Table 4.3[b]).
Summation of morbidity and mortality burden (Table 4. 3[c]) yields an estimate of the mean value of the total health burden of infections with thermophilic *Campylobacter* spp. in the

Netherlands of approximately 1400 DALYs per year. For a population of 15 million, this implies that approximately 0.01% of all possible healthy life years is lost by this infection.

4.4.2 Uncertainty and variability

There is considerable uncertainty and variability in the parameters used to obtain the estimate of the health burden of infection with thermophilic *Campylobacter* spp. in the previous section. Here, variability is defined as the inherent randomness of a system under study. Uncertainty is defined as lack of knowledge about the system. Additional data collection can reduce uncertainty but not variability. Both uncertainty and variability can be expressed in a statistical distribution function, but require a different strategy to account for in the analysis. Table 4.4 shows the frequency distributions used for uncertainty and variability analysis, and some characteristic values. Severity and duration of disease were considered to be variable parameters, whereas all other parameters were considered to be uncertain. Second order uncertainty (i.e. uncertainty in the parameter estimates of the distribution functions of the variable quantities) was not considered. The available data are not of a sufficient quality to make inference about this, and the overall effect on the final results is assumed to be relatively small. The strategy to account for uncertainty and variability depends on the estimated incidence. For diseases with a high incidence, the strategy is explained by the morbidity burden of gastro-enteritis in the total population as an example. This value is estimated from four distribution functions, two of which are uncertain (incidence rate of gastro-enteritis, *IR* and attributable proportion for *Campylobacter*, *AP*) and two of which are variable (duration *L* and severity *W*). In a population of size N, the (annual) incidence of gastro-enteritis $I = IR \times AP \times N$ is again an uncertain distribution function, which is obtained by sampling from the underlying distributions[15]. Each iteration represents one possible value of *I* cases (per year). For each case, the individual health burden yld_i is obtained by multiplying random samples from *L* and *W*. The total health burden in the population is then obtained by addition of individual estimates: $YLD = \sum_{i=1}^{I} yld_i$. For diseases with low incidence, random variation cannot be neglected, and the individual burden for each incident case in each iteration has to be simulated. According to the Central Limit Theorem, the mean value of yld_i is known with high certainty for a large population. In that case, the total population burden in a specific iteration can easily be obtained by multiplying *I* with the mean of yld_i. See Appendix 10 for spreadsheet models illustrating the methodology, and its impact on the uncertainty of the final estimate.

[15] Uncertainty and sensitivity analysis were performed in @RISK 3.5.1 (Pallisade Corporation; Anonymous, 1997) as an add-on to Microsoft Excel 97. All simulations were run using Latin Hypercube sampling, and terminated when all output parameters converged at the 1% level.

Table 4.4. Distribution functions of parameters used to estimate the health burden of infection with thermophilic Campylobacter spp.

Model parameters	Input distribution	Mean	5-%ile	Median	95-%ile
GASTRO-ENTERITIS					
GENERAL POPULATION					
Incidence rate all gastro-enteritis (per 1000 person years)	Lognormal (6.1, 0.058)	447	405	446	490
Attr. proportion *Campylobacter* spp.	Beta (12, 235)	0.049	0.028	0.047	0.073
Severity	**Beta (1.5, 21)**	**0.067**	**0.008**	**0.054**	**0.168**
Duration (days)	**Lognormal (1.5, 0.5)**	**5.08**	**1.97**	**4.48**	**10.2**
Case-fatality ratio (per 100,000 cases)	BetaPert (1, 10, 20)	10.2	4.33	10.1	16.1
Life expectancy of fatal cases (years)	Custom, see Fig. 3.4[b]	13.2	2.60	8.18	47.0
GENERAL PRACTITIONER					
Incidence rate campylobacteriosis (per 10,000 pyr)	Normal (11.7, 0.87)	11.7	10.3	11.7	13.1
Severity	**Beta (1.23, 1.90)**	**0.393**	**0.049**	**0.368**	**0.821**
Duration (days)	**Lognormal (2.0, 0.5)**	**8.37**	**3.24**	**7.39**	**16.8**
GUILLAIN-BARRÉ SYNDROME					
CLINICAL					
Incidence rate (per 100,000 pyr)	Normal (1.18, 0.05)	1.18	1.10	1.18	1.26
Attr. proportion *C. jejuni* mild cases	Bootstrapping, see Table 3.8	0.15	0.03	0.15	0.37
Attr. proportion *C. jejuni* severe cases	Bootstrapping, see Table 3.8	0.28	0.17	0.27	0.37
Sensitivity serology	Bootstrapping, see Table 3.8	0.74	0.63	0.74	0.85
Specificity serology	Fixed	0.97	-	-	-
Proportion of mild cases < 50 year	Bootstrapping, see Table 3.9	0.69	0.63	0.74	0.85
Proportion of mild cases < 50 year	Bootstrapping, see Table 3.9	0.48	0.43	0.48	0.54
Severity weights					
mild	**Beta (1.44, 15.22) + 0.003**	**0.090**	**0.008**	**0.071**	**0.225**
severe, < 50 years	**Beta (3.21, 19.91) + 0.140**	**0.277**	**0.187**	**0.236**	**0.412**
severe, =50 years	**Beta (5.22, 28.58) + 0.210**	**0.362**	**0.265**	**0.355**	**0.471**
Duration (years)	Fixed	1	-	-	-
Case-fatality ratio	BetaPert (0.01, 0.02, 0.05)	0.023	0.013	0.023	0.036
Life expectancy of fatal cases (years)	Custom, see Fig. 3.8	18.7	5.73	11.2	81.3
RESIDUAL SYMPTOMS					
Severity weights					
mild	**Beta (0.87, 29.67)**	**0.027**	**0.001**	**0.019**	**0.088**
severe, < 50 years	**Beta (2.50, 18.36) + 0.041**	**0.161**	**0.074**	**0.147**	**0.294**
severe, =50 years	**Beta (3.54, 22.34) + 0.074**	**0.211**	**0.124**	**0.200**	**0.334**
Duration	**Custom, see Fig. 3.6**	**37.1**	**11.3**	**37.2**	**66.7**
REACTIVE ARTHRITIS					
Risk after enteritis by *Campylobacter* spp.	BetaPert (0.01, 0.02, 0.03)	0.020	0.008	0.020	0.032
Severity	**BetaPert (0.00, 0.21, 0.42)**	**0.210**	**0.079**	**0.210**	**0.340**
Duration (weeks)	**BetaPert (2, 6, 10)**	**6.00**	**3.51**	**6.00**	**8.48**

Variables that are subject to uncertainty are presented in normal font, those subject to variability are **bold**

Figures 4.3 and 4.4 show the results of the uncertainty analysis for the total health burden. The resulting distributions are characterised in Table 4.5.

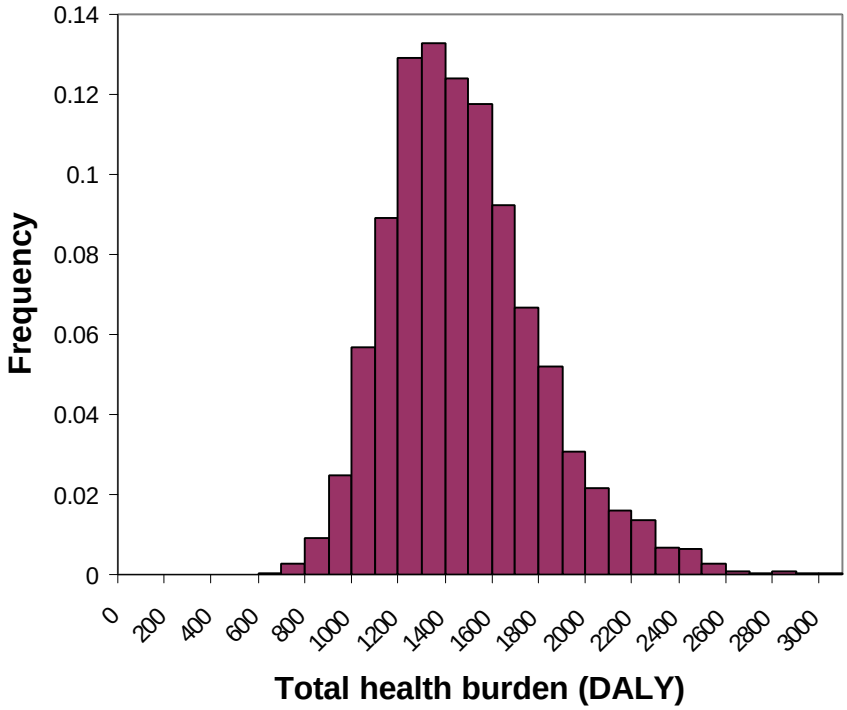


Fig. 4.3 Distribution of estimated health burden by infection with thermophilic Campylobacter spp. in the Netherlands.

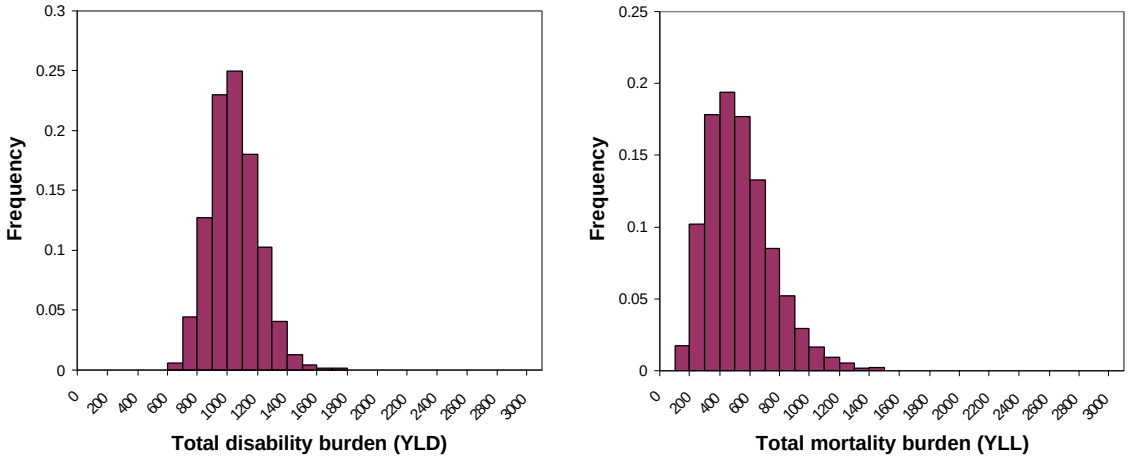


Fig 4.4. Distribution of estimated disability and mortality burden by infection with thermophilic Campylobacter spp. in the Netherlands.

Table 4.5. Characteristics of the output distributions of estimates of disease burden[1].

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

[1]Note that these results (means) do not correspond exactly to the results in Table 4.3. This is partly due to rounding-off effects, and partly to the mixed additive/multiplicative nature of the model equations.

The results show an estimate of the mean total health burden of approx. 1400 DALY per year, the uncertainty is relatively small; the 90% confidence interval is approx. 900-2000, the coefficient of variation (CV = standard deviation/mean) is approx. 0.23. The major contribution to uncertainty in the final estimate comes from uncertainty in YLL (CV = 0.49), see Figure 4.4 This is mainly related to the relatively low incidence of fatal cases. The uncertainty in YLD is much smaller (CV = 0.17 for total YLD).

4.4.3 Sensitivity analysis

Two methods were used for sensitivity analysis. One aim is to identify the model parameters that have the greatest impact on the (mean value of) the final estimate. For this purpose, the perturbation method was used, in which one parameter at a time is changed by a small fraction, e.g. $Dp = 0.0001\%$. The effect on the output Do is then evaluated and the sensitivity is expressed as $S = Do/Dp$. The larger S, the larger the effect of the parameter on the output value. The results of these calculations (Fig. 4.5) show that the parameters related to the incidence and mortality of *Campylobacter*-associated gastro-enteritis and the incidence of Guillain-Barré syndrome have the largest impact on the final result, followed by the severity and duration of residual symptoms of Guillain-Barré syndrome.

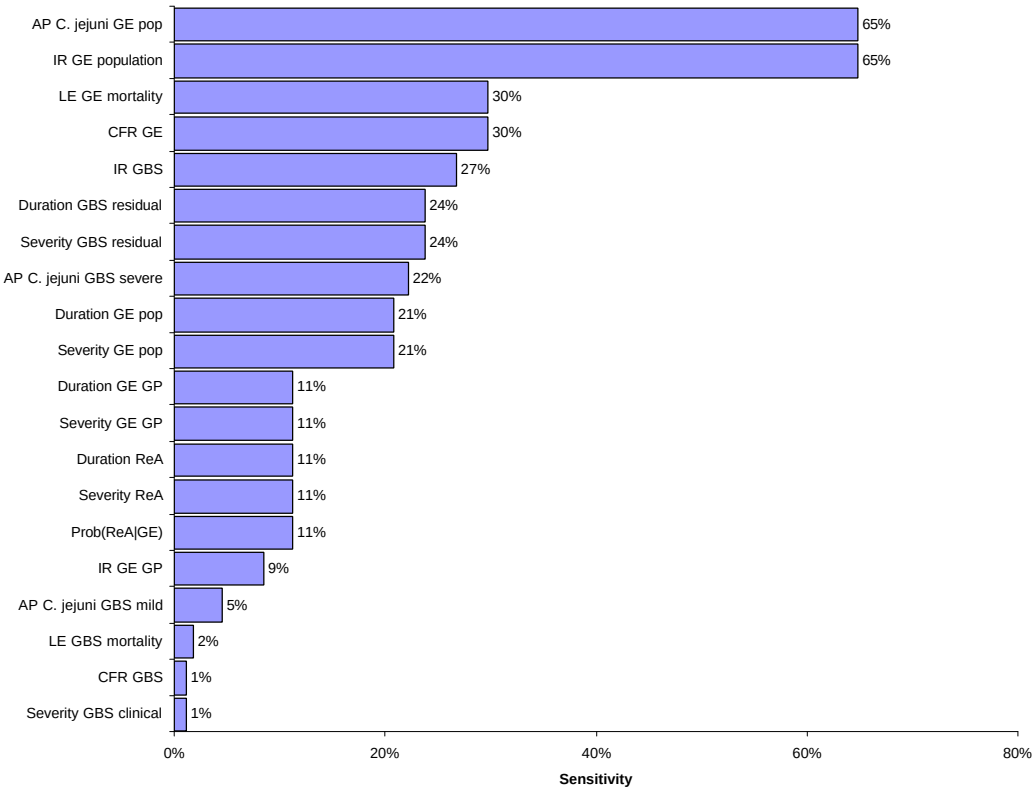


Fig 4.5. Sensitivity analysis on mean values by the perturbation method. AP: Attributable Proportion, GE: Gastro-Enteritis, IR: Incidence Rate, LE: Life Expectancy, CFR: Case-Fatality Ratio, GBS: Guillain-Barré syndrome, ReA: Reactive Arthritis, Prob: probability, pop: population, GP: general practitioner

A second aim is to investigate the possible effect of several assumptions that were made when defining the baseline model, by comparing the results with those obtained by alternative assumptions. The alternative scenarios are described on page 45, the results are shown in Table 4.5 and Figure 4.6, and are discussed below.

Table 4.6. Effect of alternative assumptions on DALY estimates for individual disease endpoints and total over all endpoints (baseline scenario in Table 4.3).

Endpoint	DALY in scenario (% change)								
	Base-line	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*
GE population	710	562 (-21%)	810 (+14%)						1071 (+51%)
GE general practitioner	159			94 (-41%)					162 (+2%)
GBS clinical	41				128 (+208%)	73 (+75%)	31 (-26%)		38 (-8%)
GBS residual	334				1031 (+208%)	586 (+75%)	247 (-26%)		224 (-33%)
Reactive arthritis	159	128 (-20%)						9 (-94%)	
Total	1403	1224 (-13%)	1503 (+7%)	1354 (-3%)	2186 (+56%)	1686 (+20%)	1305 (-7%)	1253 (-11%)	1653 (+18%)

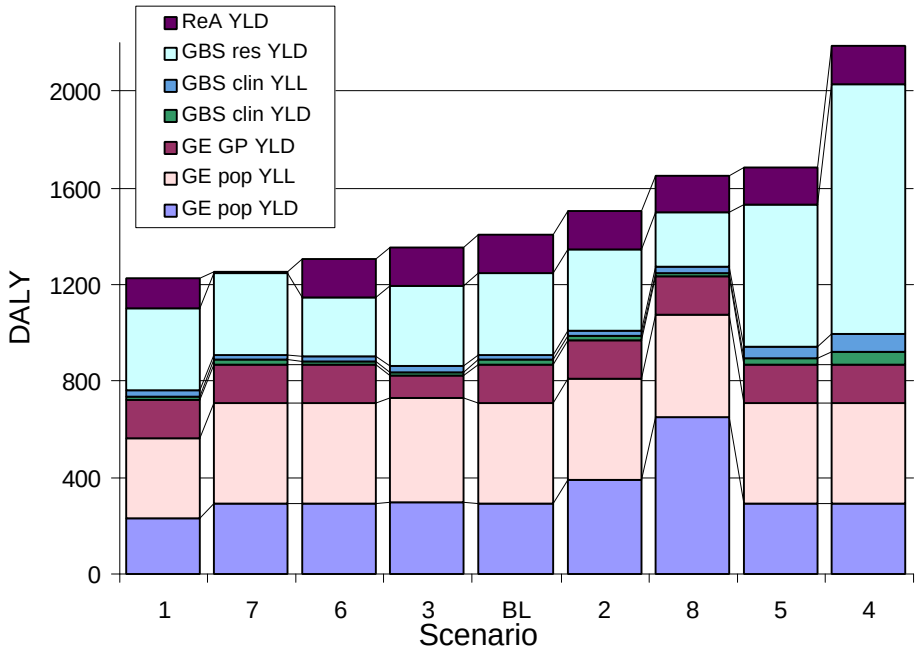


Fig. 4.6. Graphical representation of scenario analysis (see data in Table 4.6). legend see Fig. 4.5; res: residual, clin: clinical.

1. In the population based surveillance study, several case definitions for gastro-enteritis were used to analyse the data. The incidence rate estimate of 447 per 1000 person years (see p. 15) was based on a comprehensive case-definition, in accordance with WHO criteria. It was felt that this case-definition could also include many cases of gastro-enteritis of non-infectious origin and a more restrictive case-definition[16] was also applied. This resulted in an incidence rate estimate of 153 per 1000 person years. *Campylobacter* spp. were isolated from 6 faecal samples of 52 respondents. Hence, an alternative estimate for the incidence of *Campylobacter*-associated gastro-enteritis is (153/1000) x $15x10^6$ x (6/52) = 265,000 cases per year. This estimate would result in an overall reduction of the health burden by 13% to 1224 DALY, and would reduce the estimated burden by gastro-enteritis in the total population and by reactive arthritis by 21 and 20%, respectively.
2. The severity weight for gastro-enteritis in the general population as used in the baseline scenario was based on a relatively mild case-definition of watery diarrhoea. In Appendix 3 of the GBD, age-specific weights are given for “Diarrhoeal diseases (episodes)” in the treated and untreated form. These estimates range between 0.119 for the 0-4 years old to 0.086 for the 15-59 year old. An average disability weight of an episode of diarrhoeal disease of 0.09 seems to be an acceptable simplification. Using this severity increases the DALY estimate for the general population by 14% and the total estimate by 7% to 1503 DALY per year.
3. If no correction for non-response in sentinel surveillance (see p. 14) is applied, the DALY estimate for gastro-enteritis at the general practitioner decreases by 41%, but the effect on the total DALY estimate is restricted to 3%.
4. A high estimate for the incidence rate of Guillain-Barré syndrome is 3.64/100,000 pyr (see p. 22). This would increase the estimated health burden by Guillain-Barré syndrome

[16] Diarrhoea or vomiting and at least two of the following symptoms: vomiting, nausea, abdominal pain or cramps, fever, blood or mucus in faeces; these symptoms on the same day during at least tow consecutive days

by 208%, and would also have a profound effect on the total estimate, which would increase by 56% to 2186 DALY per year.

5. Assuming that the probability of acquiring Guillain-Barré syndrome after *Campylobacter*-associated gastro-enteritis is 1:1058 (see p. 22) would also have strong effects. Guillain-Barré syndrome related health burden would increase by 75%, and the total estimate by 20% to 1686 DALY per year.
6. If no correction for sensitivity of the serological test for antecedent *Campylobacter*-infection in Guillain-Barré syndrome patients was applied (see p. 24), the related health burden would decrease by 26% and the total estimate by 7% to 1305 DALY.
7. If only more severe cases of reactive arthritis were taken into account (incidence 50 cases per year, with median duration 25 weeks and severity weight 0.37), the related health burden would practically be negligible and the total burden would be reduced by 11% to 1253 DALY per year.
8. Section 4.3.4 describes a modelling approach to obtain severity weights, which is based on a standardised description of health profiles using the EuroQol-5D scales, and values obtained from the general public using the TTO protocol. Substituting these severity weights for the weights in the baseline results in an increase of the overall health burden by 18% to 1653 DALY. The difference is mainly attributable to an increase of the disability burden of gastro-enteritis in the general population from 291 to 652 DALY, or by 124%. This is now the most significant single cause of health burden. The disability burden of gastro-enteritis leading to GP consultation increases slightly and the disability burden by Guillain-Barré syndrome is reduced by 33%.
9. There is major uncertainty in the case-fatality ratio of *Campylobacter* associated gastro-enteritis and the distribution used in the baseline scenario is arbitrary. To evaluate the effect of this uncertainty more fully, a series of simulations was run in which the case-fatality ratio was kept constant at values of 1, 2, 3, …, 20 per 100,000 cases. Figure 4.7 shows the results of this analysis. The mean estimate of the total health burden varies between approximately 1000 and 1800 DALY. Comparison with the mean and standard deviation of the baseline scenario demonstrates that, even though the uncertainty in the CFR has a major impact on the mean estimate, the contribution to overall uncertainty is limited.

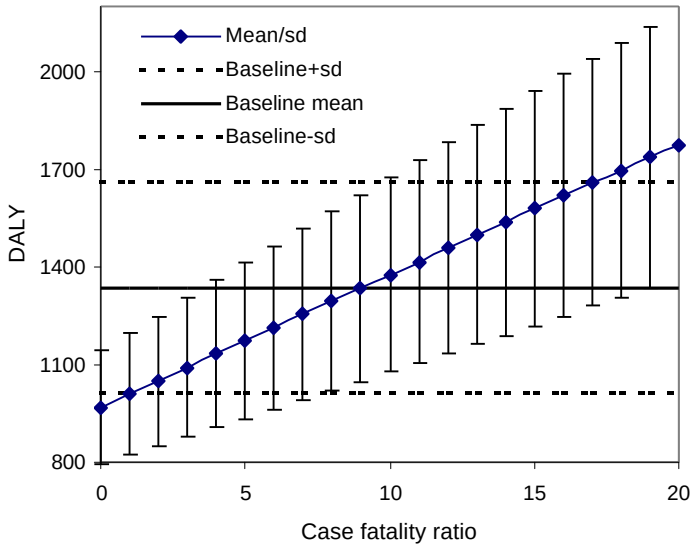


Fig 4.7 Effect of the case-fatality ratio of gastro-enteritis on the total health burden and the associated uncertainty

10. It might be argued that fatal cases by gastro-enteritis are not a random selection of the population, but in fact do have underlying diseases. These might lead to a reduced life expectancy, or to a reduced quality of life before the fatal event. Then, attribution of the standard life expectancy to these cases or assigning a weight of 1 to the lost life years would overestimate the true mortality burden. Fig 4.8 shows the effect of assuming lower life expectancies. As above, it is clear that the assumption has a major impact on the median estimate, but does not add much to overall uncertainty.

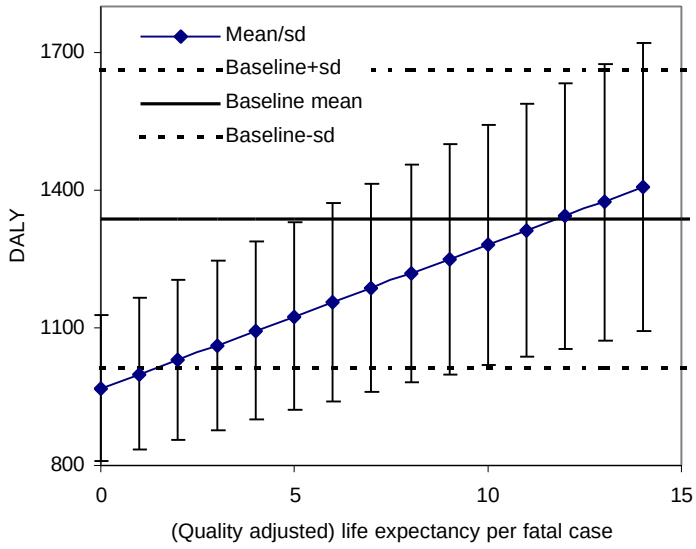


Fig 4.8 Effect of the life expectancy or quality of life of fatal cases of gastro-enteritis on the total health burden and the associated uncertainty

In summary, the alternative assumptions result in variation of the median value of the total health burden between 900 and 2200 DALY per year, which is approximately the same as the range displayed in Figure 4.3[a].

4.4.4 Discounting future health

In economic analyses, it is commonly accepted to compare costs and revenues that occur over an extended period of time on the basis of their present value, because an immediate profit is generally preferred over a profit at a later moment in time. This is achieved by applying a discount rate to future costs and benefits. This concept, although not undisputed, is also commonly applied in economic analyses of medical and other public health interventions. Murray (1996) extensively discusses the use of discounting in the calculation of DALYs. In this report, results are presented with and without discounting of future life-years. By definition, discounting does not apply to health effects that have duration of less than 1 year. Hence, the end-points of infection with thermophilic *Campylobacter* spp. that need to be considered for discounting are mortality and residual symptoms from Guillain-Barré syndrome. The method to calculate discounted DALYs is the same for both situations, because the uncertainty in valuing a year of life that may be lost in the future is the same as the uncertainty in valuing a year that may be lived with disability in the future.
Let *a* be the age of premature death or onset of disabling disease and $e^*(a)$ be the standard life expectancy at age *a*. Then, the discounted life expectancy $e^*(a,r)$ is calculated according to the general formula (using continuous time-steps)

$$e^*(a,r) = \int_0^{e^*(a)} e^{-rt}\,dt = \frac{1}{r}\left[1 - e^{-re^*(a)}\right]$$

where r = discount rate

This formula is then applied to the mean life expectancies for 5-year age classes *e*(a')* to derive discounted age-specific standard life expectancies, as shown in Appendix 8 for discount rates 3 and 5%.

Discounting accounts for the time preference of individuals in valuing health, but is does not account for the future effects of medical technology or the autonomous decline in quality of life in relation to age (Kind, 1996). These factors are not considered in this report, because no generally accepted methodology is available. Furthermore, the effects of age weighting (Murray, 1996) are not considered because of their highly controversial nature (Barendregt *et al*., 1996).

By applying a discount rate of 3 and 5%, the total burden is reduced from approx. 1400 to 1200 and 1100 DALYs or by 14 and 21%, resp. (see Table 4.7). Discounting has the greatest absolute and relative impact on the morbidity burden of residual symptoms of Guillain-Barré syndrome, which is reduced by 40 and 55% with discount rates 3 and 5%, resp.

Table 4.7. Effect of discounting on the health burden due to infection with thermophilic Campylobacter spp. in the Netherlands.

a. Morbidity

	N	W	L			YLD (years)		
Discount rate			*0%*	*3%*	*5%*	*0%*	*3%*	*5%*
Gastro-enteritis								
General population	311,000	0.067	0.014	0.014	0.014	291	291	291
General practitioner	17,500	0.393	0.023	0.023	0.023	159	159	159
Guillain-Barré syndrome								
clinical phase	58.3	0.281	1	1	1	16	16	16
residual symptoms	57.0	0.158	37.1	22.4	16.9	334	202	152
Reactive arthritis	6570	0.210	0.115	0.115	0.115	159	159	159
Total						959	827	777

b. Mortality

	N	t (years)			YLL (years)		
Discount rate		*0%*	*3%*	*5%*	*0%*	*3%*	*5%*
Gastro-enteritis	31.7	13.2	10.9	9.7	419	346	307
Guillain-Barré syndrome	1.3	18.7	14.3	12.1	25	19	16
Total					444	365	323

c. Health burden

	YLD			YLL			DALY		
Discount rate	*0%*	*3%*	*5%*	*0%*	*3%*	*5%*	*0%*	*3%*	*5%*
Gastro-enteritis									
General population	291	291	291	419	346	307	710	637	598
General practitioner	159	159	159				159	159	159
Guillain-Barré syndrome									
clinical phase	16	16	16	25	19	16	41	36	33
residual symptoms	334	202	152				334	202	152
Reactive arthritis	159	159	159				159	159	159
Total	959	827	777	444	365	323	1403	1192	1100

5. Discussion

Infection with *Campylobacter* may result in diseases that range from mild, self-limiting gastro-enteritis with limited duration to life-long sequelae of serious, debilitating disease and premature mortality. Hence, quantifying the health burden of exposure to thermophilic *Campylobacter* spp. requires using a metric that enables integrating these very different end-points. The concept of Disability Adjusted Life Years (DALYs) is uniquely suited for this purpose. Similar concepts, such as Quality Adjusted Life years, have been used extensively in medical technology assessment (MTA) and in health economics to optimise decision making, both from the perspective of individual patients and from the societal perspective. The concept is increasingly being used in public health research, as demonstrated by the hallmark publication of the Global Burden of Disease study (Murray and Lopez, 1996)., It has also been adopted as a basis for Dutch public health policy, as described in the Public Health Forecast study (Ruwaard and Kramers, 1997; Van der Maas and Kramers, 1997). Both documents provide extensive background information on the scientific and societal implications of using deliberately simplifying measures to capture intricately complex phenomena such as health in a single metric.

This report evaluates the feasibility of quantifying the health burden of diseases related to thermophilic *Campylobacter* spp. in the Dutch population, expressed in DALYs. To this aim, the available epidemiological information on most relevant end-points is extensively discussed. The DALY methodology requires the availability of high quality data for all relevant inputs, which are currently available to only a limited extent. Therefore, not only point estimates are given but also appropriate distribution functions are generated to describe uncertainty and variability in these estimates. The uncertainty in the final estimate is formally evaluated using simulation methods. The most likely value of the total health burden is approx. 1400 DALY per year with a (90%) range between 900 and 2000 DALY per year. To account for the effect of assumptions made when choosing the baseline scenario, sensitivity analysis is carried out using alternative assumptions. In these scenarios, the mean estimate ranges between 1200 and 2400 DALY per year. Hence, the final result of this study is relatively robust against alternative assumptions. This is related to the fact that the total health burden is based on different disease end-points, and that is unlikely that parameter estimates for these end-points will simultaneously have an extreme value.

The relative contribution of individual diseases to the total health burden is more uncertain, but mainly from a quantitative point of view. In the baseline scenario, gastro-enteritis in the general population, gastro-enteritis related mortality and residual symptoms from Guillain-Barré syndrome are the major determinants of health burden. In most scenarios this order is maintained. Only when extreme estimates for the incidence rate of Guillain-Barré syndrome are used (such as in recent work from the USA), will (residual disability from) Guillain-Barré syndrome be the leading cause of disability.

The most important causes of health burden affect patients that are not usually seen in clinical settings. Most detailed data are available from clinical studies, but these relate to diseases or disease stages that only have a small contribution to the overall health burden. This contrast is most striking for Guillain-Barré syndrome. There is a wealth of data on patients in their first year after hospitalisation, which adds only 40 DALY to the health burden (or 3% of the total). The residual symptoms of Guillain-Barré syndrome add 330 DALY or 24% of the total burden, but only one paper is available on this stage of the disease. There is also a lack of data on severity duration and case-fatality ratio of *Campylobacter*-associated gastro-enteritis in the general population and on all aspects of reactive arthritis. Thus, this study indicates that active surveillance for gastro-intestinal pathogens, based on population studies is preferred above passive surveillance based on clinical reports.

The Dutch VTV study (Ruwaard and Kramers, 1997, Van der Maas and Kramers, 1997) gives a first estimate for the loss of healthy life years in the Dutch population. Because of major uncertainty in the underlying parameters, the reports do not give an estimate for the total burden, but classify diagnostic groups of diseases on the basis of different indicators: prevalence, severity, life years lost, years lived with disability and health burden as expressed in DALY. In the classification according to health burden, intestinal infections rank in the category 3,000-10,000 DALY per year. Other disorders in this category are meningitis, sepsis, upper respiratory infections, stomach and duodenal ulcers, Down syndrome, violoence and accidental drowning. Thermophilic *Campylobacter* is only one of more than 50 infectious agents that may cause gastro-intestinal illness, but accounts for 5% of all cases on a population basis. Extrapolating the current estimate of 1400 DALY per year to all causes of gastro-enteritis would result in an estimated burden of 28,000 DALY per year, which is considerably higher than the VTV estimate. But probably this figure is an overestimation because (a) not all gastro-enteritis is infectious in nature, (b) not all intestinal pathogens induce severe complications such as Guillain-Barré syndrome and (c) gastro-enteritis induced by many agents (e.g. viruses and bacterial toxins) is less severe and of shorter duration than *Campylobacter*-associated gastro-enteritis. Nevertheless, the results of this study indicate that the health burden associated with gastro-intestinal pathogens may be underestimated if only diarrhoeal illness in accounted for. Finally, even though the total health burden associated with *Campylobacter* is small in comparison to major diseases such as lung cancer, psychological disorders and coronary vascular diseases, the results of this study justify further efforts to reduce the incidence of foodborne disease, and campylobacteriosis in particular. In addition to the high direct costs, related to productivity losses and medical consumption (Buzby *et al*., 1996), this study adds the dimension of preventable health loss.

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Appendix 2. Symptoms of *Campylobacter* enteritis

Study no.[1]	1[2]	2	3[3]	4	5	6	7[4]	8	9	10[5]	11	12
Country	USA	CAN	NZ	UK	UK	CAN	UK	NL	NL	NOR	AUT	n.a.
Year	1980	1985	1990	1992	1994	1994	1978-80	1987-91	1992-93	1989-90	1983-93	n.a.
Case selection[6]	OB	OB	OB	OB	OB	OB	GP	GP	GP	LS	CL	R
N	11	49	44/11	110	23	7	39	263	181	58/77	196	
Anorexia												83-90
Arthralgia	36									23/29		
Myalgia			25/18									19-69
Malaise			68/55									73-95
Headache	82		61/73									12-82
Dizziness						28						
Fainting						14						
Fever	100	90	59/64	72	70	43	54>	51	56	77/75[7]	61	52-91
Chills	73											29-75
Abdominal pain	73		80/82	91	96		92		63	86/67		
Abd. cramps						100		80	83		58	55-97
Abd. tenderness							54					
Nausea			60/40	61			46<		41	47/58		30-76
Vomiting	36	53	55/64	34	43	14	13<	25	21	26/26	34	19-55
Diarrhoea	82	96	75/91	100	91	100	100		96	97/100	92	75-100
watery								81	87			
slime								44	40			
bloody	55	16		13	26		8	27	25	41/22	48	6-57
Tenesmus										31/35		
Respiratory inf.							13					
Cough	27											
Rash	18											

[1] 1: Shandera *et al*., 1992; 2: Millson *et al*., 1991; 3: Stehr-Green *et al*., 1991; 4: Fahey *et al*., 1995; 5: Evans *et al*., 1996; 6: Ellis *et al*., 1995; 7: Kendall and Tanner, 1982; 8: Hoogenboom-Verdegaal *et al*., 1994; 9: Goosen *et al*., 1995; 10: Kapperud *et al*., , 1992; 11: Moser *et al*., 1995; 12: Peterson; 1994

[2] Bacteremic patients

[3] Cases conforming to clinical case-definition/culture-confirmed

[4] < Significantly less than control group with diarrhoea; > Significantly more than control group with diarrhoea

[5] Domestic/imported cases; underlined = significantly greater

[6] OB: outbreak; GP: general practitioner; LS: laboratory surveillance; CL: clinical (in- and outpatient); R: review

[7] Data for reported fever; documented fever 62/31

n.a.: not applicable; N: number of patients

Study no.[1]	13	14	15	16	17	18	19
Country	NL	USA	S	S	AUS	USA	DK
Year	??	1983	1981-2	1981	1994-5	1996	1991-3
Case-selection	LS	OB	CL	OB	OB	OB	Cl
N	75	79	43	35	621	14	40
Anorexia		68					
Arthralgia				6			
Myalgia	5	59		9			
Malaise				71			
Headache	12	32		69	25		
Dizziness	5						
Fainting							
Fever	72	66	70	71	73	93	63
Chills		51					
Abdominal pain			63		90		
Abdominal cramps	96	90			90	93	
Abd. tenderness							
Nausea	39	76			63	79	
Vomiting	17	41			31	36	35
Diarrhoea	93	95	100	83	99	100	98
watery							
mucus in faeces							
bloody	19	13	11		35	21	40
Respiratory inf.							
Cough/sore throat		42					
Rash							
Weakness		76					
Night sweats		48					

[1] 13: Oosterom, 1985; 14: Sacks *et al*., 1986; 15: Svanteson *et al*., 1988; 16: Bremell *et al*., 1991; 17: Eberart-Phillips *et al*., 1997; 18: Graves *et al*., 1998; 19: Munk-Petersen *et al*., 1996.

Appendix 3. Duration (days) of *Campylobacter* enteritis

Ref.[1]	Country	Year	Case sel.	N	Description	Mean	Med.	Range	Remarks
2	CAN	1985	OB	49	illness		3-7	2-77	
3	NZ	1990	OB	11	diarrhoea		3.5		culture-confirmed cases
4	UK	1992	OB	110	illness			2-24	
5	UK	1994	OB	23	illness	4		1-14	15 cases saw GP, none admitted to hospital
6	CAN	1994	OB	7	symptomatic	4.6	4	3-6	data from individual patients known
7	UK	1978-80	GP	39	diarrhoea	6.9	7	2-18	data from individual patients known; 11/35 mild infection (2-4 d), 2 patients in hospital
10	NOR	1989-90	LS	135	symptomatic diarrhoea blood in stool arthralgia absenteeism hospitalisation	14.6 10.9 3.2 5.5 3.8 4.2	11 8 2 3 1 4	2-67 1-57 1-14 1-30 0-30 1-10	13.3% were hospitalised; 1 surgery for suspected appendicitis; 16.3% antimicrobials (had no effect on duration)
11	AUT	1983-93	CL	196	hospitalisation	6		1-153	153 days was a patient with GBS without preceding enteritis
13	NL	??	LS	75	abd. cramps diarrhoea fever illness absenteeism		7 6 1 8 6	-40 -23 -5 -65 -65	
14	USA	1983	OB	79	illness	6.6	6		Estimated case-load 865; 4 patients hospitalised for acute ge, 1 case of GBS
15	S	1981-2	CL	43	diarrhoea		8		Median duration for all patients with diarrhoea 9 days, period of general discomfort coincides with presence of diarrhoea
20	UK	1984-87	CL	94	diarrhoea	5.7		2-10	Mean duration of disease by 5 viruses 4.7-6.8 days, by 4 bacteria 5.7-6.6 days; cryptosporidiosis 13 days
21	NL	??	LS	39	diarrhoea other	10	-	3-21	Erythromycin treatment had no effect on duration of illness or severity of symptoms

[1] See Appendix 2; 20: Hart & Cunliffe, 1996, 21: Herbrink *et al.*, 1988

Appendix 4. Association between infection with *Campylobacter jejuni* and the Guillain-Barré syndrome and its variants

PATIENT GROUP[1]	# OF PATIENTS (DETAILS)	# (%) POSITIVE SEROLOGY[2,3]	# (%) POSITIVE CULTURE[2]	ADDITIONAL INFORMATION	COUNTRY	REFERENCE
GBS	1 (45, M)	1 (100)	1 (100)	culture 7days after admission	UK	Rhodes & Tattersfield, 1982
GBS	1 (42, M)	ND	1 (100)	culture 23 days after onset of diarrhoea	SF	Molnar ea, 1982
MFS	1 (34, F)	1 (100)	1 (100)	culture 10 days before admission	UK	Constant ea, 1983
GBS NDC HC	56 (27 M, 29 F, average age 46.6) 27 30	21 (38) 0 (0) 0 (0)	ND	62 patients admitted in study period, no age and sex difference between CJ+ and CJ- patients	AUS	Kaldor & Speed, 1984
GBS	2 (34, M; 22, F)	ND	2 (100)			Pryor ea, 1984
MFS	1 (27, M)		1(100)		UK	Wroe &Blumhardt, 1985
GBS	1 (2, F)	1 (100)	1 (100)	excretion of C. jejuni for 2 months	AUS	De Bont ea, 1986
		ELISA BLOT	ND		AUS	Speed ea, 1987
GBS Cj-ent HC	45 24 12	19 (42) 22 (49) 23 (96) 23 (96) 0 (0) 0 (0)				
GBS	1 (69, F)	ND	1 (100)	culture during diarrhoea	USA	Kohler & Goldblatt, 1987
GBS	106	ND	4 (4)		USA	Ropper, 1988
GBS	3 (30, M; 81, M; 60, M)				F	Sovilla ea, 1988
GBS HospC	99 99	14 (14) 2 (2)	ND	See also Walsh ea, 1991 for anti-ganglioside ab serology by complement fixation test	UK	Winer ea, 1988
GBS	1 (7, F)	ND	1 (100)	culture during hospitalisation	NL	Beenen & Scholten, 1990
GBS	17	3 (18)		serology by immunoblot	USA	Gruenewald ea, 1991
		IgA IgG IgM		within 2 wks after onset pred. IgG response, later that 2 wks IgM; Cj-ent American soldiers in Thailand, HC rural Thai village	CHINA	Blaser ea, 1991
CPS Cj-ent HC	26 (age 3-35, med 7) 10 32	6 (23) 9 (35) 13 (50)	ND NR ND			

PATIENT GROUP[1]	# OF PATIENTS (DETAILS)	# (%) POSITIVE SEROLOGY[2,3]	# (%) POSITIVE CULTURE[2]	ADDITIONAL INFORMATION	COUNTRY	REFERENCE
		5 (50) 6 (60) 6 (60) 1 (3) 3 (9) 1 (3)				
GBS NDC HC	17 (10 M, 7 F; age 5-58, mean 28) 17 33	IgA IgG IgM 9 (53) 13 (76) 9 (53) 3 (18) 5 929) 3 (18) 1 (3) 1 (3) 3 (9)	0 (0)	< 30 yr 8/11 (78%) IgM +ve; > 30 yr 1/6 (17%) summer 9/14 (64%) IgM +ve, winter 0/3 (0%)	CHINA	Yuan ea, 1993)
GBS NDC HC	58 (age 36 ±22 (SD)) 42 (40 ± 22) 29 (29 ±13)	10 (17) 3 (7) 2 (7)		sera obtained within 2 wks after onset	USA	Vriesendorp ea, 1993
GBS MS MG NB Cj-ent other ent HC	38 (age 20-77, med. 45) 20 17 72 51 36 39	IgA IgG IgM 15 (39) 26 (68) 4 (11) 3 (15) 5 (25) 0 (0) 3 (18) 13 (76) 0 (0) 2 (3) 32 (44) ND 40 (78) 46 (90) ND 1 (3) 1 (3) 0 (0) 7 (18) 8 (21) 0 (0)	15 % of ???	All ab by immunoblotting; 81 % of serum samples within 2 wks after onset; IgA most specific for recent infection; 14/15 IgA +ve patients react with Lior type 11 antigen	D	Enders ea, 1993
GBS Cj-ent HC	46 (32 M, 14 F, age 3-55) 18 503	14/39 (36) 12 (67)	14 (30) NR 6 (1.2)	Serology(2 or 3 Ig-classes) and/or culture +ve: 19/46 (41 %);3 repeated stool cultures, most < 1 week after onset; 10/12 strains Penner type 19; no significant sex or age difference between Cj associated and other	JAP	Kuroki ea, 1993

PATIENT GROUP[1]	# OF PATIENTS (DETAILS)	# (%) POSITIVE SEROLOGY[2,3]	# (%) POSITIVE CULTURE[2]	ADDITIONAL INFORMATION	COUNTRY	REFERENCE
				GBS		
GBS NDC HC	118 (58% M; age 4-84, med. 41) 56 (57% M; age 2-74, med. 36) 47 (72% M; age 2-74, med. 31)	42 (36) 5 (9) 5 (11)	ND	Positive response in two or more Ig classes; sensitivity 65%; specificity 97%; greater risk for men and with increasing age and in summer	USA	Mishu ea, 1993
motor GBS other GBS total GBS	27 (17 M, 10 F; age 43.1 ± 20.7) 120 (59 M, 60 F; age 48.5 ± 18.8) 147 (76 M, 70 F)	16/24 (67) 30/109 (28) 46/133 (35)	ND	motor GBS: more rapid onset and nadir, initial distal weakness, sparing of cranial nerves, more gastro-enteritis, more often anti-GM1, better reaction to intravenous Ig than plasma-exchange	NL	Visser ea, 1995
GBS HospC HC	103 (66% M; age 48 ± 19) 81 (59% M, age 48 ± 17) 85 (39% M; age 53 ± 17)	27 (26) 1 (1) 2 (2)	8 (8) not reported 1 (1)	Patients from teaching and district general hospitals, GBS includes 7 MFS, no age difference between Cj + and - groups, but more men in Cj+ group	UK	Rees ea, 1995
AMAN AIDP other GBS all GBS HC	21 (67% M, age med. 20) 12 (42% M, age med. 6.6) 5 38 82	16 (76) 5 (42) 4 (80) 25 (66) 13 (16)	ND		CHINA	Ho ea, 1995
GBS NDC HC	43 32 35	11 (26) 0 (0) 0 (0)	3/8 (38)	Antigens against Penner type 19; three different test required positive	INDIA	Hariharan ea, 1996
GBS NDC HC	154 154 50	49 (32) 18 (12) 4 (8)	ND		NL	Jacobs ea, 1998

[1] GBS: Guillain-Barré syndrome; MFS: Miller Fisher syndrome; CPS: Chinese paralytic syndrome; NDC: neurological disease control; MS: multiple sclerosis; MG: myasthena gravis; NB: neuroborreliosis; HospC: hospital control; Cj-ent: *C. jejuni* enteritis (without neurological sequelae); other ent: other enteritis (*Y. enterocolitica, S. enteritidis*); HC: healthy control

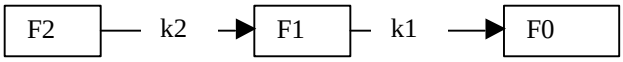
[2] ND: not done; NR: not relevant [3] ELISA unless indicated otherwise

Appendix 5. Severity of Guillain-Barré syndrome related to infection with *C. jejuni*

CRITERION	CJ POSITIVE	RISK CJ POSITIVE	CJ NEGATIVE	RR (95% CI)	REFERENCE
Respiratory support	19/21	0.90	14/35	2.26 (1.47-3.47)***	Kaldor & Speed, 1984
	1/4	0.25			Ropper *et al.*, 1987
	0/3	0.00			Sovilla *et al*., 1988
	3/10	0.30	2/48		Vriesendorp *et al*., 1993
Residual disability	5/14	0.36	4/29	2.59 (0.82-8.18)(*)	Kaldor & Speed, 1984
	1/4	0.25			Ropper *et al.*, 1987
	0/3	0.00			Sovilla *et al*., 1988
	9/14	0.64			Winer *et al*., 1988
	3/10	0.30	0/48	undefined	Vriesendorp *et al*., 1993
moderate severe all	11/26 5/26 16/26	0.42 0.19 ...	17/75 2/75 19/75	3.7 14.2	Rees *et al*., 1993
Death	3/21	0.14	1/35	5.00 (0.55-45)(*)	Kaldor & Speed, 1984
	0/4	0.00			Ropper *et al.*, 1987
	0/3	0.00			Sovilla *et al*.,1988
	3/14	0.21			Winer *et al*., 1988
	0/10	0.00	0/48		Vriesendorp *et al*., 1993
	1/26	0.04	5/75		Rees *et al*., 1993

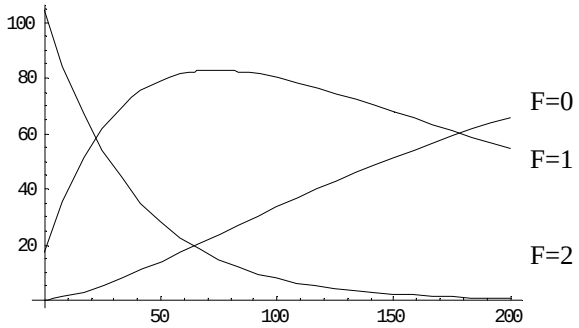
Appendix 6. Clinical course of mild cases of Guillain-Barré syndrome

Patients can be in one of three states (F2, F1, F0). Assume that recovery follows first-order kinetics with rate constants k2 and k1:

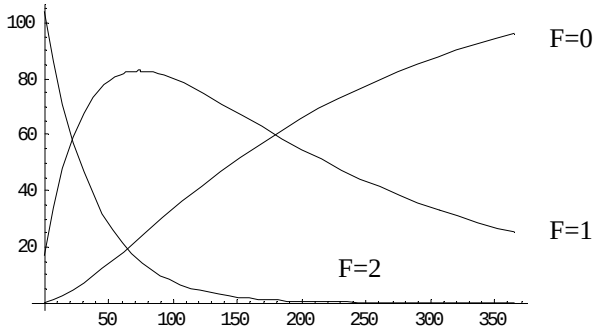


Model equations: dF2/dt = -k2 F2; dF1/dt = k2 F2 -k1 F1; dF0/dt = k1 F1

Initial conditions (for simplicity we set day 0 at nadir): F2 = 104, F1 = 17, F0 = 0
Final conditions after 180 days: F2 = 1, F1 = 60, F0 = 60 (see text, Chapter 3.3.2).
The model was solved using Mathematica 4.0.0 (Wolfram Corporation, 1999): k2 = 0.026; k1 = 0.0048
Graphic representation of the solution:



Assume that the recovery will continue at the same rate for another 6 months, and that the patient's conditions will remain stable after 1 year, we have an estimate of the residual status of mildly affected patients. Time course in one year:



After 365 days, F2 = 0, F1 = 25; F0 = 96. These values will be used for residual status.

Relationship between F-score at nadir and age:

	< 50	>=50	Total
F=1	12	5	17
F=2	72	32	104
Total	84	37	121

OR = 1.07 (0.35-3.28), so in this group age is not a prognostic factor for disease severity.

Appendix 7. Clinical heterogenity in Guillain-Barré syndrome patients related to treatment choice and antecedent infections

Reference	Van der Meché et al., 1992		Visser, 1997, Chapter 3				Visser, 1997, Chapter 4						Visser, 1997, Chapter 5	
Patient groups[1]	PE	IVIg	motor GBS		other GBS		CMV GBS		Cj GBS		other GBS		Cj GBS	
			PE	IVIg	PE	IVIg	PE	IVIg	PE	IVIg	PE	IVIg	AMN	AMSN
Number of patients	73	74	11	16	62	58	9	11	23	20	36	35	14	14
F-score at nadir														
F=3	22%	18%											7%	0%
F=4	60%	66%											64%	21%
F=5	18%	16%											29%	79%
Able to walk independently (F=2) after														
8 weeks	42%	58%	5%	67%	45%	53%	11%	55%	26%	55%	64%	60%		
6 months	73%	82%	45%	87%	77%	79%	78%	73%	39%	75%	89%	89%	57%	64%

[1]PE: plasma exchange, IVIg: intravenous immunoglobulin, CMV: cytomegalovirus, Cj: *Campylobacter jejuni*, AMN: acute motor neuropathy, AMSN: acute motor and sensory neuropathy

Appendix 8. Age- and sex specific standard life expectancy according to the Global Burden of Disease Study (Murray and Lopez, 1996) and (discounted) mean life expectancy in 5-year classes

Age (years)	Life expectancy[1]	
	Females	Males
0	82.50	80.00
1	81.84	79.36
5	77.95	75.38
10	72.99	70.4
15	68.02	65.41
20	63.08	60.44
25	58.17	55.47
30	53.27	50.51
35	48.38	45.57
40	43.53	40.64
45	38.72	35.77
50	33.99	30.99
55	29.37	26.32
60	24.83	21.81
65	20.44	17.5
70	16.20	13.58
75	12.28	10.17
80	8.90	7.45
85	6.22	5.24
90	4.25	3.54
95	2.89	2.31
100	2.00	1.46

[1] Calculated at the beginning of the age interval

Age class (years)	Mean life expectancy[1]		
	r=0%	r=3%	r=5%
0-	81.25	30.42	19.66
1-	80.60	30.36	19.64
5-	76.67	29.99	19.57
10-	71.70	29.45	19.45
15-	66.72	28.83	19.29
20-	61.76	28.11	19.09
25-	56.82	27.27	18.83
30-	51.89	26.31	18.51
35-	46.98	25.19	18.09
40-	42.09	23.90	17.56
45-	37.25	22.43	16.89
50-	32.49	20.76	16.06
55-	27.85	18.88	15.03
60-	23.32	16.77	13.77
65-	18.97	14.47	12.25
70-	14.89	12.01	10.50
75-	11.23	9.53	8.59
80-	8.18	7.25	6.71
85-	5.73	5.26	4.98
90-	3.90	3.68	3.54
95+	2.60	2.50	2.44

[1] r = discount rate (see 4.4.4)

Appendix 9. Disability weights of indicator conditions according to the Global Burden of Disease study (Murray, 1996) and the Dutch Public Health Forecast (Van der Maas and Kramers, 1997)

A. Global Burden of Disease (GBD)

Disability class	Severity weights	Indicator conditions
1	0.00-0.02	vitiligo on face, weight-for heigth less than 2 SD's
2	0.02-0.12	watery diarrhoea, severe sore throat, severe anemia
3	0.12-0.24	radius fracture in a stiff cast, infertility, erectile dysfunction, rheumatoid arthritis, angina
4	0.24-0.36	below-the-knee amputation, deafness
5	0.36-0.50	rectovaginal fistula, mild mental retardation, Down syndrome
6	0.50-0.70	unipolar major depression, blindness, paraplegia
7	0.70-1.00	active psychosis, dementia, severe migraine, quadriplegia

B. Dutch Public Health Forecast (VTV)

Severity weight	Euroqol-5D+C score[1]	Indicator condition
0.00	111111	gingivitis
0.03	111111	mild asthma
0.06	212211	lower backpain
0.07	111111 (90%), 112221 (10%)	uncomplicated disabetes mellitus
0.08	111121	mild angina pectoris
0.11	222111	moderate limitations of daily activities
0.14	112121	light depression
0.26	111221	mammacarcinoma (disease-free)
0.43	123121	severe visual handicap
0.49	222122	condition after asfyxia
0.57	222111 (85%), 332221 (15%)	paraplegia
0.63	222222	moderate cardiovascular accident
0.83	112231	intestinal cancer (metastases)
0.94	222331	severe rheumatoid arthritis
0.94	233123	severe dementia
0.98	233333	severe schizophrenia

[1] Dimensions of Euroqol-5D+C score: mobility, self-care, usual activities, pain/discomfort, anxiety/depression, cognition; 1 no problem, 2 some problems, 3 extreme problems. The dimension cognition is an extension of the standard EuroQol-5D score (Krabbe *et al*., 1999).

Appendix 10. Accounting for uncertainty and variability

The spreadsheet below shows the calculation of the population health burden for diseases with high incidence, by the example of gastro-enteritis in the general population. The uncertain variables to simulate the incidence are entered in cells B5 and B6, and the annual incidence is calculated in cell B7 the number of patients consulting their general practitioner is simultaneously calculated in sheet GE Gen. Pr., and is subtracted to avoid double counting of cases). The mean burden per case in cell B9 is the average of 10,000 simulations of the product of duration and severity (not shown). Multiplication of the incidence and mean burden per case results in one simulation of YLD for gastro-enteritis in the general population in cell B11.

	A	B
1	YLD	
2	Gastro-enteritis	
3	General population	
4		
5	Incidence rate (per 1000 pyr)	=RiskLognorm2(6.1,0.058)
6	Attr. Proportion *C. jejuni*	=RiskBeta(12,235)
7	Incidence (per year)	**=B5*B6*15000-'GE Gen. Pr.'!D6**
8		
9	Mean burden per case	0.000927631152968599
10		
11	YLD GE population	**=B7*B9**

The frame below shows one iteration of the simulation model of YLD by gastro-enteritis in the general population.

	A	B
1	YLD	
2	Gastro-enteritis	
3	General population	
4		
5	Incidence rate (per 1000 pyr)	427
6	Attr. Proportion *C. jejuni*	0.052
7	Incidence (per year)	**314942**
8		
9	Mean burden per case	9.28E-04
10		
11	YLD GE population	**292**

For diseases with low incidence, the strategy is illustrated by example of mortality from gastro-enteritis. The incidence of gastro-enteritis is copied in cell G5 from cell B7. Rows 16 and below each simulate one individual fatal case. Cells F15 and below accumulate the total health burden if the incidence were equal to the number in the corresponding cell of row D (Count). Finally, row G returns the accumulated burden if the simulated incidence is equal to Count, and returns a zero value in all other cases. Therefore, the sum of all entries in row G is also equal to the total health burden for that specific iteration, and is calculated in cell G11.

	D	E	F	G
1	LYL			
2	Gastroenteritis			
3	Population			
4				
5	Incidence			=B7
6	Case fatality ratio (per 100,000)			=RiskPert(1,10,20)
7	Number of fatal cases			**=G5*G6/100000**
8				
9				
10				
11	LYL GE population			**=SUM(G15:G135)**
12				
13				
14	Count	Duration	Cumsum	Conditional
15	0		0	=IF(ROUND(G$7,0)=D15,F15,0)
16	1	=RiskDiscrete('SLE"s'!B$8:E	=F15+E16	=IF(ROUND(G$7,0)=D16,F16,0)
17	2	=RiskDiscrete('SLE"s'!B$8:E	=F16+E17	=IF(ROUND(G$7,0)=D17,F17,0)
18	3	=RiskDiscrete('SLE"s'!B$8:E	=F17+E18	=IF(ROUND(G$7,0)=D18,F18,0)
19	4	=RiskDiscrete('SLE"s'!B$8:E	=F18+E19	=IF(ROUND(G$7,0)=D19,F19,0)
20	5	=RiskDiscrete('SLE"s'!B$8:E	=F19+E20	=IF(ROUND(G$7,0)=D20,F20,0)
21	6	=RiskDiscrete('SLE"s'!B$8:E	=F20+E21	=IF(ROUND(G$7,0)=D21,F21,0)
22	7	=RiskDiscrete('SLE"s'!B$8:E	=F21+E22	=IF(ROUND(G$7,0)=D22,F22,0)
23	8	=RiskDiscrete('SLE"s'!B$8:E	=F22+E23	=IF(ROUND(G$7,0)=D23,F23,0)
24	9	=RiskDiscrete('SLE"s'!B$8:E	=F23+E24	=IF(ROUND(G$7,0)=D24,F24,0)
25	10	=RiskDiscrete('SLE"s'!B$8:E	=F24+E25	=IF(ROUND(G$7,0)=D25,F25,0)
26	11	=RiskDiscrete('SLE"s'!B$8:E	=F25+E26	=IF(ROUND(G$7,0)=D26,F26,0)
27	12	=RiskDiscrete('SLE"s'!B$8:E	=F26+E27	=IF(ROUND(G$7,0)=D27,F27,0)
28	13	=RiskDiscrete('SLE"s'!B$8:E	=F27+E28	=IF(ROUND(G$7,0)=D28,F28,0)
29	14	=RiskDiscrete('SLE"s'!B$8:E	=F28+E29	=IF(ROUND(G$7,0)=D29,F29,0)
30	15	=RiskDiscrete('SLE"s'!B$8:E	=F29+E30	=IF(ROUND(G$7,0)=D30,F30,0)

The frame below shows one iteration of the simulation model of LYL by gastro-enteritis. Note that row G only displays a non-zero value at Count=10, which is the same as the incidence estimate in this iteration.

	D	E	F	G
1	LYL			
2	Gastroenteritis			
3	Population			
4				
5	Incidence			148235
6	Case fatality ratio (per 100,000)			6.7
7	Number of fatal cases			**10**
8				
9				
10				
11	LYL GE population			**55**
12				
13				
14	Count	Duration	Cumsu	Conditional
15	0		0.000	0
16	1	3.9	3.9	0
17	2	2.6	6.5	0
18	3	8.2	14.7	0
19	4	2.6	17.3	0
20	5	3.9	21.2	0
21	6	5.7	26.9	0
22	7	5.7	32.6	0
23	8	8.2	40.8	0
24	9	11.2	52.0	0
25	10	2.6	54.6	54.625
26	11	80.6	135.2	0
27	12	3.9	139.1	0
28	13	2.6	141.7	0
29	14	5.7	147.5	0
30	15	11.2	158.7	0

The effect of differentiating uncertainty and variability results in narrower ranges in the final estimates, which can now be considered pure uncertainty.