RIVM report 330080001/2006

Priority setting of foodborne pathogens
Disease burden and costs of selected enteric pathogens

J.M. Kemmeren, M.-J.J. Mangen, Y.T.H.P. van Duynhoven, A.H. Havelaar

Contact: A.H. Havelaar
Microbiological Laboratory for Health Protection
e-mail: arie.havelaar@rivm.nl

This investigation has been performed by order and for the account of the Ministry of Public Health, Welfare and Sports; Nutrition, Health Protection and Prevention Department, within the framework of project V/330080, Microbial Food Safety.

RIVM, P.O. Box 1, 3720 BA Bilthoven, telephone: 31 - 30 - 274 91 11; telefax: 31 - 30 - 274 29 71

Abstract

Priority setting of foodborne pathogens – disease burden and costs of selected enteric pathogens.

Toxoplasmosis causes the highest disease burden among seven evaluated foodborne pathogens. This is the preliminary conclusion of a major study of the disease burden and related costs of foodborne pathogens. The other micro-organisms that were studied are *Campylobacter* spp., *Salmonella* spp., *Listeria monocytogenes*, *Escherichia coli* O157, noroviruses and rotaviruses. The viruses caused the highest costs (mainly due to sickness leave). The study aims to support the setting of priorities in food safety policy. Currently, all transmission routes of the micro-organisms were evaluated, the specific contribution of food will be evaluated later. Attention will also be paid to trends, the effectiveness of preventive measures and risk perception by consumers.

Key words: foodborne illness, priority setting, disease burden, cost of illness, gastro-enteritis, toxoplasmosis, listeriosis.

Rapport in het kort

Prioritering van voedsel-overdraagbare micro-organismen – ziektelast en kosten van geselecteerde enterale pathogenen.

Toxoplasmose veroorzaakt van zeven onderzochte ziekteverwekkende micro-organismen de hoogste ziektelast. Dit is een voorlopige conclusie in een groot onderzoek naar ziektelast van door voedsel overdraagbare micro-organismen en de daaraan gerelateerde kosten. De andere onderzochte micro-organismen zijn *Campylobacter* spp., *Salmonella* spp., *Listeria monocytogenes*, *Escherichia coli* O157, norovirussen en rotavirussen. De virussen brachten de hoogste kosten met zich mee (vooral vanwege ziekteverzuim). Het onderzoek is bedoeld als basis voor het stellen van prioriteiten bij het voedselveiligheidsbeleid. Tot dusverre zijn alle overdrachtsroutes van de micro-organismen beschouwd, later zal de specifieke bijdrage van voedsel worden onderzocht. Er zal ook aandacht worden besteed aan trends, de effectiviteit van preventieve maatregelen en de perceptie van het risico door consumenten.

Trefwoorden: voedselinfecties, prioritering, ziektelast, ziektegebonden kosten, gastro-enteritis, toxoplasmose, listeriose.

Contents

Abbreviations

Health Outcomes

CNS abnormalities	Central Nervous System abnormalities
CR	Chorioretinitis
GE	Gastroenteritis
GBS	Guillain-Barré Syndrome
HC	Hydrocephalus
IBD	Inflammatory Bowel Disease
ReA	Reactive Arthritis
IC	Intracranial Calcifications
GP	General practitioner
ICU	Intensive Care Unit
ORS	Oral Rehydration Solution
PHL	Public health laboratories

Health Status measures

DALY	Disability-adjusted life years
YLD	Years Lived with a Disability
YLL	Years of Life Lost

Pathogens

NV	Norovirus (formerly known as Norwalk-like virus)
RV	Rotavirus
STEC O157	Shiga toxin producing *Escherichia coli* serotype O157

Economic terms

COI	Cost-of-illness
DHC	Direct health care costs
DNHC	Direct non-health care costs
INHC	Indirect non-health care costs

Studies

CaSa	Case-control study of Salmonella and Campylobacter laboratory-confirmed cases, April 2002 – April 2003
LSI	Laboratory surveillance of infectious diseases (Laboratorium Surveillance Infectieziekten)
NIVEL	GP-based study on gastroenteritis, 1996-1999
Pienter	Population-based sero-prevalence study on toxoplasmosis, 1995-1996
SENSOR	Community-based study on gastroenteritis, 1999
TIP	Prospective cohort study to the effects of prevention on congenital toxoplasmosis, 1987

Organisations

CBS	Statistics Netherlands (Centraal Bureau voor de Statistiek)
CTG	National Health Tariffs Authority (College Tarieven Gezondheidszorg)
RBM	Netherlands Reference Laboratory for Bacterial Meningitis
WHO	World Health Organization

Summary

Background

Human health is threatened by a wide variety of pathogens transmitted by food. Effective and efficient policy-making on control, prevention and surveillance of these foodborne pathogens requires focusing on the most relevant ones. This study aims to develop a model that helps Dutch decision makers to establish the priority of pathogenic micro-organisms that can (also) be transmitted by food, as a basis for effective and efficient policy-making on control, prevention and surveillance.

Priority setting of communicable diseases for surveillance or foodborne pathogens has been studied in several countries. Most studies are based on a semi-quantitative approach, combining scores on several criteria to an overall score. However, there is no objective basis to combine highly divergent criteria on the same scale and then simply add up or multiply all scores. In the present study a quantitative approach is used, also quantifying the uncertainty of the results caused by insufficient or incomplete data.

In most studies disease burden was considered as an important domain. This is in line with general trends in public health research that increasingly present disease burden as a major tool for priority setting. Besides the burden of disease, the costs for the Dutch society of foodborne infections are considered important. In the present study, the disease burden and costs were calculated for all cases, indepent from for example transmission routes. However, this is an on-going project and it is foreseen to expand the framework in the future with other criteria such as trends in incidences; the fraction of illness cases attributable to different food products; efficiency and effectiveness of interventions and risk perception.

Methods

Selected pathogens

For the present study, five enteric and two non-enteric pathogens that can (also) be transmitted by food, were selected: norovirus (NV), rotavirus (RV), thermophilic *Campyobacter* spp., *Salmonella* spp., Shiga-toxin producing *Escherichi coli* O157 (STEC O157), *Listeria monocytogenes* and *Toxoplasma gondii*. NV and RV were observed to be the most frequent pathogens causing community-acquired gastroenteritis (GE), and *Campylobacter* spp. and *Salmonella* spp. were the most frequently observed bacterial pathogens. Although most NV and RV cases are acquired in the community, both viruses are responsible for nosocomial infections. NV is a common source of nosocomial infections acquired during a stay in health-care institutions, such as hospitals, nursing homes and homes for elderly. RV is one of the major pathogens triggering nosocomial infections in paediatrics. Programs to reduce foodborne pathogens in the population would have no or only an indirect impact on nosocomial infections. Therefore in the current study only community-acquired NV and RV cases were considered. STEC O157 is an uncommon cause of illness in the

Netherlands, but is associated with severe illness, in particular Haemolytic Uraemic Syndrome (HUS) in children. Similarly, *Listeria monocytogenes* and *Toxoplasma gondii* are rare causes of disease but are associated with severe illness and high case-fatality ratios. Both pathogens may cause prenatal or perinatal death or congenital disease. It is planned to expand the model in the future for other (foodborne) pathogens and emerging zoonoses.

Outcome trees and incidence

In order to assess the burden of disease and the cost of illness for the various pathogens under study, the disease outcomes following infection need to be defined. Therefore, for each pathogen, separate models of the disease process were designed, resulting in outcome trees. Each block in an outcome tree represents a health outcome and transition probabilities between all blocks must be established. In this study the incidence approach was used to estimate the disease burden and cost of illness, i.e. calculating the present (discounted) expected sum of current and future costs accruing to all incident cases of disease in a specific time period, taking into account age-specific disease risk and related illness costs.

All enteric pathogens may cause acute GE, which in most cases is self-limiting within a few days to weeks. For few patients the disease will be fatal. Apart from GE, no other illnesses are known to be related to a NV infection or a RV infection in humans. Campylobacter and Salmonella infections, however, do occasionally result in complications. Reactive arthritis (ReA) is the most significant sequel occurring after salmonellosis. ReA, Guillain-Barré syndrome (GBS), and inflammatory bowel disease (IBD) are the most significant sequelae occurring after campylobacteriosis. GBS is a neurological disease frequently preceded by an acute infectious illness and affecting at least the motor, sensory, and autonomic nerves supplying the limbs. ReA is an acute aseptic arthritis triggered by an infection elsewhere in the body. Crohn's disease and ulcerative colitis are collectively classified as IBD. IBD is characterized as chronic intestinal disorders of unknown etiology. The frequency of other post-infectious complications following campylobacteriosis or a salmonellosis is low and was therefore disregarded in the current study.

Listeriosis is potentially life-threatening for risk groups like neonates, elderly (especially with co-morbidity) and patients with impaired cell-mediated immunity, mainly because of complications like meningitis and septicemia. Infections in previously healthy individuals may cause febrile gastroenteritis and are usually mild and self-limiting. Infection of pregnant women and their foetuses or newborns may lead to abortion or premature labour. Infected newborns may suffer from severe systemic infection which may result in death or long-term neurological sequelae. *Toxoplasma gondii* infections may be congenitally or postnatally acquired. The severity of congenital toxoplasmosis depends on the stage of pregnancy at the time of infection. Infants born from mothers who acquire their infection in the first and second trimester, more frequently show severe congenital toxoplasmosis or the infection may cause abortion / stillbirth. In contrast, the majority of children born of women who acquire their infection during the third trimester are born with the subclinical form of the infection. Clinical manifestations of congenital toxoplasmosis in the first year of life vary from signs of

the classic triad of toxoplasmosis (chorioretinitis, intracranial calcifications and hydrocephalus) to abnormalities of the central nervous system and neonatal death. Surviving infants may suffer from neurological deficiencies or may develop clinical signs (mostly affecting the eyes) later in life.

Postnatal infection with *T. gondii* in immunocompetent humans is usually asymptomatic. Severe manifestations, such as encephalitis, sepsis/shock, myocarditis, or hepatitis may occur, but are very rare. Chorioretinitis, however, may be an important consequence.

Data

For all enteric pathogens, the incidence of acute GE in the entire population and the fraction of cases visiting a general practitioner (GP) were based on SENSOR, a community based cohort study in 1999, and NIVEL, a GP based cohort study from 1996-1999. Except for NV and STEC O157, incidences were extrapolated to 2004 following the trend observed in laboratory-confirmed cases. Age-distributions were also based on these studies (RV and NV) or on laboratory surveillance because the observed number of cases in SENSOR and NIVEL was too low. The incidence of hospital admission data was based on data from the National Disease Registry for hospitalisation (Prismant), laboratory surveillance, and additionally studies from England/Wales and the US. The incidence of fatal cases was based on international risk estimates, applied to Dutch age-specific incidence data. The incidence of Campylobacter-associated GBS, ReA and IBD and STEC O157 associated HUS was based on previous work. The incidence of Salmonella-associated ReA and IBD was estimated by the same approach as for Campylobacter, using specific risk estimates obtained from the literature.

The incidence of listeriosis and resulting fatalities was based on enhanced surveillance, implemented in the Netherlands since 2005 by the Center for Infectious Disease Epidemiology (RIVM). Data on long-term sequelae were not yet included. The incidence of congenital toxoplasmosis was based on the TIP-study, a cohort study in the South-West of the Netherlands in 1986. The incidence of postnatal Toxoplasma infection was back-calculated from highly uncertain data on the incidence of chorioretinitis not attributed to congenital infections.

Disease burden

The public health impact of different outcomes of infectious disease can be combined in one single measure, the Disability Adjusted Life Year (DALY). DALYs are the sum of years of life lost (YLL) and years lived with disability (YLD). YLL is the number of years of life lost due to early mortality and YLD is the number of years lived with a disability, weighted with a factor between 0 and 1 for the severity of the disability.

The burden of disease, attributable to one agent, is obtained by adding up the impact of all health outcomes associated with this agent. The disease burden is presented both discounted at a rate of 4% and not discounted. Calculating the present (discounted) expected sum of

current and future disease burden is applied because an immediate profit is generally preferred over a profit at a later moment in time.

Severity weights for the different health states were obtained from the Public Health Status and Forecast studies or, GE and GBS on previous specific studies. Estimates on the duration of the adverse health outcomes were derived from the results of earlier studies in the Netherlands, supplemented with the results of international studies.

Cost of illness

Cost of illness (COI) was calculated for NV, RV, thermophilic *Campylobacter* spp. and *Salmonella* spp., taking all costs to society into account. Direct health care costs (DHC), direct non-health care costs (DNHC) and indirect non-health care costs (INHC) were based on Dutch cost estimates for the year 2004. In accordance with current guidelines, we did not consider indirect health care costs, which would comprise the future savings in health care costs in the life years lost due to premature death. Costs are presented both discounted and not discounted.

DHC included medical services such as general practice (GP) consultations, specialists' consultations, hospitalisation, drugs, rehabilitation and other medical services. Travel costs of patients, costs for additional diapers, informal care and co-payments by patients, are some examples of DNHC. INHC are defined as the value of production lost to society due to disease. Production losses could be the consequences of: a) temporary absence from work; b) permanent or long-term disability; and c) premature mortality. Productivity losses were considered for sick individuals and, where available, also for third persons taking care of patients using the friction cost method. The cost estimates as presented in this paper are not exhaustive. In particular, outbreak related costs and the opportunity costs associated with sickness leave from unpaid work have not yet been considered.

Volumes for use of resources and sickness leave were derived using Dutch and international studies. Actual economic costs were derived from Dutch publications and guidelines and, if required, updated to 2004 using published price indices.

Uncertainty

Due to restrictions in available resources, uncertainty analysis for NV, RV, listeriosis and toxoplasmosis was restricted to using low values, most likely values and high values for uncertain parameters only. Variability was not explicitly modelled. Mean or median values were used as point estimates.

For Campylobacter, STEC 0157 and Salmonella, however, second-order stochastic simulation models were available from previous work. With the help of these models it was possible to explicitly and separately model variability and uncertainty. Given that variability is less important from a decision making point of view, it was chosen to present only the uncertainty around the most likely estimate in the disease burden or cost. For Campylobacter-associated ReA and Salmonella-associated ReA, however, the uncertainty was too large to be represented by low, most likely and high values or a single frequency distribution. In that

case, results were calculated using different data sources or assumptions. These scenario analyses were carried out for the incidence of ReA and toxoplasmosis, and for the burden of prenatal deaths.

Results

The incidence estimates as used in the current study are summarized in Tables I and II. The estimates relate to a population of 16 million people in 2004.

Table I. Incidence (cases per year) for selected enteric pathogens in the Netherlands, 2004.

	Incidence estimate (cases per year)		
	Most likely	Low	High
Norovirus GE	470,000	360,000	645,000
No GP	460,000	350,000	625,000
GP	10,000	7,000	16,000
Hospitalisation	1,000	790	2,100
Fatal	5	0	13
Rotavirus GE	190,000	110,000	325,000
No GP	170,000	100,000	305,000
GP	11,000	6,900	17,000
Hospitalisation	3,000	2,000	3,700
Fatal	1.4	0.9	1.7
Campylobacter GE	59,000	25,000	140,000
No GP	45,000	19,000	110,000
GP	14,000	5,000	33,000
Hospitalization	570	500	650
Fatal	25	18	34
Campylobacter sequelae			
GBS	60	40	85
ReA	1,000	430	2,600
IBD	22	17	29
Salmonella GE	35,000	9,000	140,000
No GP	30,000	7,000	110,000
GP only	5,400	700	20,000
Hospitalisation	640	540	740
Fatal	39	34	42
Salmonella sequelae			
ReA	460	100	1,900
IBD	7	6	9
STEC O157 GE	1250	85	7200
No GP	1070	75	6300
GP	180	10	860
Fatal	0.6	na	na
HUS	21	16	29

na: not available

Table II. Incidence (cases per year) for selected non-enteric pathogens in the Netherlands, 2004 (toxoplasmosis) and 2005 (listeriosis).

	Incidence estimate (cases per year)		
	Most likely	Low	High
Listeriosis			
Perinatal - Death	4	0.7	0.7
- Long term sequelae	na	na	na
Acquired - Sepsis	25	15	40
- Meningitis	15	7	30
- Gastroenteritis	15	7	30
- Pneumonia	10	3	20
- Death	10	5	25
- Long term sequelae	2	1	4
Toxoplasmosis			
Postnatal - Still birth	7	6	19
- Chorioretinitis in first year of life	15	5	35
- Intracranial calcifications	11	0	22
- Hydrocephalus	2	0	5
- CNS abnormalities	16	0	30
- Death	0.5	0	1
- Chorioretinitis later in life	18	6	51
Acquired - Mild symptoms	9,300	6,700	11,000
- Severe symptoms (chorioretinitis excluded)	470	0	1,500
- Chorioretinitis	200	0	470

na: not available

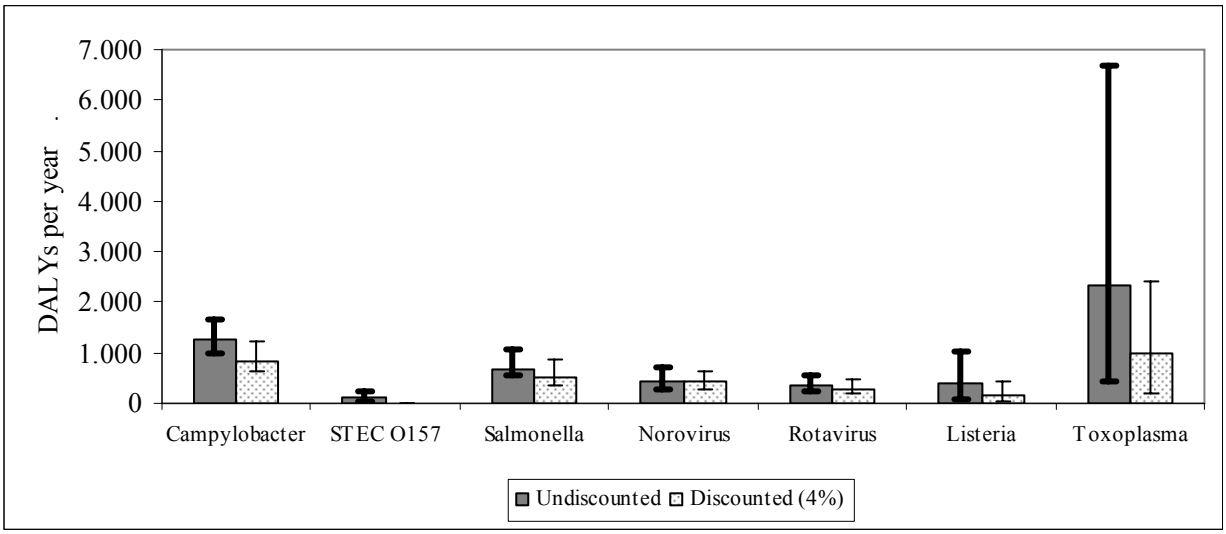


Figure I. Disease burden of infectious diseases that can (also) be transmitted by food in the Netherlands, 2004 (for listeriosis: 2005). The figure shows the total disease burden associated with different pathogens, undiscounted and discounted at 4%, and the uncertainty around the most likely estimate.

In Figure I the estimated disease burden, most likely estimates and uncertainty range are shown, both undiscounted and discounted at 4%. Most likely estimates for YLD, YLL and DALYs separately are summarized in Table III.

Table III. YLD, YLL and DALY estimates for 2004 (for Listeriosis: 2005) (most likely estimates) of infectious diseases that can (also) be transmitted by food in the Netherlands[a]

	Campylobacter	STEC O157	Salmonella	Norovirus	Rotavirus	Listeria	Toxoplasma
YLD	810	30	230	390	260	6	1800
YLL	430	84	440	55	110	380	590
DALY	1300	110	670	450	370	390	2400

[a] Summations do not necessarily tally

The most likely estimates and the uncertainty range of total cost of illness for 2004 for four pathogens are shown in Figure II. Most likely estimates for DHC, DNHC, INHC separately and total costs are summarized in Table IV.

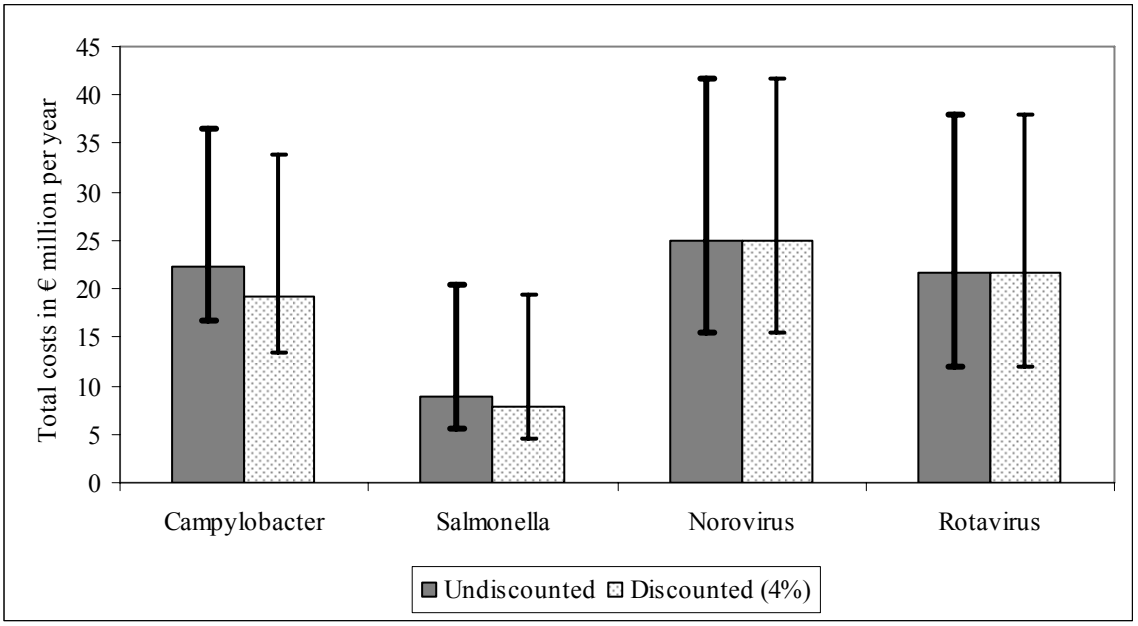


Figure II. Costs-of-illness of infectious diseases that can (also) be transmitted by food in the Netherlands. The figure shows the total costs-of-illness associated with different pathogens, undiscounted and discounted at 4%, and the uncertainty around the most likely estimate for the year 2004.

Table IV. DHC, DNHC, INHC and total costs in € million (most likely estimates) of infectious diseases that can (also) be transmitted by food in the Netherlands, 2004[a]

	Campylobacter	Salmonella	Norovirus	Rotavirus
DHC	10.5	4.0	1.9	7.1
DNHC	0.3	0.1	0.3	0.2
INHC	11.7	4.6	22.8	14.3
Total costs	22.3	8.8	25.0	21.7

[a] Summations do not necessarily tally

The results of our study can also be presented on an individual level instead of a population level. Figures III and IV show the disease burden per case for enteric and non-enteric pathogens, respectively. Note the difference in scale between the two figures, indicating that the individual burden of non-enteric diseases is considerable higher than that of enteric diseases. Discounting has a major effect on the disease burden per case of congential infections.

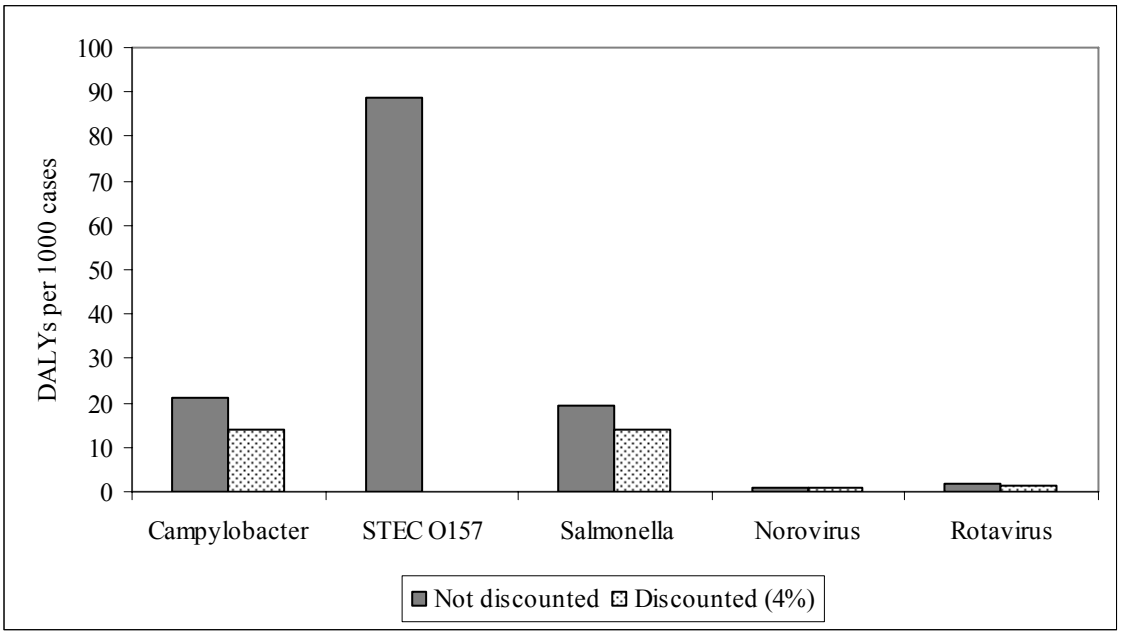


Figure III. Individual disease burden of enteric infectious diseases that can (also) be transmitted by food in the Netherlands, 2004. Data are presented as average burden per1000 cases of gastro-enteritis in the total population.

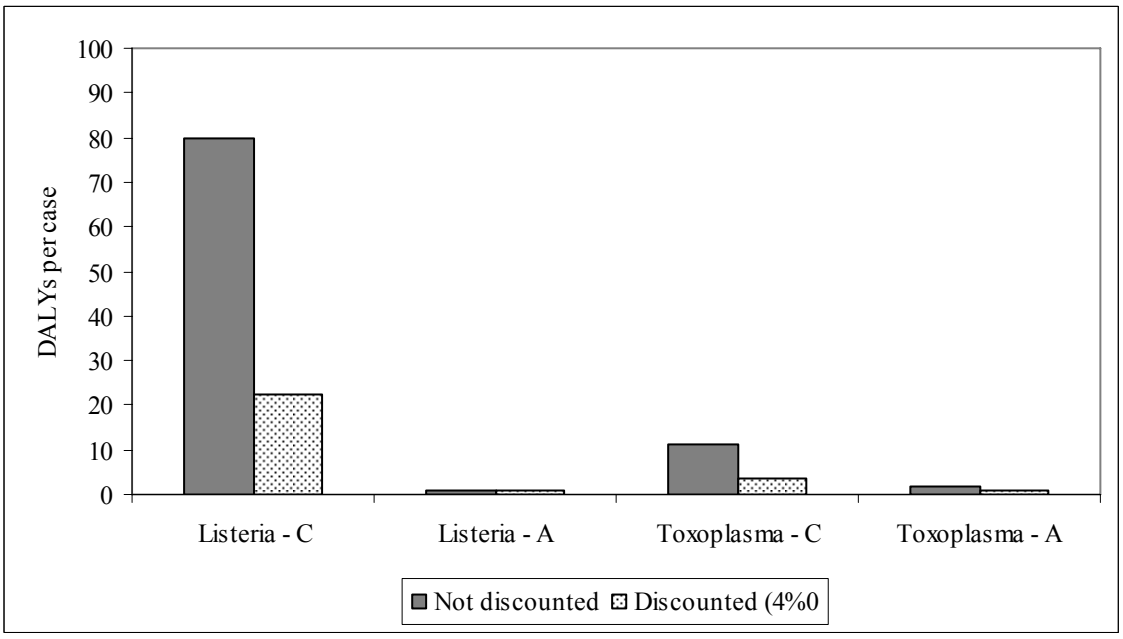


Figure IV. Disease burden of non-enteric infectious diseases that can (also) be transmitted by food in the Netherlands, 2004 (toxoplasmosis) and 2005 (listeriosis). Data are presented as average burden per case of reported congenital or acquired listeriosis, per case of congenital Toxoplasma infection or per case of severe acquired toxoplasmosis. Note the difference in scale with Figure III.

Figure V shows the cost of illness per individual case of gastro-enteritis for four pathogens.

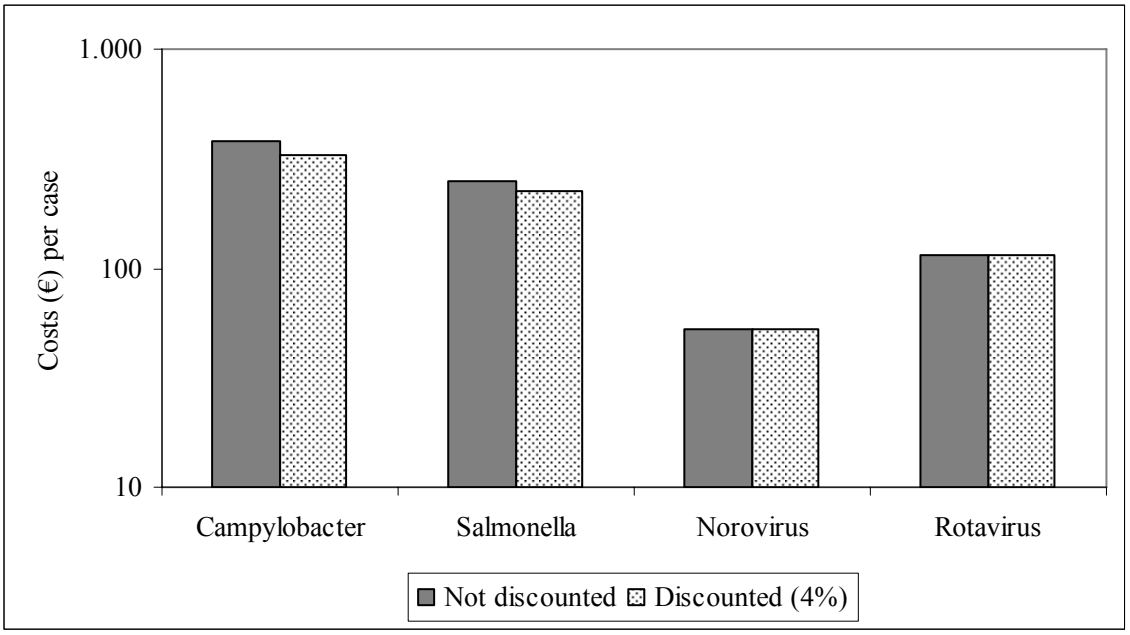


Figure V. Individual cost of illness of enteric infectious diseases that can (also) be transmitted by food in the Netherlands, 2004. Data are presented as average cost per case of gastro-enteritis in the total population.

Scenario analysis was applied for Campylobacter and Salmonella-associated ReA. In the baseline model, it was assumed that only patients visiting a GP would be at risk for ReA. The alternative assumption, that also patients who did not visit their GP would be at risk, raised the total disease burden associated with Campylobacter from 1,300 to 1,500 DALYs per year. For Salmonella the burden would increase from 670 to 870 DALYs per year. The cost of illness estimates would increase by less than € 0.5 million for Campylobacter and less than € 0.2 million for Salmonella.

Incidence data for congenital toxoplasmosis were also subjected to scenario analysis. An indirect estimate based on serosurveillance in 1996 (Pienter study) resulted in an estimated incidence rate of 23 cases per 10,000 live births, which is almost threefold the estimate based on the TIP study. Consequently, the disease burden estimate for congenital toxoplasmosis increased from 1,200 to 2,300 DALYs per year. There are no guidelines how to include the impact of abortion or stillbirth in a DALY estimate. In our baseline model we included all prenatal deaths after a gestation period of 24 weeks. Not including any prenatal death would reduce the disease burden of congenital toxoplasmosis to 630 DALYs. If the data from the Pienter study are used to assess the incidence of acquired toxoplasmosis, the disease burden would increase to 4,000 DALYs. Hence, the total disease burden of toxoplasmosis is highly uncertain, but at least 600 DALYs per year, up to a maximum of 5,700 DALYs per year.

Conclusions

Priority setting is a complex process that involves consideration of many different factors and there is no generally accepted single process that will lead to unequivocal conclusions. It is

therefore not expected, nor desirable, that a project on priority setting will lead to a single list of priorities. Rather, the process of priority setting should help to integrate complex information eventually leading to a structured framework so that it is easily accessible to decision makers, and can easily be updated if new information becomes available. This report presents one step in this direction, by integrating a large body of evidence on the social impact of several infectious diseases that can (also) be transmitted by food into two indicators: disease burden and cost of illness. The choice for these indicators is based on experience from other projects on priority setting. In contrast to other studies on priority setting, a quantitative approach was chosen rather than a qualitative or ranking approach. One advantage of a quantitative approach is that the end result is less dependent on arbitrary choices such as the choice of the type and number of indicators. Also, all factors are weighed in proportion to their true values, instead of on some simplified scale. A disadvantage is that the process is very resource intensive, requiring careful consideration of a large volume of data while many data gaps may exist. Such data gaps result in uncertainties about the final results, but the quantitative approach also helps to prioritize among data needs and to identify key research questions.

Among the pathogens that were evaluated, NV and RV are the agents that cause most cases of gastro-enteritis in the general population. Yet, the disease burden is somewhat lower than that of Salmonella and less than half of that of Campylobacter. This is related to the fact that most cases of viral gastroenteritis are mild, of relatively short duration, and have a low case-fatality ratio. Also, in contrast to viral infections, bacterial gastroenteritis results in more serious sequelae. Often, sequelae associated with bacterial infections are long-lasting and/or chronic, resulting in a considerable disease burden. However, discounting affects the disease burden of both, Campylobacter and Salmonella considerably, because it includes a relatively important component of chronic residual disabilities. For STEC O157, the disease burden in the population is relatively low, but per case it is the highest of all evaluated pathogens. This is mainly related to the relatively high mortality of young children. The disease burden per case of listeriosis and toxoplasmosis is even higher because of high case-fatality ratio's. Even though the incidence of toxoplasmosis in the Dutch population is very uncertain, our results show that on a population basis Toxoplasma causes the highest disease burden of the seven evaluated pathogens. However, it should be kept in mind that in the disease burden calculation of acute GE no threshold value was included so no distinctions were made in duration and severity of the disease. Including a threshold value (for example excluding cases who do not visit the GP for their illness) would probably give more valid estimations. This possibly would have resulted in different ranking of the evaluated pathogens.

Using cost of illness as the indicator, the impact of viral gastroenteritis is somewhat larger than that of Campylobacter. Salmonella has the lowest total COI of the four pathogens considered. In all cases, the indirect health care costs (mainly temporary absence from work) were much higher than the direct health care costs. For chronic and long-lasting diseases, such as those associated with bacterial infections, the direct health care costs do contribute significantly to the total cost. Direct non-health care costs were very low for all four

pathogens. These results show that costs associated with foodborne pathogens may have an impact on very different sectors of the society, namely the public health sector, ill citizens and employers. The effects of discounting are limited because most costs relate to acute effects.

The results show that the relative societal impact of foodborne pathogens differs according to the criteria chosen. For example, are all cases considered or only cases searching medical services; what is the indicator chosen (e.g. incidence of illness, incidence of fatal cases, COI or DALYs); what is the perspective taken (for example the society (all costs) or the public health sector only); is the impact on the total population or on an individual considered.

1. Introduction

The Dutch Ministry of Health, Welfare and Sports wishes to focus its food safety policy on the most relevant pathogens as a basis for effective and efficient decision making on control, prevention and surveillance of foodborne disease. Therefore, the RIVM has been asked to perform a study to establish the priority of pathogenic micro-organisms in food. This report presents the first results of the project. Chapter 1 gives a brief overview of the literature on priority setting of communicable diseases in general and specifically on pathogens in food. It also provides a demarcation of the current project. Chapter 2 describes the methods used in this report. Chapters 3-9 provide information on the primary indicators chosen for priority setting, disease burden and cost of illness, for key enteric pathogens that are (also) transmitted by food and discuss pathogen-specific issues. Finally, Chapter 10 gives a general discussion of the results obtained so far and an outlook on further work.

1.1 Review of existing literature

In several countries, priority setting of communicable diseases and foodborne pathogens has been studied. In the next paragraphs a short overview of these studies is given, as available at the start of the project (beginning 2004)[1].

1.1.1 Surveillance of communicable diseases

Since 1988 several studies have been performed to assess which communicable diseases warranted surveillance. In the studies of the Canadian National Advisory Committee on Epidemiology[1 2] on priority setting of several communicable diseases, the sum of the scores on different criteria (i.e. international considerations, other sector interest, incidence, severity, potential to spread to the general population, socioeconomic burden, preventability potential to drive public health policy, risk perception, appearing to or changing patterns over the past five years) were ordered, resulting in an estimation of the importance of the disease for national surveillance. The results of their first study[1] showed that from all communicable diseases that were under surveillance, three foodborne pathogens ranked high: salmonellosis (rank 6), botulism (rank 16), and hepatitis A (rank 17). The same kind of strategy was followed in their study in 1998[2]. Now botulism (rank 10), Creutzfeld-Jacob disease (rank 12), salmonellosis (rank 16) and hepatitis A (rank 17) were the most important foodborne infections.

In early 1997, the Overview of Communicable Diseases Committee from the Public Health Laboratory Service in the UK carried out a consultation exercise to inform the development of PHLS priorities in communicable diseases for the years 1997 to 1999[3]. The views of PHLS senior staff and scientific committees and consultants in communicable disease control in district health authorities were sought by postal questionnaire, and several organizations of health professionals were asked for their views on the initial findings. The main findings of the exercise were summarized in three areas of priority. High priority foodborne diseases

were: *Campylobacter jejuni/coli*, Salmonella infections, antimicrobial resistant *Salmonella Typhimurium* DT104 infections, Verocytotoxin producing *Escherichia coli* O157, viral gastroenteritis (rotavirus and SRSV), and Creutzfeld-Jacob/prion disease. In their study in 1999, the most important foodborne diseases were: *E. coli* O157 (rank 6), salmonellosis (rank 8) and Campylobacter infections (rank 12)[4]. More recent studies have not been found.

1.1.2 Food safety

Four publications were found which studied the prioritization of foodborne pathogens more specifically. In a study of the American Food Safety and Inspection Service[5] infectious agents transmissible to humans through consumption of undercooked beef were prioritized. Each infectious agent was numerically scored based on potential hazard and potential exposure to human. Highest scores were found for *Escherichia coli* O157, *Salmonella* spp. and *Listeria monocytogenes*.

In 2002, Ross and Sumner described the development and use of a simple tool for semi-quantitative food safety risk assessment, which has utility for ranking and prioritizing risks from diverse sources[6]. This tool was used to generate a risk ranking for 10 seafood hazard/product combinations[7]. Highest priorities were found for algal biotoxins from uncontrolled waters in an algal event, viruses in shellfish from contaminated waters, and ciguatera from recreational fishing in susceptible areas.

In Canada, the Ontario Ministry of Agriculture and Food is developing a method of systematically ranking food-safety-risks to help prioritize the allocation of food safety resources[8]. Results from this project are not yet available.

In the USA, the Food Safety Research Consortium is developing decision tools for policy makers to better identify and prioritize opportunities to reduce-food-safety risks and allocate government resources accordingly. With the model, users can produce rankings by pathogens, by food, and by pathogen-food combination, according to five measures of the impact on public health: number of cases of illness, number of hospitalizations, number of deaths, monetary valuations of health outcomes, and loss of Quality Adjusted Life Years. The model uses a quantitative approach and quantifies the uncertainty of rankings and other results. In practice, the final ranking of the pathogens and pathogen-food combinations depend highly on the criteria[9].

1.1.3 Evaluation

Except for one, all studies are based on a semi-quantitative approach: the scores on several criteria (see 2.1.1) are summed to an overall score. However, comparing the studies shows important differences between them with regard to the number of criteria used and the number of criteria per domain (i.e. disease burden, social costs, trends, response, perception, organisation interest, exposure, infectivity). As a consequence, the overall score is dependent on the number of criteria per domain: domains with more than one criterion have implicitly

[1] Detailed summaries of results are available from the authors

more weight compared to domains with only one criterion. Also, the arithmetic method for calculating the overall scores differs between the studies which make them less comparable, and the attribution of scores to criteria is arbitrary. For example: is a disease with a high incidence and a low severity (e.g. scores 5 and 1 on the Canadian scale) equally important compared to a disease with a moderate incidence and severity (both score 3)? And do combinations of incidence and severity add as much weight as the sum of scores for risk perception and interest in other sectors? There is no objective basis to combine such highly divergent criteria on the same scale and then simply add up all scores. In this respect, more recent studies in the food safety domain are more balanced; they are based on a more consistent view of the relatedness between different criteria and try to design scales so that they reflect the actual risks. Another disadvantage of the attribution of scores to intervals is the loss of information. For example, if intervals for the incidence of illness are arbitrarily defined as 100-1000 and 1,000-10,000, then two diseases with incidences of 900 and 1,100 would carry different weights, whereas disease with incidence 1,100 and 9,000 would not.

So, the validity of semi-quantitative studies is doubtful, and it is difficult to develop consistent criteria and scores. Therefore, in the present study we will use a quantitative approach, although we have to keep in mind that it is important to quantify the uncertainty of the results caused by insufficient data.

1.2 Criteria for priority setting

1.2.1 Disease burden

The previous review showed that disease burden is an important domain. This is in line with general trends in public health research that increasingly present disease burden as a major tool for priority setting. Some examples are the Global Burden of Disease Study by WHO and the World Bank[10] and the Dutch series of Public Health Forecast studies[11]. Accordingly, in the present study, disease burden will be used as primary criterion for the prioritization of foodborne pathogens. To calculate the disease burden an epidemiologic approach will be used, i.e. the surveillance of food-related morbidity and mortality in the Dutch population. Another approach would be one based on risk estimates, which is based on the surveillance of incidence of pathogens in the food chain, combined with consumption and dose-response data. A disadvantage of the latter approach is the lack of data. Besides that, it requires separated risk-assessments for many combinations of pathogens and foods which is unfeasible. Finally, information about the morbidity and mortality gives a better picture of the influence of foodborne infections on public health, compared to data about microbial concentrations in food.

1.2.2 Cost of illness

Besides the burden of disease, the costs for the Dutch society of foodborne infections are important as well. Therefore, in the present project we will calculate the direct health care costs and direct non-health care costs as well as indirect non-health care costs associated with foodborne infections and its sequelae. For time reasons, we estimate the cost-of-illness only

for those pathogens for which the disease burden is calculated. For some relevant syndromes (like gastroenteritis and Guillain-Barré syndrome) the costs will be derived from previous Dutch studies[12 13]. For other syndromes the costs will be derived from international studies. The costs per case for the different illnesses and the different health states combined with the incidence of the syndromes provide us the total costs-of-illness per pathogen.

1.2.3 Food attributable fraction

The estimated incidence and valuation of illnesses caused by each pathogen will be attributed, by percentage, to food (categories), to obtain estimated incidence and valuation of illnesses caused by each pathogen-food combination. Although in the current report not yet applied, in a later stage the disease burden and cost of illness for the selected pathogens will be expressed in a food attributive fraction. Depending on the availability of the data, the estimates of these food attributed fractions will be based on outbreak studies, case-control studies and expert elicitation.

1.2.4 Trends

Although in some cases the disease burden is still relatively limited, from a policy view an upward trend may be important. Also a downward trend may indicate the efficacy of the current effort. For such reasons, in the present project trends in incidence will be analyzed. Depending on the pathogen and the availability of data, the results will be descriptive or based on regression analysis. Besides trends in incidence, trends in prevalence in the food chain will be assessed as well. The prevalence for a specific pathogen can vary due to changes in the degree of contamination of domestic or imported food products, changes in the consumption pattern, or changes in volume and origin of imported food. All these trends will be assessed qualitatively.

1.2.5 Involved food products and effectiveness of preventive measures

For all pathogens the proportion of attribution to different food products or categories will be estimated. Some pathogens, like *Taenia saginata*, can only be transmitted by one product, so this proportion is equal to the total food attributive fraction. Other pathogens can be transmitted by several products. The proportion for each food category will be estimated (quantitatively, when possible) in such a way that the summation is equal to the food attributive fraction. Data for these estimations will be derived from literature and expert elicitation. In the analysis, the uncertainty in the estimates will be taken into account. For the most important pathogens, in terms of disease burden, preventive measures for reducing disease burden will be studied qualitatively. Furthermore, the expected efficacy of these measures and related costs will be indicated.

1.2.6 Perception

The risk concept does not consist exclusively of objectively measurable characteristics of systems but is also a social construct, in which qualitative, socio-psychological characteristics play an important role. This is how existing large differences in money spent on reducing

health risks – where the yield is expressed in terms of postponing death or extending (healthy) life expectancy – are largely explained. So, besides quantitative criteria, subjective criteria play an important role in the risk perception among the general population.

1.2.7 Other criteria

Besides the criteria included in phase 3, several other criteria are theoretically relevant to study, like health benefits gained in the past, and the efficacy of food inspection. However, making these criteria operational is difficult. Therefore, prioritizing food born pathogens is limited to the earlier mentioned criteria.

1.3 Demarcation of the project

It is impossible to collect and interpret the necessary data for calculating disease burden for all foodborne pathogens. So, the disease burden was only calculated for the most important pathogens. Therefore, pathogens who met one or more of the following criteria were excluded:

1. The incidence in the Netherlands is low (< 20, usually 10 cases per year on a population of 16 million);
2. The infection is usually contracted during a stay in a foreign country;
3. The etiologic significance of the pathogen is not well established.

The results of this selection are shown in Table 1. The remaining pathogens are summarized in Table 2.

Table 1. Eliminated pathogens with reasons for elimination.

Pathogen	Criterion[1]	Remarks
Aeromonas spp.	3	
Brucella melitensis/abortus/suis	1, 2	IGZ[2]: 3
Coxiella burnettii	1	IGZ: 11, average for 1988-2001: 19[14]
Enterobacter sakazakii	1	Since 1958 worldwide 70 cases reported[15]
Francisella tularensis	1, 2	0 cases per year[16]
Myobacterium bovis	1, 2	
Myobacterium avium ssp. *paratuberculosis*	3	
Salmonella (para)typhi	2	IGZ: 56; stay abroad in > 80% of the cases[17]
Vibrio cholerae	1, 2	IGZ: 2
Clostridium botulinum	1	IGZ: 1
BSE prion	1	IGZ: 0
Cyclospora cayatenensis	1	
Entamoeba histolytica	2	
Anisakis simplex	1	
Echinococcus granulosis	1, 2[3]	
Echinococcus multilocularis	1, 2[3]	[18]
Fasciaola hepatica	1	
Taenia solium	1, 2[3]	
Trichinella spiralis	1, 2	[19]

[1] 1 = low incidence; 2 = infection contracted mainly during stay abroad; 3 = aetiology not established

[2] Number of reported cases by the Dutch Health Care Inspectorate (per year), average for 1998-2002[20]

[3] Personal communication J. van der Giessen, RIVM/MGB

Table 2. Selected micro-organisms for calculation of their disease burden.

Bacteria - infectious	**Viruses**	**Protozoa**
Arcobacter spp.	Adenovirus	*Cryptosporidium*
Campylobacter spp.*[#]	Astrovirus	*parvum*
Escherichia coli – Shiga-toxin producing*	Enteroviruses	*Giardia lamblia*
Escherichia coli – other	Hepatitis-A virus	*Toxoplasma gondii**
*Listeria monocytogenes**	Hepatitis-E virus	
Myobacterium avium ssp. *avium*	Norovirus*[#]	
Salmonella spp. – other*[#]	Rotavirus*[#]	**Helminths**
Shigella spp.	Sapovirus	*Taenia saginata*
Vibrio – marine species		
Yersinia enterocolitica		
Bacteria - toxin producing		
Bacillus cereus		
Clostridium perfringens		
Staphylococcus aureus		

Note: the present report concentrates on disease burden estimates for pathogens marked with an asterix (*) and cost of illness estimates for pathogens marked with a cross ([#]).

2. Methods

2.1 Outcome trees and incidence

In order to assess the burden of disease and the cost-of-illness for the various pathogens under study, the disease outcomes following each specific exposure and ingestion or infection had to be defined. Therefore for each pathogen, separate models of the disease process had to be collected or designed, resulting in outcome trees. Each block represents a health outcome and transition probabilities between all blocks must be established. In this study we used the incidence approach to estimate the disease burden and cost-of-illness. In the incidence approach, the disease burden and costs-of-illness are defined as the present discounted expected sum of current and future DALYs and costs accruing to all incident cases of disease in a specific time period, taking into account lifetime probabilities of transiting to each disease state[21]. In the present study, data for the various outcome trees were abstracted, where available, from Dutch sources and international literature.

2.2 Disease burden

2.2.1 Calculation of the disease burden

The different outcomes of infectious disease can be combined in one single measure, the Disability Adjusted Life Year (DALY), following the methodology proposed by Murray and co-workers[22 23]

$$\text{DALY} = \text{YLL} + \text{YLD}$$

YLL is the number of years of life lost due to mortality and YLD is the number of years lived with a disability, weighted with a factor between 0 and 1 for the severity of the disability. The YLL due to a specific disease in a specified population is calculated by summation of all fatal cases (n) due to the health outcomes (l) of that specific disease, each case multiplied by the expected individual life span (e) at the age of death. Thus:

$$YLL = \sum_{l} d_l \times e_l$$

We derive the expected life span of fatal cases from the standard life tables as reported by Statistics Netherlands or used specific life expectancies for sensitive subgroups as necessary.

YLD is calculated by accumulation over all cases (n) and all health outcomes (l) of the product of the duration of the illness (t) and the severity weight (w) of a specific disease:

$$YLD = \sum_{l} n_l \times t_l \times w_l$$

Information on the incidence of illness and death is typically objective data derived from clinical, epidemiological and surveillance studies, whereas information on severity weights is typically derived from elicitation of special panels, preferably from the general population.

Elicitation follows an elaborative protocol. Patients are not well-suited to value their own health or disease state due to coping effects, or, if being aware of the purpose of the use of these data, for risk of aggravation.

The following data were needed for the calculation of DALYs:

Morbidity and mortality

To assess the morbidity and mortality for pathogens, all relevant syndromes associated with a specific pathogen, fatal or not, should be determined. For most of the pathogens, gastroenteritis is the most common syndrome. However, for a number of pathogens, other syndromes are also important.

For all relevant syndromes the incidence was estimated for 2004, based on syndrome and/or laboratory surveillance data including relevant trends. When no incidence data for the general population were available, data from other sources were used and the degree of underreporting was estimated.

Duration of the disease

Estimates on the duration of the adverse health outcomes were preferably derived from Dutch studies and where necessary, supplemented with international studies or outbreak studies. Due to selection bias towards more severe and long-term disease, data from laboratory surveillance are not representative for disease in the general populations.

Life expectancy

The mean age of death could be derived from several sources: registrations from Statistics Netherlands for 2004, results from outbreak studies and more specific epidemiological surveys. The life expectancy was based on standard life tables for the general population from Statistics Netherlands. If certain pathogens are associated with severe co-morbidity, life expectancy was, if possible, adjusted for the reduced life span due to these others diseases.

Severity of the disease

The DALY uses explicit preference weights for health status. A major project had been carried out to derive weights for 53 diseases of public health importance, involving the estimation of weights for 175 disease stages and/or severity levels[24 25]. These weights have the advantage of great detail in terms of severity levels and disease stages. Furthermore, weights for severity were derived from ongoing research in the Netherlands[26]. Otherwise, severity weights were based on analogous diseases for which weights were already available. For example, for sepsis no severity weight is available. Because of the low incidence, the Dutch Burden of Disease Group decided not to derive a disability weight for this disease. Therefore, we derived a severity weight by taking the disability weight of a disease with a comparable Euroqol-code (i.e. Euroqol-code of sepsis is 333333; Euroqol-code of the terminal stage of an unspecified disease is 333332 with a severity weight 0.93[25]). In that case, when necessary the uncertainty was assessed by scenario analysis. The disability weights used in this report are mentioned in Table 3.

Table 3. Disability weights used in this report.

	Disability weight	Source
Chorioretinitis	0.17	Haagsma *et al.* (2005) [26]
CNS abnormalities	0.09	Melse *et al.* (1998) [25]
Death	1.00	
Gastroenteritis		
Not visiting GP	0.067	Havelaar *et al.* (2000a, b)[27 28]
Visiting GP	0.393	Havelaar *et al*. (2000a, b) [28,27]
Hospitalized	0.393	Havelaar et al (2000a, b) [28,27]
Guillain-Barré Syndrome (GBS) [a]		
F-score 1	0.10	Havelaar *et al*. (2000b) [27]
F-score 2	0.30	Havelaar *et al.* (2000b) [27]
F-score 3	0.44	Havelaar *et al.* (2000b) [27]
F-score 4	0.80	Havelaar *et al.* (2000b) [27]
F-score 5	0.94	Havelaar *et al.* (2000b) [27]
Hydrocephalus [b]	0.36	Melse *et al.* (1998) [25]
Inflammatory bowel disease (IBD)	0.26	Mangen *et al.* (2004, 2005)[12 29 h]
Intracranial calcifications[c]	0.01	Melse *et al.* (1998) [25]
Listeriosis		
Mild symptoms (not further specified)[c]	0.01	Melse *et al*. (1998) [25]
Severe symptoms (not further specified)[g]	0.11	Melse *et al*. (1998) [25]
Meningitis	0.32	Melse *et al.* (1998) [25]
Neurological disorders[d]	0.25	Melse *et al*. (1998) [25]
Pneumonia	0.04	Melse *et al*. (1998) [25]
Reactive arthritis (ReA) [e]		
Not visiting GP	0.127	Melse *et al*. (1998) [25]
Visiting GP	0.21	Melse *et al*. (1998) [25]
Hospitalized	0.37	Melse *et al*. (1998) [25]
Sepsis[f]	0.93	Melse *et al*. (1998) [25]

[a] The functional status of patients with GBS is scored on a seven-point disability scale, ranking from F-score 0 = healthy (severity weight is 0); to F-score 6 = Death (severity weight is equal to 1).

[b] Disability weight derived from the disease description 'Residual symptoms after bacterial infection after birth'

[c] Disability weight derived from the disease description 'no to mild difficulties with activities of daily life (ADL)'

[d] Disability weight derived from the disease description 'cognitive restrictions after bacterial meningitis'

[e] Similar as Mangen *et al*. [12 29] we used disability weights for mild and moderate rheumatoid arthritis, which were derived from Melse *et al*.[25].

[f] Disability weight derived from the disease description 'terminal stage of an unspecified disease'

[g] Disability weight derived from the disease description 'large difficulties or not able to ADL'

[h] Assuming an average clinical course of an average IBD patient, based on Silverstein *et al*.[30], Mangen *et al*.[12 29] estimated the average disability weight /case, using disability weights derived from Melse *et al*. [25] for different stages.

2.3 Cost of illness

2.3.1 General approach

Besides the estimation of the burden of disease for the various pathogens under study, the associated costs-of-illness (COI) were estimated. Cost-of-illness studies were applied for

each pathogen separately, using the societal perspective. Following the guidelines of Oostenbrink *et al*.[31], we estimated the cost-of-illness, considering direct health care costs, direct non-health care costs and indirect non-health care costs, using cost estimates for the year 2004. In accordance with the guidelines of Oostenbrink *et al*.[31], this study did not consider indirect health care costs. Indirect health care costs would comprise the future savings in health care costs in the life years lost due to premature death.

Direct health care costs (DHC)

The direct health care cost category included valuation for medical services such as general practice (GP) consultations, specialists' consultations, hospitalisation, drugs, rehabilitation and other medical services. The direct health care costs were estimated for each pathogen separately, the total direct health care costs were estimated by accumulating the costs for the different medical services for all illness and for all disease severity states related to this pathogen.

For each health outcomes (*l*) of that specific disease and for each specific medical service, the direct health care costs related to a specific pathogen were estimated by multiplying the number of cases requiring health care service (*m*) by the required health care service units per case (*p*) and by the costs per health care service unit (*mc*). The formula for direct health care costs for a specific pathogen for health outcomes *l* and for health care service *i* are in basic notation:

$$DHC = \sum_{l} \left(\sum_{i} m_i \times p_i \times mc_i \right)_l$$

Direct non-health care costs (DNHC)

Travel costs of patients, costs for additional diapers, informal care and co-payments by patients, are some examples of direct non-health care costs. The direct non-health care costs were estimated for each pathogen separately. For each health outcomes (*l*) of that specific disease and for each specific non-health care service j, the direct non-health care costs related to a specific pathogen were estimated by multiplying the number of cases requiring non-health care service (*r*) by the required non-health care service units per case (*q*) and by the costs per non-health care service unit (*rc*). The formula for direct non-health care costs for a specific pathogen for health outcomes *l* and for non-health care service *j* are in basic notation:

$$DNHC = \sum_{l} \left(\sum_{j} r_j \times q_j \times rc_j \right)_l$$

Indirect non-health care costs (INHC)

Indirect non-health care costs, which are defined as the value of production lost to society due to disease, were considered in the current study. Production losses could be the consequences of: a) temporary absence from work; b) permanent or long-term disability; and c) premature mortality. We estimated the productivity losses that occur due to sickness leave of sick

individuals, and, where available, information on third persons taking care of patients. In this study we applied the friction cost method to estimate the indirect non-health care costs. In this method, production losses are only considered for the period needed to replace a sick, invalid or dead worker, the so-called 'friction period[32 33]. The friction cost method takes into account the economic processes a sick, invalid or dead person can and will be replaced after a period of adaptation[32]. The length of the friction period depends on the situation on the labour market. A high unemployment rate generally allows fast replacement of a sick, invalid or dead person, whereas in the case of a low unemployment rate, on average more time is needed to find someone on the labour market that could fill in the position. We assumed for the year 2004 a friction period of 154 days, similar to the friction period reported in Oostenbrink *et al*.[31] for the year 2002.

The indirect non-health care costs for a specific pathogen were estimated for each health outcomes (*l*) of that specific disease and for each types of sickness leave (*k*) separately by multiplying the number of cases with sickness leave (s) by the duration of sickness leave (u) by the wage costs (v) per day. The formula for indirect non-health care costs for a specific pathogen for health outcomes *l* and for each episode of sickness leave *k* are in basic notation:

$$INHC = \sum_{l}\left(\sum_{k} s_k \times u_k \times v_k\right)_l$$

General

To calculate the cost-of-illness for the different pathogens, we needed data on the number of cases per age group, the volumes for use of resources and the actual economic costs of each of these items. We needed the information per age group, because of differences in incidence and type of costs (e.g. sickness leave). Details with respect to the assumptions made for the different cost categories are given either in section 2.3.2, if applicable to all pathogens, or are described in more detail in the subsequent chapters, if disease specific.

For some relevant syndromes the associated costs were derived from previous Dutch studies[12] and updated to the year 2004. For pathogens where no Dutch cost studies were available, we used published data on medical use and sickness leave, assuming that these data would be similar for the Netherlands. However, wherever possible, Dutch cost unit prices for medical use and sickness leave for the year 2004 were used when estimating the related costs-of-illness for these pathogens.

2.3.2 Assumptions made

Drug use

The only direct health care costs of gastroenteritis patients (GE) not visiting a GP are those for over-the-counter medicines. GE patients visiting a GP, whether hospitalised or not, also use over-the-counter medicines. But apart from these medicines, patients might also have a prescription from their doctor for antibiotics or the like. Hardly any information was available on the drug use for GE cases with specific pathogens, neither over-the-counter medicine nor

other drugs. The only available information on medicine use was that collected in the SENSOR study[34], a community-based cohort study conducted in 1999 in the Netherlands. In this study, data on the drug use in the Netherlands of GE cases not visiting a GP and GE cases visiting a GP were collected[13]. The percentage of patients using medicines, as observed in SENSOR, is summarised in Table 4.

Table 4. Percentage of patients not visiting a GP and patients visiting a GP, respectively, using painkillers, oral dehydration solution (ORS), anti-diarrhoea, antibiotics and other medicines as reported in the SENSOR study (Source: Mangen et al. [12]).

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

n.a. = not applicable

Based on this information, average costs for drug use of patients not visiting a GP and patients visiting a GP, respectively, were estimated. Results are reported in Table 5. We do know that for small children, in the case of GE, painkillers are hardly used. But on the other hand, ORS and anti-diarrhoea application might be more common in small children than found in the SENSOR study. Therefore, the here presented average drug costs are only an approximation of the potential daily drug costs.

Table 5. Average costs for over-the-counter medicine (in €) per day per patient for GE patients not visiting a GP and GE patients visiting a GP, respectively, and average costs for prescription medicine (in €) per patient for GE patients visiting a GP.

	Average costs of over-the-counter medicine (in €) per day per patient	Average costs of prescription medicine (including prescription fee) (in €) per patient
Not visiting a GP	0.2	-
Visiting a GP (hospitalised and not hospitalised)	0.5	37.1

GP consultation

Consultation of a GP in the Netherlands might occur either by phone, by a GP practice visit or by a house call from the GP to the patient. Although, inquired by De Wit *et al.*[35], GP telephone consultations of the doctors' assistant were not included as consultations in their analyses when estimating the incidence of GE cases visiting a GP. Of the considered GP consultations, approximately 90% were GP practice visits and the remaining 10% were house calls from the GP to the patient[35]. But also the telephone consultations of the doctors'

assistant are a health care service that does cost money. For the recorded 61 GP consultations in the community-based study of De Wit *et al*.[35], an additional 59 telephone consultations were reported. Based on these figures, we assumed that on average per estimated GP consultation 0.97 additional telephone consultations would occur. For sensitivity reasons, we assumed in our *low* cost estimate that GP consultations would be limited to GP practice visits, and costs for telephone consultation were not considered in the *low* cost estimate. No information were available that would have allowed us a realistic estimate of even more GP consultations than assumed for the most likely estimate. We therefore assumed, similar as for the most likely value that per average estimated GP consultation 0.97 additional telephone consultations would occur. The unit prices for the different GP consultation services are reported in Table 6.

Laboratory-confirmed cases

For some of the patients consulting their GP, a faecal sample is submitted for laboratory testing in order to determine the etiologic agent. In this study we assumed that for each hospitalised patient a faecal sample was submitted for laboratory testing. Subtracting the estimated hospitalised cases from the total number of estimated laboratory-tested positive pathogen-specific cases[36 37], we obtained the number of laboratory-tested positive pathogen-specific cases within the group of patients that only visited a GP. Assuming that in general 6 pathogens would be tested, similar as van den Brandhof *et al*.[13]; the costs for testing were estimated to be € 67/sample submitted (see Table 6).

Hospitalisation

In the Dutch public health system where the GP is the 'gatekeeper' to specialized care, hospitalised patients were assumed to have visited their GP first, before being transferred to a hospital. Based on the total number of Dutch hospital beds, we assumed that approximately 14% of the patients would be admitted to a university hospital and 86% would be admitted to a general hospital[38]. If not otherwise stated, we assumed that GE patients would stay in a regular ward room and not in an intensive care unit (ICU). According to the Dutch system, we calculated for each GE patient admitted to the hospital a 'short subscription'[2] for a paediatrician, if younger than 9 years, and an internist, if 9 years and older. For most medical services we used the cost estimates as reported by Oostenbrink *et al*.[31], but updated to 2004. Furthermore, it was assumed that for each hospitalised GE patients a faecal sample was submitted for laboratory testing. The different costs assumed per medical unit used are given in Table 6.

[2] In the Netherlands, apart from their consultation fee and their medical services, specialists charge their patients a so-called 'subscription fee'. Different forms of fees exist. The short subscription fee is valid for about 1-2 months. If patients return after those 1-2 months an 'additional subscription fee' is charged that is then valid for the rest of the year. Patients who need a longer treatment are charged an 'annual subscription fee'. These fees vary from specialist to specialist. However, only one specialist is allowed to charge these subscription fees per illness. A second specialist involved in the treatment of the illness can only charge what is referred to as a 'clinical subscription fee', which is less than the normal subscription fee. For more details see CTG[40].

Table 6. Cost estimates per medical service unit for 2004.

Medical service	Costs/unit (in €)	Source
GP consultation by phone	10	Oostenbrink *et al.*[31]
GP practice visit	21	Oostenbrink *et al.*[31]
House call from the GP	41	Oostenbrink *et al.*[31]
Faecal sample	67	Van den Brandhof *et al.*[13]
Hospitalisation: Ward room/day	367 [a]	Oostenbrink *et al.*[31]
Hospitalisation children: Ward room/day	461	Hoogendoorn *et al.*[39] [b]
Hospitalisation: ICU/day	1721	Oostenbrink *et al.*[31]
'Short subscription fee' for an internist	62	CTG [40]
'Short subscription fee' for a paediatrician	88	CTG [40]

[a)] Hospitalisation in a ward room costs in a general hospital € 344 per day and in a university hospital € 486 per day.
[b)] Based on Hoogendorn *et al*[39], the costs for a children ward room were assumed to be 1.3 times higher than for adults.

Travel costs

We assumed, similar as Mangen *et al.*[29], that no additional travelling was required in order to buy over-the-counter medicines. Medicines on prescription were assumed to be bought in a pharmacy on the way back from the GP. Travel costs were only considered when visiting a GP and when being hospitalised. According to Oostenbrink *et al.*[31] the average distance from a patient's home to their GP in the Netherlands is approximately 1.8 km and from a patient's home to a hospital approximately 7 km. The cost of travelling with public transport or private car was assumed to be approximately € 0.16/km in 2004[31]. The cost of travelling by car, no parking fees included, or public transport in order to visit a GP was therefore estimated to be € 0.6 per visit, and travelling to a hospital/specialist was estimated to cost € 2.3 per visit. Average parking fees were assumed to be € 2.6 [31]. However, no information was available about what transport services patients used. We therefore assumed in this study, similar to Mangen *et al.*[29] that hospitalised patients would have always used either a car or public transport. While for patients visiting their GP, we did assume that most likely half of the patients would bike or walk, whereas the other half would take a car or public transport, following the assumption made by van den Brandhof *et al.*[13]. For our *low* (*high*) *cost estimate* we assumed that 10% (90%) of the patients would take either a car or public transport. When travelling by car or public transport, we further assumed that half of the patients would have taken a car and the other half would have used public transports.

Cost for additional diapers

If babies and small children do have GE, the daily use of diapers is increased. These are direct non-health care costs paid by the parents. In the current study it was assumed that the daily use during illness would have increased most likely by 2 diapers for each child between 0 and 3 years old, ranging from minimum 1 additional diaper (*low cost estimate*) to maximum 4 additional diapers (*high cost estimate*). The costs per diaper, including a baby wipe, were assumed to be € 0.3 in 2004, based on the estimations of Welte *et al.*[41]

Informal care

No information was available on informal care, for example time costs of a neighbour taking care of a sick child. Therefore the costs for informal care were not considered in this study.

Sickness leaves

The duration of sickness leave corresponds only to the length of the period in which patients are absent from paid work because of illness. Productivity losses due to sickness leave are only estimated for patients in the working life years, which is in the Netherlands every person between 15 and 64 years as defined by Statistics Netherlands.

In order to determine the indirect non-health care costs, we need to know for each pathogen and for the different illnesses and disease severity grades separately, the duration of sickness leave. However, information on sickness leave is rather scarce in the Netherlands. During the SENSOR study, additional data with respect to sickness and sickness leave were collected from 50 GE patients, who were between 18 and 64 years old and that had not visited a GP[13]. The average number of days with symptoms for these 50 cases was 8.2 days. But only seven of the 50 cases, or 14%, reported to have been absent from paid work for an average duration of 5.1 days. This corresponded to an overall average absence from paid work of 0.7 days, or 9% of the average duration of illness, per GE patient in working life age and not visiting a GP. For all pathogens where we did not have detailed information, the assumption was made, that, if adult, the number of days of paid employment lost corresponded to approximately 9% of the average pathogen-specific length of illness in the most likely situation. This was slightly lower than found in the English IID study for the community component, - but including both, community cases not consulting a GP and community cases consulting a GP-, where the number of days of paid employment lost, if adult, was 11.7%[3] of the average duration of illness [42 43]. However, if the calculated number of days absent from paid employment for a specific pathogen was higher (lower) than published elsewhere, we considered the published values for sensitivity reasons in our *high cost estimate* (*low cost estimate*). The average productivity losses used for an average working person in the working life population was € 36.5 per hour off work (see Table 7).

The severities of symptoms are in general worse for patients visiting a GP, than for those who do not visit a GP. For the patients in the GP case-control component from the English IID study, the number of days of paid employment lost, if adult, was approximately 28.4% of the average duration of illness [42 43]. According to de Wit *et al*.[44] 60% of working patients, who consulted a GP because of GE symptoms, were absent from work for an average duration of 3.1 days (median duration 2 days). In 2004, approximately 64% of all persons between 15 and 64 did have a paid employment[45]. We therefore assumed that for all GE patients between 15 and 64 years old and visiting a GP, 38% would be absent from paid employment for an

[3] The overall average of number of days paid employment lost in the community component, if adult, was 0.46 days. The average number of days of illness for *all* GE patients (n=555) in the community component was 3.92 days. By dividing 0.46 by 3.92, we obtained the 11.7%.

average of 3.1 days. De Wit *et al*. [44] did report only the median duration of symptoms before a GP was consulted to be 6 days. But no information was collected about the average total length of illness. For simplification reasons, we therefore assumed that the average length of symptoms for GE patients visiting a GP in the Netherlands would be similar to the one reported in the English IID GP-case control component, which was 8.6 days. The overall average absence from paid work would than be 1.2 days, or 14.1% of the average duration of illness, per GE patient in working life age and visiting a GP. For sensitivity reasons, we did consider higher (lower) published estimates in our *high cost estimate* (*low cost estimate*).

Being hospitalized is related to even more severe symptoms. We therefore assumed that hospitalised patients would have been absent from their work for the time between symptom onset until leaving hospital. Given that 65% of GE patients in working life age did have an employment and given an average working week of 30.5 hours[46] per average employed person in the Netherlands, the overall average absence from paid employment was estimated to be equal to 35% of the period between symptom onset and leaving hospital for each hospitalised GE patient between 15 and 64 years.

For long-term illness and for fatal cases in the working life years (15-64 years), we assumed for each episode a friction period of maximum 154 days. The friction period implied that we consider only productivity losses for the period needed to replace (an ill or deceased) worker. However, given that we did not know if a patient would have been working or not, we used in the calculation for the friction period the average productivity loss for an average person in the working life age group, which was equal to € 23.4 per hour off work (see Table 7).

Table 7. Productivity losses per hour in 2004 for an average 'person' and an average 'working person' in working live (15 years to 64 years), depending on age class.

Life years/ 'average'	Productivity losses (in €) per hour	
	Person[a]	Working person
15-24	8.3	20.8
25-34	25.9	32.2
35-44	30.0	38.7
45-54	30.8	41.8
55-64	18.0	45.2
'average'	23.4	36.5

a) Standardized for total population in working life in 2004, based on Oostenbrink *et al* [31] and CBS[45].

Absence of work of third person taking care of sick person

We further estimated productivity losses due to absence from work of third persons taking care of sick persons. Information of third persons that were absent from their work in order to take care of a sick person with GE, depending on the age of patients, were collected in the Dutch Sensor study [13]. In the SENSOR study, only 68 patients had visited a GP, whereof only six cases were 12 years or older. In order to receive more observations per age group, we considered both, GP visitors and non-GP visitors together when estimating, depending on the

age of the patient, the percentage of patients that needed a third person to be absent from his/her work in order to take care of the sick person. The results are reported in Table 8. Apart from the SENSOR study, there was also a GP study conducted, the so-called NIVEL study[44]. Also within the NIVEL study, some data were collected on sickness leave of third persons in order to take care of a sick person. The percentage of third persons taking care of a sick child (0-11 years) and being absent from work was in the NIVEL study 15% and in the SENSOR study, this was 13%, if considering only patients not visiting a GP, and 14% if considering all patients. The percentage of third persons taking care of sick persons older than 11 years, was 4.8% in the NIVEL study and in the SENSOR study this was 4.4%, if all patients were considered, and 4.8%, if considering only patients not visiting a GP. So, there were only very small differences between both studies. Because more detailed information was available from the SENSOR study than from the NIVEL study, we used the data from the SENSOR study, as reported in Table 8, as base for our cost-of-illness estimations.

Table 8. Estimated percentage of third persons being absent from their work in order to take care of a sick person, depending on the age of the patient.

Patients age groups	0-4 years	5-9 years	10-14 years	≥ 15 years
Percentage of patients needing care from a 3rd person (SENSOR study)	13%	19%	6.7%	4.2%
Percentage of patients needing care from a 3rd person (NIVEL study)		15.1%[a]		4.8%[a]

[a)] There were only two age classes considered in the NIVEL study, which were 0-11 years and >11 years.

The duration of work absence for a third person taking care of a sick person was on average 1.9 days, if a patient had not visited a GP[13], and on average 2.0 days, if a patient had consulted a GP[44]. Assuming an average length of illness of 8.2 days for patients not visiting a GP and 8.6 days for patients visiting a GP, than in both cases, the average length of sickness leave of a third person taking care of a sick person corresponded to 23% of the average duration of illness. In both studies, the questions with respect to work absence of a third person taking care of a sick person were unspecified. It could not be assessed whether work absence was from paid work or from unpaid work. We therefore assumed as most likely productivity losses, the average of productivity losses for an average working person, € 36.5/hour, and the opportunity costs for informal care, € 8.5/hour[31], which was equal to € 22.5/hour. In our *low cost estimate* and *high cost estimate*, however, we assumed that productivity losses were equal to € 8.5/hour and € 36.5/hour, respectively.

2.3.3 Other costs related to foodborne pathogens

Monitoring and follow-up of foodborne pathogen outbreaks are other public costs. A reduction of foodborne pathogens in the food chain, would probably also decrease the number of outbreaks, and hence the related costs for follow-up. However, no information about these aspects is available here. It was therefore decided that these costs would in first

instance not be considered. But in the following years efforts will be put in collecting the required information, allowing us to calculate also these costs.

Another important cost category that is indirectly linked to foodborne pathogens, are the costs for prevention measures taken in hospitals, nursing-homes and elderly homes to avoid the spread of foodborne pathogens from hospitalised community-acquired cases to other patients, resulting in nosocomial infections. Again, information on costs was scarce. We did not consider them in the current study.

2.4 Discounting

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 or other public health interventions. By definition, discounting does not apply to health effects that have duration shorter than 1 year. Hence, acute endpoints of foodborne illness (e.g. gastroenteritis) or illnesses of short duration (e.g. reactive arthritis) are not affected by discounting. Other end-points, in particular mortality and life-long disabilities, are strongly affected. Hence, the effect of discounting will differ per pathogen.

Let *a* be the age of premature death or onset of disabling diseases and *e(a)* be the standard life expectancy at age *a*. Then, the discounted life expectancy, *e(a,r)* is calculated according to the formula:

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

where *r* = discount rate. In accordance with the Dutch guidelines for public health interventions[31], in this report a discount rate of 4% per year was applied for both diseaswe burden and costs.

2.5 Uncertainty

Data necessary for the quantitative estimates of the disease burden and the associated costs are often limited and/or absent, which leads to some degree of uncertainty. Total uncertainty is broken down into variability and uncertainty. Variability is defined as ‘the inherent heterogeneity of a system’; e.g. variations in the length of the hospital stay of different patients. Uncertainty is usually defined as ‘a lack of perfect knowledge about a factor in the model that represents the system’[47]. Variability can not be reduced. It is not considered in the present study however, with the availability of more information on a system, the uncertainty might be reduced. For example the incidence of illness is not known but is estimated from observational data on a sample of the population. The larger the sample, the smaller the uncertainty in the incidence estimate. Both uncertainty and variability can be expressed in a statistical distribution function, but require a different strategy to account for in the analysis.

In the current analysis three kinds of uncertainty were distinguished:

- Statistical uncertainty, due to small sample sizes;
- Systematical uncertainty, due to the use of data which are not fully representative for the Dutch situation;
- Uncertainty due to a lack of data and the use of data from expert opinions.

Statistical uncertainty is best analyzed by representing uncertain parameters with an appropriate frequency distribution, followed by Monte Carlo simulation to estimate predictive intervals, as was done in the current study for Campylobacter, STEC O157and Salmonella, whereas systematical uncertainty and uncertainty due to a lack of data and the use of data from expert opinions are best represented by scenario analysis.

Due to restrictions in available resources we limited ourselves for most uncertain parameters in the current study to *low* values, *most likely* values and *high* values only. Whereby *low, most likely* and *high* values might have been either, the estimated 5th, 50th and 95th percentile of a statistically uncertain parameter, respectively, or an *optimistic, most likely* and *pessimistic* parameter value for systematical uncertainty and/or uncertainty due to a lack of data and the use of data from expert consultations, respectively. For some specific parameters, however, the uncertainty was too large, and scenario analysis was the only possible and sensible way to model and to analyze these model parameter uncertainties. Due to restrictions in available resources, we did not explicitly model variability as a frequency distribution, but used instead a *most likely* value, which might have been either a point estimate, or where available, the mean of a variability distribution.

For Campylobacter, STEC O157and Salmonella, however, we used second-order stochastic simulation models. With the help of these models we were able to explicitly and separately model variability and uncertainty. A detailed description of the models is given in Havelaar *et al*. [48 49] for the STEC O157 model and in Mangen *et al*.[12 29] for the Campylobacter model. The Salmonella model is identical to the Campylobacter model, of course adapting the numbers and distributions with specific information on Salmonella-associated GE and sequelae, whereby omitting GBS and IBD. Methodological adaptations, if then required, are made explicitly in the current report. In order to account for uncertainty and variability, we run the Campylobacter and Salmonella model with 200 simulations and 2000 iterations per simulation. The STEC O157 model was run with 250 simulations of 1500 iterations each. Given that variability is less important from a decision making point of view, we have chosen to present for these three pathogens only the uncertainty around the most likely estimate in the burden (or cost) in our summary tables and figures. The most likely estimate was always the median of estimated uncertainty, and the 5th and 95th percentile represent the attendant uncertainty. It has to be noted, that for each outcome individually the 5th, 50th and 95th percentile was estimated and presented, but these figures do not need to come from the same simulations. The sum of the medians is not necessary the median of the sum. Therefore adding up values in tables might give slightly other results than the totals shown in the table.

Scenario analyses, if applied, are presented hereafter as alternative scenarios. In contrast to the baseline, only one parameter value was changed. The most likely estimate with the estimated range of uncertainty is shown for alternative results.

3. Thermophilic *Campylobacter* spp.

Thermophilic campylobacters are the most commonly reported bacterial cause of acute gastroenteritis [50]. Farm animals, wild animals and pets are the most important reservoirs of Campylobacter. From these reservoirs food products and the environment undergo continuous contamination, resulting in many pathways by which humans can come in contact with Campylobacter.

Campylobacter infections in humans may cause acute GE, which in most cases, is self-limiting within a few days to weeks. For few patients the disease is fatal. Sporadically Campylobacter infections do result in complications. Guillain-Barré syndrome (GBS), reactive arthritis (ReA) and inflammatory bowel disease (IBD) are the most significant sequelae occurring after campylobacteriosis. GBS is a neurological disease frequently preceded by an acute infectious illness and affecting at least the motor, sensory, and autonomic nerves supplying the limbs [51]. The term reactive arthritis (ReA) describes an acute aseptic arthritis triggered by an infection elsewhere in the body, such as infections in the gut or in the urogenital tract[52]. In sterile compartments with reactive arthritis, elevated antibody levels to the triggering organisms are present in the host, but triggering organisms are not found in the affected joints and also no rheumatoid factor is present [53]. Crohn's disease and ulcerative colitis are collectively classified as inflammatory bowel disease (IBD). IBD is characterised as chronic intestinal disorders of unknown etiology[54]. For more background information on the different illnesses under study, see Mangen *et al.* [12]. The frequency of other post-infectious complications of Campylobacter is low, so we disregarded them in the current study.

3.1 Outcome tree, incidence and duration of illness

3.1.1 Outcome tree and incidence

Extrapolated by the trend in laboratory-confirmed Campylobacter infections[37] as observed for 1996 until 2004 within LSI[36], and based on the outcomes from SENSOR[34] and NIVEL[44], we estimated the number of acute GE Campylobacter cases in the entire population and the number of cases visiting a GP, both hospitalised or not hospitalised for 2004. The number of laboratory-confirmed GE Campylobacter cases were assumed to be about 6,100 cases in 2004[37]. Based on the CaSa study[55 56], - a case-control study of laboratory-confirmed patients with Salmonella and Campylobacter infections conducted from April 2002 to April 2003, we assumed that 9% of all laboratory-confirmed GE Campylobacter cases[55] would be admitted to hospital because of GE. Helms *et al*.[57] estimated the relative excess mortality for patients with campylobacteriosis, correcting for co-morbidity, to be 1.86 (range 1.56-2.20) higher than for control cases in the same life age. Based on Helms *et al*.[57] and using age-specific mortality risks[58] and age-specific incidences as observed over the years within LSI[36], and confirmed by the CaSa study[55], the median number of fatal Campylobacter-associated GE

cases was estimated to be 25 cases/year. Incidences of Campylobacter-associated GE, total and split up in the different health states, are summarized in Table 9.

Mangen *et al.*[29] had estimated in a previous study the number of Campylobacter-associated GBS cases, Campylobacter-associated ReA cases and Campylobacter-associated IBD cases. These estimates were used in the current study, updating ReA and IBD according to the estimated number of Campylobacter cases in 2004. Based on a retrospective study applied in the Southwest Netherlands[59], but corrected by Havelaar *et al.* [27,28]for published performance characteristics of the serological tests, Mangen *et al.*[29] had estimated the annual number of Campylobacter-associated GBS cases in the Netherlands to be 60, whereof two fatal GBS cases. No trend information is available. Based on Hannu *et al.*[60] it was assumed that 7% of all Campylobacter GE cases visiting a GP would develop ReA. But given the uncertainty of this latter assumption, we applied, similar as Mangen *et al.*[29], scenario analyses assuming that 1) 7% of all Campylobacter-associated GE cases in the population would develop ReA; and 2) 7% of only laboratory-confirmed Campylobacter GE cases would develop ReA. It was assumed that most ReA patients (85.8%) would not need medical help, 22% would visit a doctor and 2.2% would be hospitalized[60]. Based on a Danish study (Helms *et al.*[61]), the estimated additional risk to develop IBD after a laboratory-confirmed Campylobacter case was assumed to be 22% higher than for the general population in the same life age. With an average of 6,100 laboratory-confirmed cases in the Netherlands, the estimated average Campylobacter-associated IBD incidence would be 22 per year. Incidences of Campylobacter-associated GBS cases, Campylobacter-associated ReA cases and Campylobacter-associated IBD cases, total and split up in the different health states, are summarized in Table 9.

The outcome tree of Campylobacter-associated GE and sequelae, as considered in the current report, is shown in Figure 1.

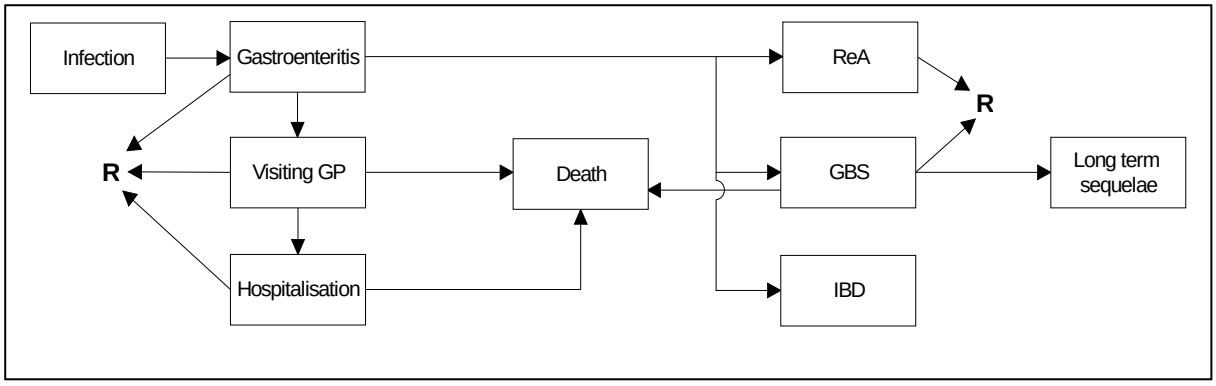


Figure 1. Outcome tree Campylobacter-associated GE and sequelae (R: recovery).

3.1.2 Duration of illness and age distribution

Only 9 campylobacteriosis cases were reported in the Dutch SENSOR study[34]. We therefore based our assumptions of symptom length of campylobacteriosis patients on the English IID

study[42]. Based on the number of days of illness found in the community-cohort, but corrected for the patients visiting a GP, we assumed 3.48 days of illness. The Food Standards Agency[42] reports an overall duration of illness of 9.94 (range 0 -56), for all GP cohort cases, whereof an overall length of 0.22 days in hospital. Based on the Dutch National Disease Registry on hospitalisation for 'other bacterial pathogens' we assumed an average hospital stay of 5.9 days for a hospitalised case, similar as Mangen *et al.*[29]. Assuming that patients visiting a GP, hospitalized or not hospitalized, would have the same overall mean for the period 'at home because of the illness' and the period 'feeling ill but able to do normal daily activities (work/school/shops)', we estimated an average illness duration of 9.72 days for Campylobacter GE patients visiting only a GP and average illness duration of 14.39 days for hospitalized patients, see Table 9. These figures correspondent with the reported length of illness, about 10 days (median), for the Campylobacter-laboratory-confirmed cases recovered (about 70% of all cases) at the time the questionnaire was completed[55]. No information was available on the age distribution of campylobacteriosis in the population. The only information available was from laboratory-confirmed Campylobacter infections within LSI, namely for the years 1996 until 2003 of laboratory-confirmed cases diagnosed by two regional PHLs[36] only, and for 2003 from the CaSa study[55] and for 2004 from the LSI study, but this time for all reported laboratory-confirmed cases diagnosed by all regional PHLs. All three sources showed the same age distribution. We assumed that the age distribution in the population, both, not visiting GP and visiting GP, would be similar to that observed in laboratory-confirmed cases, see Table 10 and Figure 1. Based on the CaSa study[55], however, we were able to estimate the age distribution of hospitalized cases, which was slightly different than the observed for all laboratory-confirmed cases, both hospitalized and not hospitalized. With the help of age-specific mortality risks[58] and age-specific incidences for all laboratory-confirmed cases[36], the age of death was simulated and the expected life span was sampled from the standard life table as reported by Statistics Netherlands for the year 2004 for each fatal case individually. No distinction between men and women was made.

Within this study, we made the same assumptions on the duration of illness of GBS cases as Havelaar *et al*.[27] and Mangen *et al*. [12 29], distinguishing between mildly and severely affected GBS patients. The age at disease onset was randomly drawn from the observed age distribution of Dutch GBS cases[59]. Age and severity class reached at the worsted point of illness, the so-called nadir, are of influence when recovering. The recovery process of GBS patients was therefore reflected by a gradual increase of patients in less severe classes over time. For a detailed description see Mangen *et al.* (2004)[12]. Due to non-availability of data, we assumed, similar as Mangen *et al*[12 29], that the ReA duration was independent of the severity of symptoms and independent of age, assuming an exponential distribution with a mean duration of 0.608 years. Assuming that each patient with a Campylobacter infection, and visiting a GP, had on average a probability of 7% to get Campylobacter-triggered ReA, the age distribution of Campylobacter-associated ReA cases was the same as assumed for Campylobacter-associated GE cases in the population. IBD symptoms were assumed to persist life-long. Assuming same life expectancy as the general population, the age at disease

onset for each simulated IBD case was randomly drawn from the simulated laboratory-confirmed positive campylobacteriosis cases[36], taking into account the age-dependent additional risk to develop IBD.

Table 9. Incidence and duration of illness of Campylobacter-associated GE and sequelae for 2004 [a].

	Incidence estimate (cases per year)			No. of days of illness
	Most likely	Low	High	
Gastroenteritis	59,000	25,000	140,000	-
No GP	45,000	19,000	110,000	3.48
GP	14,000	5,000	33,000	9.72
Hospitalization	570	500	650	14.39
Fatal	25	18	34	[b]
Sequelae				
GBS	59	40	84	-
Mild GBS	9	0	28	[c]
Severe GBS	49	33	68	[c]
Fatal GBS	2	1	3	[b, c]
ReA	1,000	430	2,600	-
ReA – No GP	860	350	2,200	222
ReA – GP	170	60	480	222
ReA – Hosp.	16	1	90	222
IBD	22	17	29	Life-long

[a] Summations do not necessarily tally, see section 2.5.

[b] Not shown as we used here the expected individual life span at the age of death.

[c] Not shown as it varies strongly between cases. Details are given in Appendix V in Mangen *et al.*[12]

Table 10. Age distribution of Campylobacter-associated GE.

	Age classes				
	0-4 years	5-9 years	10-14 years	15-64 years	> 65 years
Gastroenteritis					
No GP [a]	11.0%	5.2%	4.1%	70.1%	9.6%
GP [a]	11.0%	5.2%	4.1%	70.1%	9.6%
Hospitalisation	12.1%	7.1%	5.0%	59.6%	16.3%

[a] No specific information available; we used the age distribution as observed in LSI[36] over the years 1996-2003.

3.2 Disease burden

Community-acquired Campylobacter-associated GE and sequelae incidences, used disability weights, and the most likely estimates for YLD, YLL and DALY, total and split up for the different health states, are shown in Table 11. In Figure 2 DALY estimates for the most likely estimate and the attendant uncertainty (low and high estimate) are shown split up for the different health states and the sum over all health states. Non-fatal GE cases recover within few days, whereas IBD and GBS are chronic sequelae. Discounting (4%) the disease burden

of chronic disease as well as of fatal cases did have an impact as is shown in Table 11, second DALY column, and in Figure 2 (dotted bars).

Table 11. Incidence and disease burden of Campylobacter-associated GE and sequelae for 2004 (most likely estimate = median) [a]

	Incidence	Disability weight per case/year	YLD (0%)	YLL (0%)	DALY (0%)	DALY (4%)
Gastroenteritis	59,000	-	180	390	600	460
No GP	45,000	0.0006	30	-	30	30
GP	14,000	0.010	140	-	140	140
Hospitalisation	570	0.015	9	-	9	9
Fatal	25	1	-	390	390	260
Sequelae						
GBS	60	[b]	260	35	290	160
ReA	1,000	[b]	100	-	100	100
IBD	22	0.26	250	-	250	110
Total		-	810	430	1,300	830

[a] Summations do not necessarily tally, see section 2.5.
[b] Depends on severity, see Table 3. For more details see Mangen et al. [12]

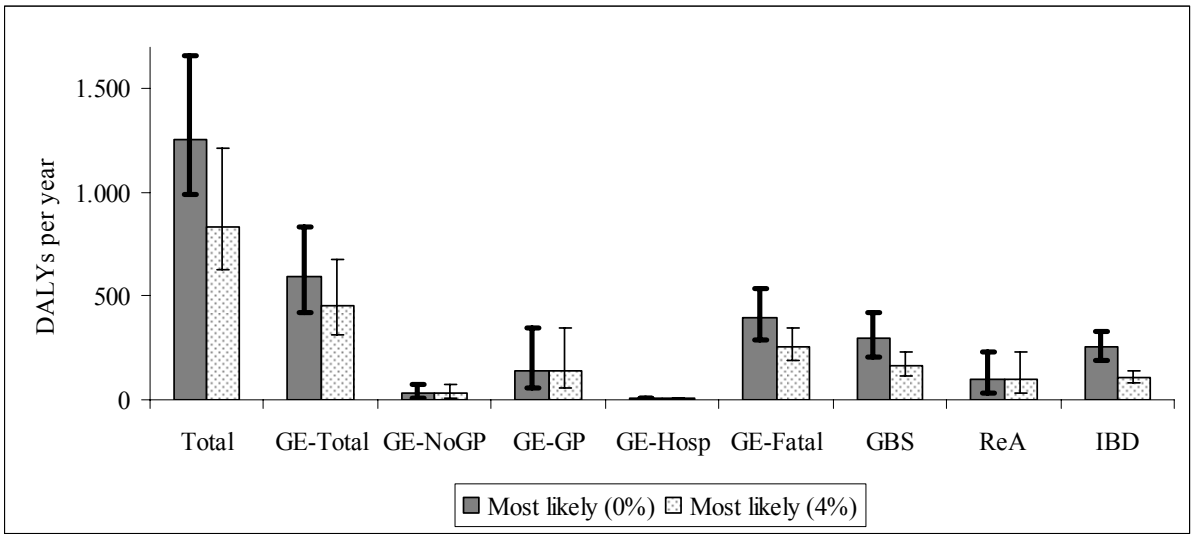


Figure 2. Disease burden of Campylobacter-associated GE and sequelae for 2004, using most likely estimates, discounted (4%) and undiscounted (0%). Error bars express an uncertainty interval that results from using low and high estimates.

3.3 Cost-of-illness

Using the incidences and duration of illness listed in Table 9 and following the method and assumptions described in section 2.3.1 and in section 2.3.2, we estimated the direct health care costs for the different non-fatal health states of Campylobacter-associated gastroenteritis. Hospitalized Campylobacter-associated GE patients were assumed to spend on average 5.9 days in hospital[12 29]. Most hospitalized Campylobacter patients are dehydrated, but some

might have also a bacteraemia. But apart from some additional intravenous application of antibiotics, hospitalised treatments are similar. Therefore to avoid double counting, as well as for reasons of simplification, we considered them in the current study within the group of hospitalised campylobacteriosis cases, similar as did Mangen *et al*. [12] DHC results of community-acquired Campylobacter-associated GE are summarized in Table 12, most likely estimate only.

The DHC estimates for GBS, ReA and IBD were only an update of the cost estimates of Mangen *et al*. [12] to 2004, we corrected for changes in IBD and ReA incidence numbers. Detailed information with respect to medical service use and assumptions made for the different illnesses and different health states are given in Mangen *et al*. [12]. No new information was available with respect to the use of medical services for the different sequelae. In Table 12 we have summarized for GBS, ReA and IBD only the most likely total cost estimate for DHC in 2004. A detailed description over the distributions of DHC over the different subcategories can be found in Mangen *et al*. [12]

Table 12. DHC of Campylobacter-associated GE and sequelae in million € for 2004 (most likely estimates) [a]

	Drugs & medicine	GP consultations	Hospitalization	Other	Σ DHC
Gastroenteritis [b]	0.14	0.83	1.3	-	2.3
No GP	0.02	-	-	-	0.02
GP	0.12	0.80	-	-	0.9
Hospitalisation	0.00	0.05	1.3	-	1.4
Sequelae					
GBS	- [d]	- [d]	1.9 [c]	2.2	4.2
ReA	- [d]	- [d]	- [d]	- [d]	0.06
IBD	- [d]	- [d]	- [d]	- [d]	3.9
Total	-	-	-	-	10.5

a) Summations do not necessarily tally, see section 2.5.

b) Direct health care costs of fatal cases were included in the other non-fatal health states.

c) Including also the costs for the GP visit and the outpatient clinic visit before being admitted in hospital.

d) For details see Mangen *et al*.[12]

DNHC considered in the current study were travel costs and additional diapers used for children of 3 years and younger, following the method and the assumptions described in section 2.3.1 and section 2.3.2 for Campylobacter-associated gastroenteritis cases. In the case of chronic sequelae, apart from travel costs, also some co-payments by patients were included in the DNHC estimates, which were an update of Mangen *et al*. [12] to 2004. DNHC are only of minor importance with a total of € 0.2 million (most likely estimate), see Table 14.

In the current study, we considered paid employment lost due to work absence of Campylobacter-associated GE patients, as well as due to work absence of third persons taking care of Campylobacter-associated GE cases, according to the method and assumptions described in section 2.3.1 and section 2.3.2. Based on SENSOR and NIVEL the number of

days paid employment lost for patients and for third persons taking care of a GE case were estimated (see Table 13). But with a reported 0.91 days in the community-cohort, and 2.93 days in the GP-case control study, the English IID study reported a higher number of days off work[42]. Although, in the 0.91 days off work, also some GE cases visiting a GP were included, we considered both figures in the current study as being a *high estimate* of days off work. Most likely estimates, as shown in Table 9 were used as *low estimate* of days off work. The used length of work absence in the current study was a more conservative estimate than the one used by Mangen *et al*. [12] Having no information on work absence of unpaid employment, we preferred to calculate in the current study only productivity losses of paid employment. Details of INHC for the different health states of GE are given in Table 13.

In the case of chronic sequelae, only the work absence of patients was considered. No information was available with respect to third persons taking care of chronically ill persons. The updated INHC estimates of Mangen *et al*. [12] to 2004 are given in Table 13.

Table 13. INHC of Campylobacter-associated gastroenteritis and sequelae in € million for 2004 (most likely estimates) [a]

	No. of days paid employment lost		Productivity losses		Σ INHC
	Patient	3rd person	Patient	3rd person	
Gastroenteritis	-	-	8.5	0.7	9.2
No GP	0.31	0.81	3.7	0.4	4.0
GP	1.35	2.26	4.1	0.3	4.4
Hospitalisation	5.10	3.35	0.5	0.02	0.5
Fatal	154	- [b]	0.2	- [b]	0.2
Sequelae					
GBS	- [c]	- [b]	1.1	- [b]	1.1
ReA	- [c]	- [b]	0.06	- [b]	0.06
IBD	- [c]	- [b]	1.3	- [b]	1.3
Total	-	-	-	-	11.7

[a)] Summations do not necessarily tally, see section 2.5.

[b)] Including also the costs for the GP visit and the outpatient clinic visit before being admitted in hospital.

[c)] For details see Mangen *et al.*[12]

In Table 14 and Figure 3 we have summarized the most likely estimate and the most likely estimate with attendant uncertainty, respectively, for the total costs of community-acquired Campylobacter associated GE and sequelae. Given that almost all costs occur within one year, discounting costs is not an important issue, except for IBD and some of the costs related to GBS.

Table 14. Cost-of-illness of Campylobacter-associated gastroenteritis and sequelae in € million for 2004 (most likely estimates) [a]

	DHC (0%)	DNHC (0%)	INHC (0%)	Σ Costs (0%)	Σ Costs (4%)
Gastroenteritis	2.3	0.02	9.2	11.4	11.5
No GP	0.02	0.01	4.0	4.1	4.0
GP	0.9	0.01	4.4	5.2	5.3
Hospitalisation	1.4	0.00	0.5	1.8	1.9
Fatal		-	0.2	0.2	0.2
Sequelae					
GBS	4.2	0.00	1.1	5.3	5.3
ReA	0.06	0.00	0.06	0.1	0.1
IBD	3.9	0.29	1.3	3.0	5.6
Total	10.5	0.31	11.7	19.6	22.3

a) Summations do not necessarily tally, see section 2.5.

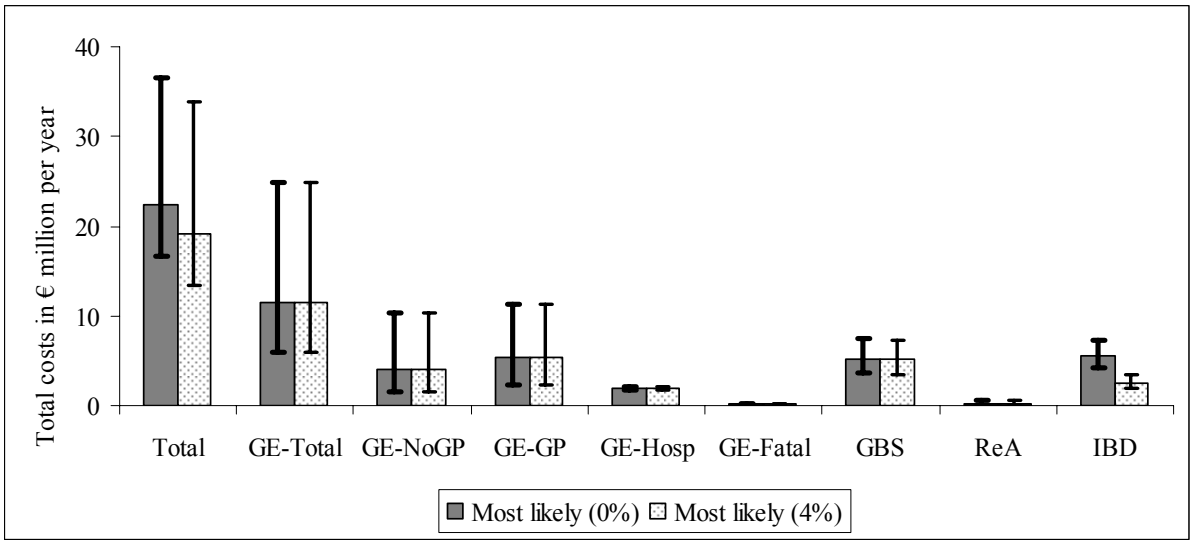


Figure 3. Cost-of-illness of Campylobacter-associated gastroenteritis and sequelae, using most likely estimates, discounted (4%) and undiscounted (0%). Error bars express an uncertainty interval that results from using low and high estimates.

3.4 Scenario analysis for Campylobacter-associated ReA

In the current study we assumed that 7% of Campylobacter GE cases visiting a GP would develop ReA. But given the uncertainty of this latter assumption, we applied scenario analyses assuming that 1) 7% of all Campylobacter-associated GE cases in the population would develop ReA (*population*); and 2) 7% of only laboratory-confirmed Campylobacter GE cases would develop ReA (*lab only*). In Table 15 we have summarized the incidence and the DALY, total and split up per health state, for the baseline, as well as for the two alternative scenarios, but only most likely estimate. Whereas in Figure 4 the attendant uncertainty around the most likely estimate is shown. But apart from the incidence numbers and the estimated disease burden, also the cost-of-illness estimated is changing from € 0.12

million to € 0.50 million; if than total population would be at risk, and to € 0.05 million, if than only laboratory-confirmed cases would be at risk.

Table 15. Incidence and DALY of Campylobacter-associated gastroenteritis and sequelae, for baseline and alternative scenarios (most likely estimates) [a].

	Incidence			DALY (0%)		
	BASE	Lab only	Population	BASE	Lab only	Population
GE	59,000	59,000	59,000	600	600	600
GBS	60	60	60	290	290	290
IBD	22	22	22	250	250	250
ReA (all)	1,000 [b]	450 [b]	4,400 [b]	100 [b]	40 [b]	390 [b]
No GP	860	370	3,600	70	30	280
GP	170	75	730	20	10	90
Hospitalisation	16	7	70	4	2	20
Sum	-	-	-	1,300	1,200	1,500

[a)] Summations do not necessarily tally, see section 2.5.

[b)] In the baseline we assume that 7% of the campylobacteriosis cases visiting a GP would develop ReA. In the two alternative scenarios we assumed that 7% of laboratory-confirmed cases (lab only) would develop ReA, and 7% of all cases in the population (population) would develop ReA, respectively.

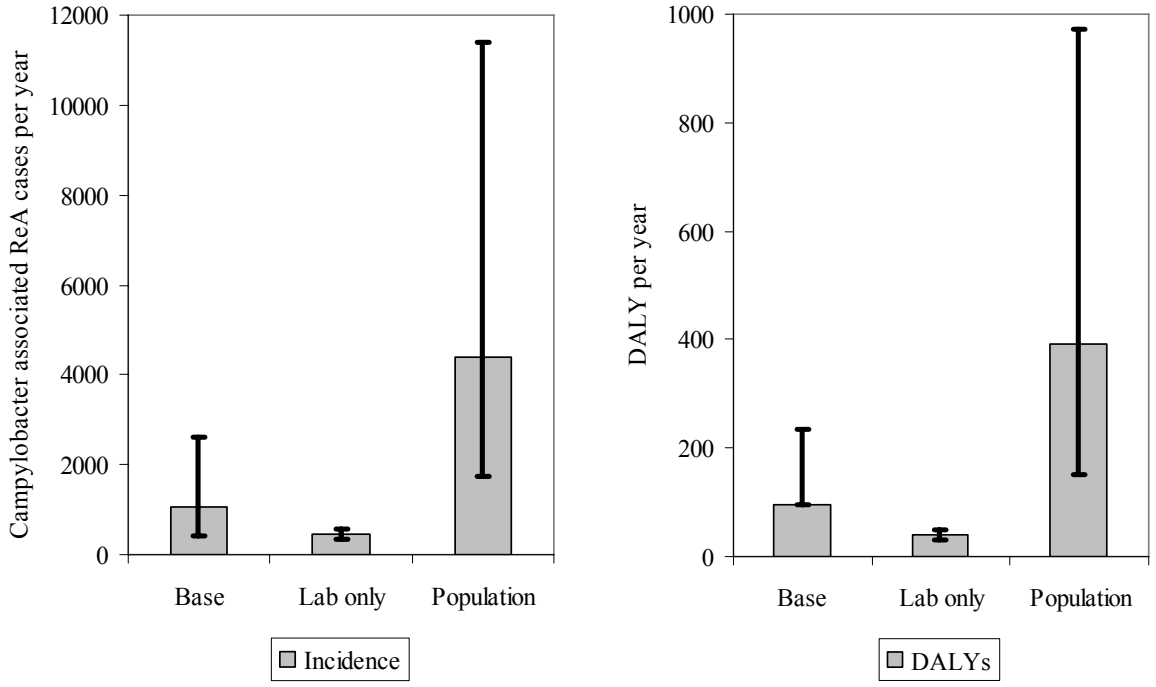


Figure 4. Incidence and DALY of Campylobacter-associated ReA cases, for baseline and alternative scenarios, using most likely estimates. Error bars express an uncertainty interval that results from using low and high estimates. Discounting was not required as most cases had recovered by the end of the first year.

3.5 Discussion

More than 20% of all Campylobacter-associated GE cases request medical help. In 25 cases of the total 59,000 GE cases, the disease is even fatal, mostly in elderly patients. Campylobacter infections results in sequelae, in total 60 cases of GBS, 1,050 cases of ReA and 22 cases of IBD. The estimated disease burden is equal to about 1,300 DALY per year (90% C.I.: 1,000 – 1,700) and the associated costs-of-illness total to about € 22 million per year (90% C.I.: € 17 million - € 37 million). Half of the estimated disease burden is due to sequelae. Of the estimated 600 DALYs associated with GE, more than 65% is due to fatal cases. Approximately 50% of the total costs are related to gastroenteritis and 50% to sequelae. However, more than 75% of the DHC, about € 8.2 million per year of the total DHC (€ 10.5 million), are due to sequelae, whereby GBS accounts for € 4.2 million and IBD for € 3.9 million. DHC associated with Campylobacter-associated ReA are negligible.

In comparison to Mangen *et al*. [12] the number of Campylobacter-associated IBD cases doubled. Reason herefore was that Mangen *et al*. [12] had based their assumptions on preliminary results made available in 2003 by Helms and colleagues (SSI, Copenhagen, Denmark; personal communication), not being aware that the group of IBD was a rather broad group actually comprising IBD, inflammatory bowel syndrome (IBS) and other similar symptoms. In a very recent publication (February 2006), Helms and colleagues[61] published their definitive results. However, in this final version, IBD and IBS were considered separately with a far higher odds ratio for IBD than earlier communicated for the whole group. An update of the IBD estimates was quickly made and included in the current report. However, for IBS no information was available with respect to incidence in general population, disease burden and costs. We therefore decided that in the current study IBS would not be considered, although according to Helms *et al.*[61] the risk to develop IBS after Campylobacter infections is quite considerable (adjusted odds ratio: 8.08). It is foreseen to gather and include information on IBS in a following update of the current model.

The estimated costs-of-illness are comparable to the one estimated by Mangen *et al*. [12] The current study was an update to 2004, but with a slightly lower number of Campylobacter GE cases per year, however, twice as much IBD cases. According to the costs estimates of Mangen *et al*. [12] more than 70% would be related to GE. This was slightly higher than our estimated 50%. Reasons for the differences are to be found in the more conservative estimate used for productivity losses in the current study, as well as in the significant higher, mainly direct health care costs associated with IBD.

Given the absence of information with respect to use of medical services, as well as with respect to work absence in the case of ReA, we opt in the current study, similar as Mangen *et al*. [12] for a conservative cost estimate, and more than probably underestimating the true costs. Including economic questions in case-control study questionnaires would be a great help to close this data gap.

The assumption made about what part of Campylobacter-associated GE cases would be at risk to develop ReA had a large impact on the estimated disease burden. For example, by

assuming that every infected person with Campylobacter in the community is at risk, compared to the assumed 7% of Campylobacter-associated GE cases that visit a GP, the estimated total disease burden associated to Campylobacter, both GE and sequelae, would increase from an estimated total of 1,300 DALY to 1,500 DALY per year. The assumption, however, has only little impact on the cost-of-illness estimate due to the relatively low costs assumed per ReA case.

4. Shiga-toxin producing *Escherichia coli* O157

4.1 Outcome tree and incidence

Data in this chapter were taken from Havelaar *et al*.[49], not updated for trend in laboratory surveillance. Intensive laboratory surveillance[62] indicates a slight, non-significant increase in the incidence of STEC O157 related gastroenteritis. However, given the large uncertainty in the incidence estimates, we did not apply a trend correction. Figure 5 shows the outcome tree for STEC O157.

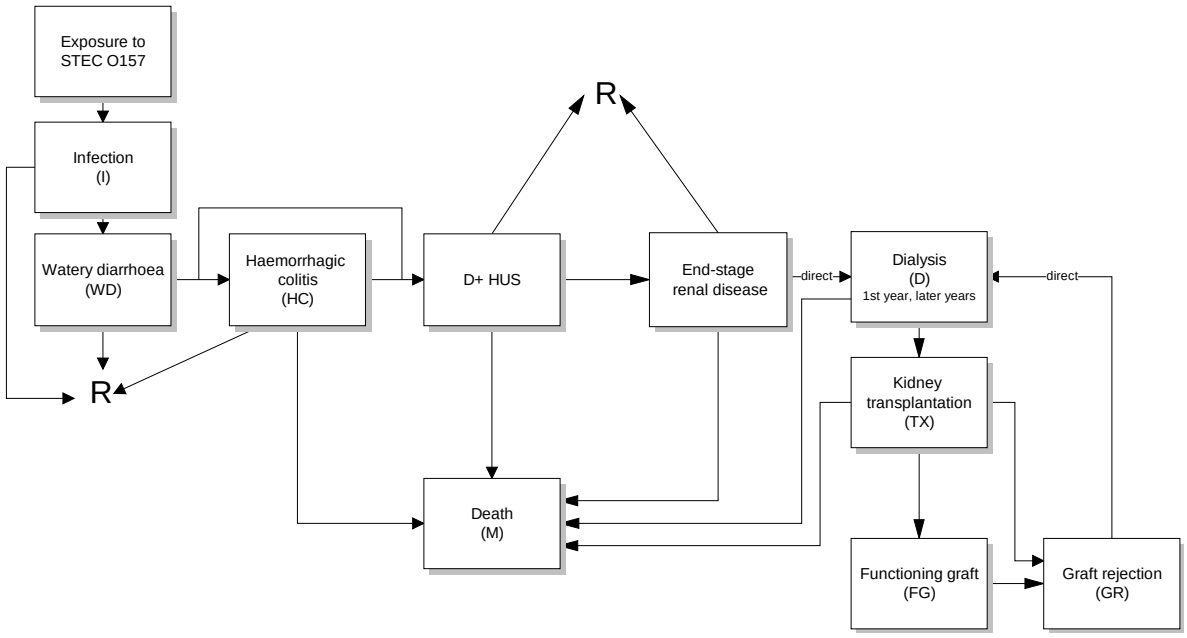


Figure 5. Outcome tree for infection with Shiga-toxin producing Escherichia coli *O157; R: recovery*

The incidence of STEC O157 associated gastro-enteritis is relatively low (see Table 16) but there is a high probability of developing haemolytic –uremic syndrome (HUS), particularly in children below 5 years of age. While most children recover from HUS after hospital treatment, end-stage renal disease may result in some patients who will depend on dialysis and/or kidney transplantation for their entire life.

Table 16. Incidence and duration of illness of STEC O157 associated gastroenteritis and haemolytic-uraemic syndrome (HUS) for 2004 [a].

	Incidence estimate (cases per year)			No. of days of illness
	Most likely	Low	High	
Gastroenteritis				
Bloody diarrhoea	590	40	3400	5.0
Non-bloody diarrhoea	670	40	3800	3
Fatal	0.6	na	na	13.2 years
HUS	21	16.4	21.2	[c]

[a)] Summations do not necessarily tally, see section 2.5.

[b)] Not available.

[c)] Not shown as there are many sub stages of HUS.

4.2 Disease burden

Table 17 shows the disease burden associated with STEC O157, which is 110 DALYs per year. Approximately 90% of this burden is associated with HUS, see also Figure 6.

Table 17. Incidence and disease burden of STEC O157 associated gastroenteritis and haemolytic-uraemic syndrome (HUS) (most likely estimate=median) [a]

	Indicence	Disability weight	YLD (0%)	YLL (0%)	DALY (0%)
Gastroenteritis	1300	[b]	4	6	10
HUS	20	[b]	25	76	100
Total	-	-	30	84	110

[a] Summations do not necessarily tally, see section 2.5.

[b] Composite

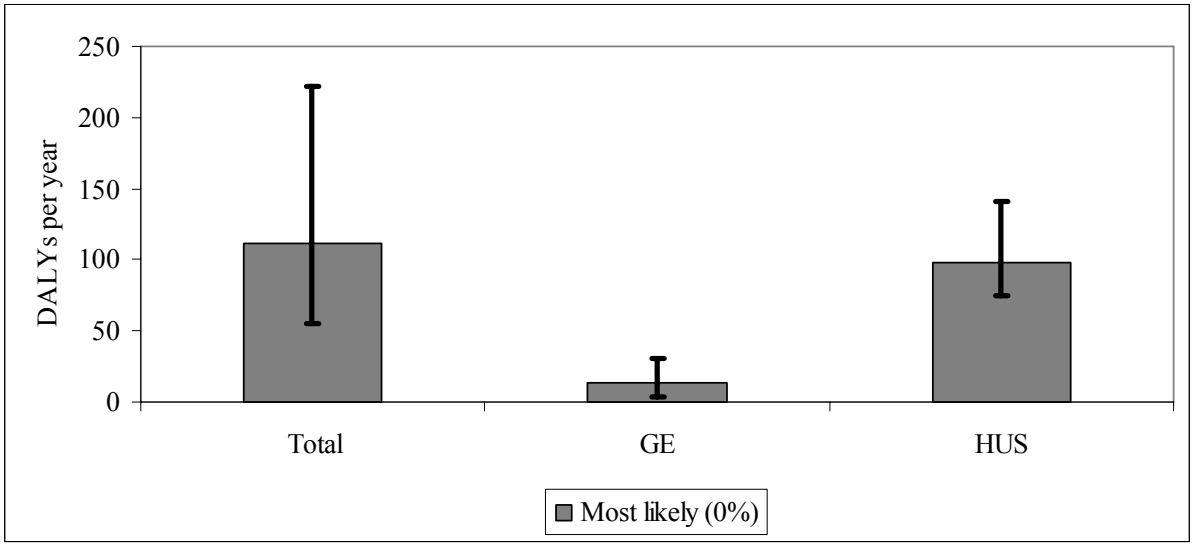


Figure 6. Disease burden of STEC O157 GE and sequelae for 2004, using most likely estimates, discounted (4%) and undiscounted (0%). Error bars express an uncertainty interval that results from using low and high estimates.

5. *Salmonella* spp.

Salmonella is probably one of the best known bacteria. Chicken and eggs, but also other farm animals are important reservoirs of Salmonella [63]. Acute gastroenteritis associated with Salmonella infections in humans is in most cases self-limiting within a few days to weeks, but for some patients the disease is fatal. Salmonella can also result in reactive arthritis (ReA) and IBD, similar as Campylobacter infections. ReA is the most significant sequelae occurring occasionally after Salmonella infections[64-66]. IBD is characterised as chronic intestinal disorders of unknown etiology[54]. Helms *et al.*[61] were the first authors to associated IBD with previous Salmonella infections. The frequency of other post-infectious complications following a salmonellosis is low so we disregarded them in the current study.

5.1 Outcome tree, incidence and duration of illness

5.1.1 Outcome tree and incidence

Based on the SENSOR[34] and the NIVEL[44] studies, and corrected for the trend observed in laboratory-confirmed cases[37] collected within LSI[36], we estimated the number of Salmonella-associated GE cases in the entire population and cases visiting a GP, both hospitalised or not hospitalised. Van Pelt *et al*.[37] estimated for 2004 a total of 2,500 laboratory-confirmed Salmonella cases. Based on to the Dutch National Disease Registry for hospitalisation, the same authors reported for 2004 a total of 650 hospitalised salmonellosis cases (our *most likely estimate*). Within the years 1996 to 2004 the year 2003 was a year with an extremely high number of hospitalised salmonellosis cases, whereas the year 2002 was a year with an extremely low number of hospitalised salmonellosis cases. Using the reported 483 hospitalised salmonellosis cases in 2002 as our *low estimate*, and the reported. 788 salmonellosis cases hospitalised in 2003 as our *high estimate*, the hospitalised salmonellosis cases were modelled in the current study using a pert-distribution. Based on Helms *et al*.[57], who estimated the relative mortality for patients with Salmonella infections, and using age-specific mortality risks[58] and age-specific incidences as diagnosed within LSI[36 37] for the years 1996-2004 and in the CaSa[56] study for the year 2003, the number of fatal Salmonella-associated GE cases was estimated to be 39 cases/year (median). Incidences of Salmonella-associated GE, total and split up in the different health states, are summarized in Table 18.

ReA is the most significant long-term sequelae following salmonellosis[65 66]. When reviewing published studies Raybourne *et al*.[66] estimated that 8% (2.3% - 15%) of acute foodborne illness cases would develop ReA. Although, the authors referred to acute foodborne illness, the majority of the studies considered by Raybourne *et al*.[66] were salmonellosis outbreaks. However, the level of the studied population varied from entire exposed population to those who required medical services only. Yu and Thomson[52], who also reviewed the literature with respect to ReA, concluded that the duration of diarrhoea correlated with development of ReA. We therefore assumed in the current study that most likely 8% of the Salmonella GE cases visiting a GP would develop ReA. The attendant uncertainty was modelled with the

help of a pert distribution, whereby 2.3% and 15% represented the *low estimate* and the *high estimate*, respectively. But given the systematical uncertainty of this latter assumption, we applied scenario analyses assuming that 1) 8% of all Salmonella-associated GE cases in the population would develop ReA; and 2) 8% of only laboratory-confirmed Salmonella GE cases would develop ReA. Most of the Salmonella-triggered ReA cases would not require medical services, whereas others would. Little is known about Salmonella-ReA specifically. We therefore based our assumption with respect to the different severity states on the findings of Hannu *et al*. [60] for Campylobacter-triggered ReA: 85.8% of ReA patients would not need medical help, 22% would visit a doctor and 2.2% would be hospitalized. Incidences for Salmonella-associated ReA cases, total and split up in the different health states, are summarized inTable 18. Based on Helms *et al*.[61] it was assumed that the additional risk to develop IBD after a laboratory-confirmed Salmonella would be 24.6 % higher than for the general population in the same life age. With an average of 2,500 laboratory-confirmed cases in the Netherlands, the estimated average Salmonella-associated IBD incidence would be 7 per year.

In Figure 6 we show the outcome tree for Salmonella-associated GE and sequelae.

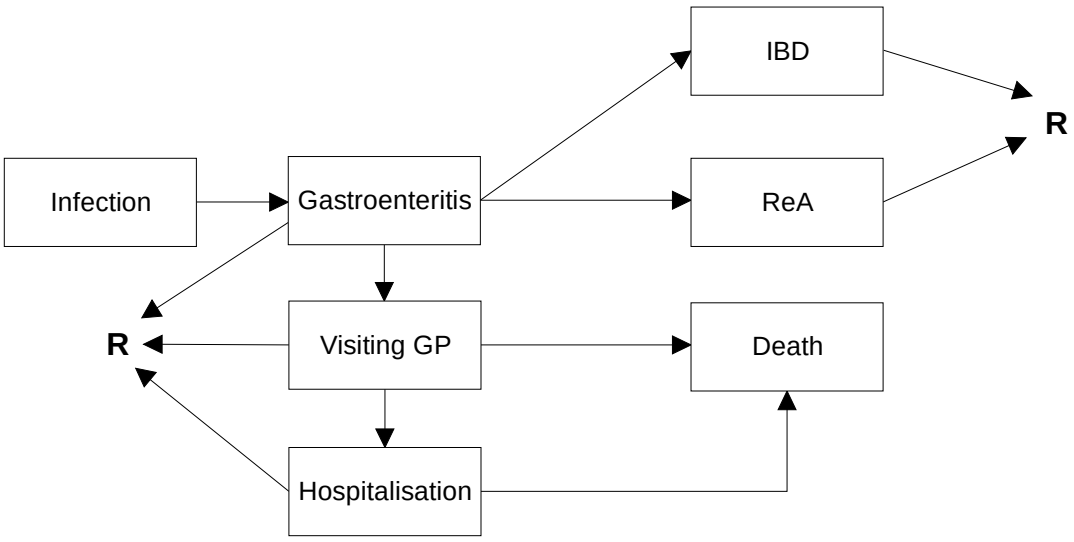


Figure 7. Outcome tree Salmonella-associated GE and sequelae(R: recovery).

5.1.2 Duration of illness and age distribution

In the Dutch SENSOR study[34] only 3 Salmonella cases were detected. We therefore based our assumptions of duration of illness of salmonellosis patients on the English IID study[42]. Based on the number of days of illness found in the community-cohort, but corrected for the patients visiting a GP, we assumed 5.58 days of illness per case. The Food Standards Agency[42] reports an overall duration of illness of 10.65, for all GP cohort cases, whereof an overall length of 0.25 days in hospital. The average hospital stay for four reported hospitalised salmonellosis cases was estimated to be on average 5.5 days[42]. Assuming that patients visiting a GP, hospitalized or not hospitalized, would have the same overall mean for

the period ‘at home because of the illness’ and the period ‘feeling ill but able to do normal daily activities (work/school/shops)’, we estimated an average illness duration of 10.65 days for Salmonella GE patients visiting only a GP and average illness duration of 16.15 days for hospitalized patients, see Table 18. According to the CaSa study, the median duration of symptoms of recovered *Salmonella* Enteritidis (about 77% had recovered when filling in questionnaire) and recovered *Salmonella* Thyphimurium (about 67% had recovered when filling in questionnaire) was 10-11 days. However, it has to be noted that according to the Dutch National Disease Registry for hospitalisation, the average length of hospitalisation per hospitalised salmonellosis cases was in 2004 about 8.4 days, which was longer than the earlier estimated 5.5 days. We used then also the estimated average 8.4 days when estimating the DHC for hospitalised patients. No information was available on the age distribution of Salmonella infections in the population. The only information available was from laboratory-confirmed Salmonella infections[36]. We assumed that the age distribution in the population would be similar to that observed in laboratory-confirmed cases, see Table 19. Based on the CaSa study[56] we were additionally able to estimate the age distribution of hospitalized cases, which was slightly different from that observed in laboratory-confirmed cases. For each fatal salmonellosis GE case the age at death is simulated and the expected life span is sampled from the standard life table as reported by Statistics Netherlands for the year 2004. No distinction between men and women was made.

Due to non-availability of data, we assumed that the duration of symptoms of Salmonella-associated ReA would also be the same as assumed for Campylobacter-associated ReA. Independent of the severity of symptoms, we simulated an exponential distribution with a mean duration of 0.608 years. Assuming that each patient with a Salmonella infection and visiting a GP had on average a probability of 8% to get Salmonella-triggered ReA, the age distribution of Salmonella-associated ReA cases was the same as assumed for Salmonella-associated GE cases in the population. Independent if now triggered by a previous Campylobacter or Salmonella infections, we assumed that IBD symptoms would persist life-long. Assuming same life expectancy as the general population, the age at disease onset for each simulated IBD case was randomly drawn from the simulated laboratory-confirmed positive salmonellosis cases[36], taking into account the age-dependent additional risk to develop IBD.

Table 18. Incidence and duration of illness of Salmonella-associated GE and sequelae for 2004 [a]

	Incidence estimate (cases per year)			No. of days of illness
	Most likely	Low	High	
Gastroenteritis	35,000	9,000	140,000	-
No GP	30,000	7,000	110,000	5.58
GP only	5,400	700	20,000	10.65
Hospitalisation	640	540	740	16.15
Fatal	39	34	42	-[b]
Reactive arthritis (ReA)	460	100	1,900	-
No GP	370	80	1,500	222
GP only	80	14	300	222
Hospitalisation	7	0	60	222
IBD	7	6	9	Life-long

a) Summations do not necessarily tally, see section 2.5.

b) Not shown as we used here the expected individual life span at the age of death.

Table 19. Age distribution of Salmonella-associated GE.

	Age classes				
	0-4 years	5-9 years	10-14 years	15-64 years	> 65 years
Gastroenteritis					
No GP [a]	25.0%	10.8%	6.0%	44%	14.2%
GP [a]	25.0%	10.8%	6.0%	44%	14.2%
Hospitalisation	26.5%	7.7%	6.8%	34.2%	24.8%

a) No specific information available for GP and no-GP cases; we used the age distribution as observed for all 16 regional PHLs[36] over the years.

5.2 Disease burden

Detailed information on severity of ReA is missing. We therefore assumed that the ReA symptoms were similar, independent if now Salmonella or Campylobacter was the triggering agent. The incidence, the used disability weights, the estimated YLD, YLL and DALY for all health states associated with community-acquired Salmonella-associated GE and sequelae, total and split up per health state, are shown in Table 20 for the most likely estimate only. In Figure 8 the most likely estimate for disease burden, total and per health state, as well as the attendant uncertainty is shown, both discounted (4%) and undiscounted. Non-fatal GE cases recover within few days, and also ReA symptoms were assumed to recover mostly within a year time. IBD symptoms, in contraty, are chronic and persist life-long. Premature death, however, is spread over several years. Therefore discounting the disease burden of fatal cases and IBD cases did have an impact as is shown in Figure 8.

Table 20. Incidence and disease burden of Salmonella-associated GE and sequelae for 2004 (most likely estimates) [a]

	Incidence	Disability weight per case/year	YLD (0%)	YLL (0%)	DALY (0%)	DALY (4%)
Gastroenteritis	35,000	-	100	440	550	420
No GP	30,000	0.001	30	-	30	30
GP	5,400	0.011	60	-	60	60
Hospitalization	640	0.017	11	-	11	11
Fatal	39	1	-	440	440	310
ReA	460	- [b]	40	-	40	40
IBD	7	0.26	80	-	80	33
Sum	-		220	440	670	500

[a)] Summations do not necessarily tally, see section 2.5.

[b)] Depends on severity, see Table 3. For more details see Mangen *et al.*[12].

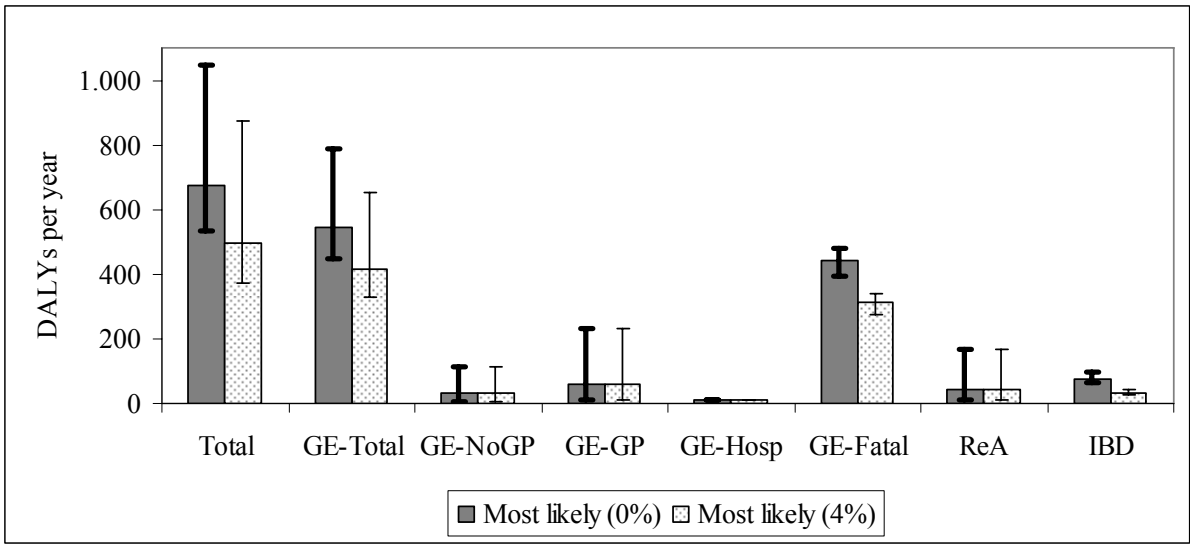


Figure 8. Disease burden of Salmonella-associated GE and sequelae for 2004, using most likely estimates, discounted (4%) and undiscounted (0%). Error bars express an uncertainty interval that results from using low and high estimates.

5.3 Cost-of-illness

Using the incidences and duration of illness listed in Table 18 and following the method and assumptions described in section 2.3.1 and in section 2.3.2, we estimated DHC for the different non-fatal health states of Salmonella-associated GE. Hospitalized Salmonella-associated GE patients were assumed to spend on average 8.4 days in hospital[29]. Hospitalized Salmonella patients are dehydrated, but also a bacteraemia might be the indication for admission. However, apart from some additional intravenous application of antibiotics, hospitalised treatments would be similar. To avoid double counting, as well as for reasons of simplification, we considered them in the current study, similar as for Campylobacter, within the group of hospitalised Salmonella GE cases. DHC results of community-acquired Salmonella-associated GE are summarized in Table 21, most likely estimate only.

Hardly any information was available with respect to the use of medical services for ReA cases. We therefore used the ReA cost estimates of Campylobacter-associated ReA of Mangen *et al*.[12], as a proxy, knowing that these cost estimates are probably an underestimation, rather than an overestimation of the true costs. The DHC estimates for IBD were based on Mangen *et al*.[12], whereby updating to the year 2004. Results are summarized in Table 21.

Table 21. DHC of Salmonella-associated GE and sequelae in million € for 2004 (most likely estimates) [a]

	Drugs & medicine	GP consultations	Hospitalization	Other	Σ DHC
Gastroenteritis [b]	0.06	0.35	2.27	-	2.7
No GP	0.01	-	-	-	0.01
GP	0.04	0.29	-	-	0.3
Hospitalisation	0.00	0.06	2.27	-	2.3
ReA	- [c]	- [c]	- [c]	-	0.02
IBD	- [c]	- [c]	- [c]	-	1.2
Total	-	-	-	-	4.0

[a)] Summations do not necessarily tally, see section 2.5.

[b)] Direct health care costs of fatal cases were included in the other non-fatal health states.

[c)] For details see Mangen *et al*.[12].

For Salmonella-associated GE, cases the considered DNHC were travel costs and additional diapers used for children of 3 years and younger, following the method and assumptions described in section 2.3.1 and section 2.3.2 for Campylobacter-associated gastroenteritis cases. In the case of ReA, only travel costs, were included in the DNHC estimates, which were an update of Mangen *et al*. [12] to 2004. In the case of IBD, apart from travel costs, also some co-payments by patients were included in the DNHC estimates (for more details see IBD estimates of Mangen *et al*.[12]). DNHC are only of minor importance with a total of € 0.03 million (most likely estimate), see Table 23.

For Salmonella-associated GE patients, we considered paid employment lost due to work absence of adult patients, as well as due to work absence of third persons taking care of sick persons, according to the method and assumptions described in section 2.3.1 and section 2.3.2. However, for Salmonella-associated cases that visit a GP the days off work were estimated to be 1.48 days. But with a reported 4.83 days in the GP-case control study, the English IID study[42] reported a higher number of days off work. We therefore used a pert distribution when estimating productivity losses for adult patients, with 1.48 days being *minimum* and *most likely value*, and with 4.83 days being our *maximum value*. The estimated 0.49 days off work for Salmonella-associated cases that would not visit a GP were similar with the findings in the English community-cohort. Most likely values for the number of days paid employment lost for patients and for third persons taking care of a sick GE case are summarized in Table 22. Details of INHC for the different health states of GE are given in Table 22.

In the case of ReA and IBD, only the work absence of patients was considered (for more details see Mangen *et al*. [12]). No information was available with respect to third persons

taking care of these sick persons or informal care. The INHC estimates for Salmonella-triggered ReA and IBD estimates are given in Table 22.

Table 22. INHC of Salmonella-associated GE and sequelae in € million for 2004 (most likely estimates)

	No. of days paid employment lost		Productivity losses		Σ INHC
	Patient	3rd person	Patient	3rd person	
Gastroenteritis			3.5	0.7	4.2
No GP	0.49	1.29	1.7	0.5	2.2
GP	2.06	2.48	1.2	0.2	1.4
Hospitalisation	5.73	3.76	0.4	0.03	0.4
Fatal	154	-	0.1	-	0.1
ReA	-[b]	-	0.02	-	0.02
IBD	-[b]	-	0.4	-	0.4
Sum	-	-	-	-	4.6

[a] Summations do not necessarily tally, see section 2.5.

[b] For details see Mangen *et al.*[12].

In Table 23 and Figure 9 we have summarized the most likely estimate and the most likely estimate with attendant uncertainty, respectively, for the total costs of community-acquired Salmonella-associated GE and Salmonella acquired ReA and IBD cases.

Table 23. Cost-of-illness of Salmonella-associated GE and sequelae in € million for 2004 (most likely estimates)[a]

	DHC (0%)	DNHC (0%)	INHC (0%)	Σ Costs (0%)	Σ Costs (4%)
Gastroenteritis	2.7	0.03	4.2	7.0	7.0
No GP	0.01	0.02	2.2	2.3	2.3
GP	0.3	0.01	1.4	1.7	1.7
Hospitalisation	2.3	0.00	0.4	2.7	2.7
Fatal	-	-	0.1	0.1	0.1
ReA	0.02	0.00	0.02	0.04	0.04
IBD	1.2	0.09	0.4	1.7	0.8
Sum	4.0	0.13	4.6	8.8	7.8

[a] Summations do not necessarily tally, see section 2.5.

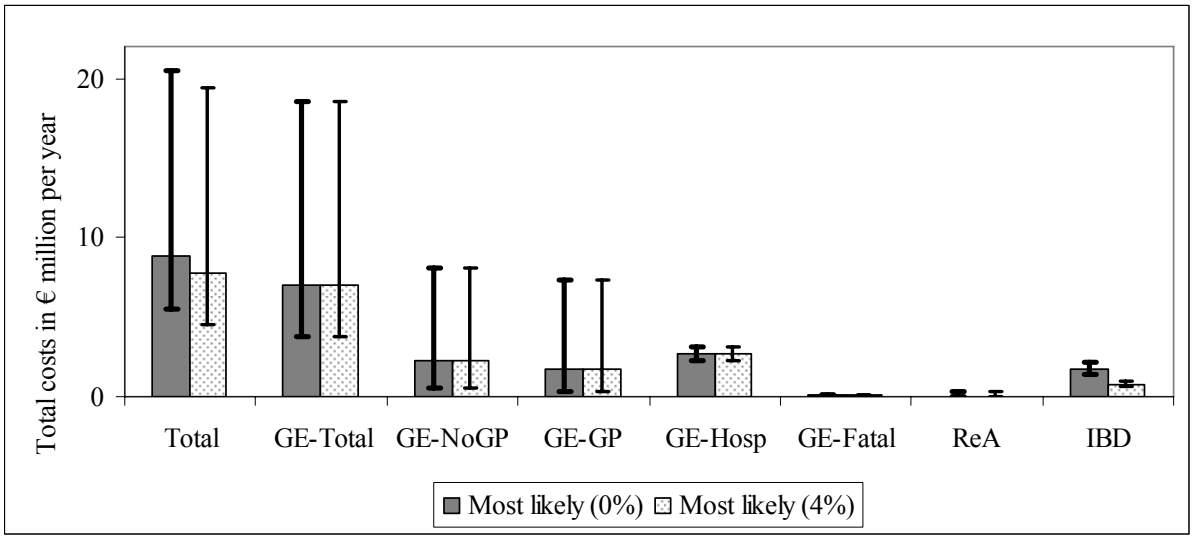


Figure 9. Cost-of-illness of Salmonella-associated gastroenteritis and sequelae, using most likely estimates, discounted (4%) and undiscounted (0%). Error bars express an uncertainty interval that results from using low and high estimates. Discounting was not required, as all costs occur within the first year.

5.4 Scenario analysis of Salmonella-associated ReA

In the current study we assumed that 8% (2.3% - 15%) of Salmonella gastroenteritis cases visiting a GP would develop ReA. But given the uncertainty of this latter assumption, we applied scenario analyses assuming that 1) 8% of all Salmonella-associated GE cases in the population would develop ReA (*population*); and 2) 8% of only laboratory-confirmed Salmonella GE cases would develop ReA (*lab only*). In Table 24 we have summarized the incidence and the DALY, total and split up per health state, for the baseline, as well as for the two ReA alternative scenarios, but only for the most likely estimate. In Figure 10 the attendant uncertainty around these most likely estimates is shown. Apart from the incidence and the estimated disease burden, also the cost-of-illness for the ReA health state only estimated is changing from € 0.04 million to € 0.24 million when the total population would be at risk and to € 0.02 million when only laboratory-confirmed cases would be at risk to develop ReA. However, these costs seem negligible compared to the costs of almost € 8.8 million for Salmonella-associated GE.

Table 24. Incidence and DALY of Salmonella-associated GE and sequelae, for baseline and alternative scenarios (most likely estimates) [a].

	Incidence			DALY (0%)		
	BASE	Lab only	Population	BASE [a]	Lab only	Population
Gastroenteritis	35,000	35,000	35,000	550	550	550
IBD	7	7	7	78	78	78
ReA (all)	460 [b]	205 [b]	2,700 [b]	40 [b]	20 [b]	240 [b]
No GP	370	170	2,220	30	13	170
GP	81	34	490	10	4	60
Hospitalisation	7	3	40	1	1	9
Sum	-	-	-	670	650	880

a) Summations do not necessarily tally, see section 2.5.

b) In the baseline we assume that 8% of the salmonellosis cases visiting a GP would develop ReA. In the two alternative scenarios we assumed that 8% of the laboratory-confirmed cases (lab only) would develop ReA, and 8% of all cases in the population (population) would develop ReA, respectively.

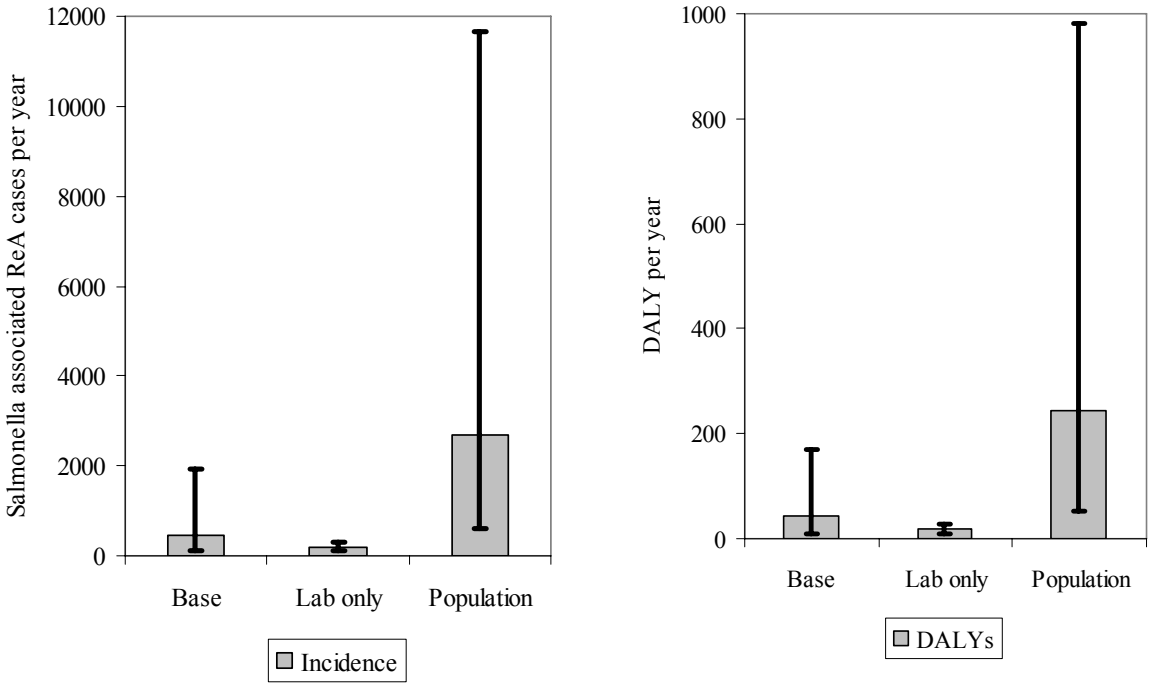


Figure 10. Incidence and DALY of Salmonella-associated ReA cases, for baseline and alternative scenarios, using most likely estimates. Error bars express an uncertainty interval that results from using low and high estimates. Discounting was not required as all costs occur within the first year.

5.5 Discussion

About 15% of all Salmonella-associated GE cases request medical help. In 39 cases of the total 35,000 GE cases, the disease is even fatal, mostly elderly patients. Salmonella infections result in about 460 cases of ReA and 7 cases of IBD. The estimated disease burden is equal to about 670 DALY per year (90% C.I.: 530 – 1050) and the associated costs-of-illness total to € 8.8 million per year (90% C.I.: € 5.5 million - € 20.5 million). The majority of the estimated

disease burden is due to GE (>80%). Of the estimated 550 DALYs associated with GE more than 80% is due to fatal cases. DHC accounts for about 45% of total costs (€ 4.0 million) and INHC for about 55%. IBD, although only 7 cases, accounts for 20% of the total, but undiscounted, costs and for 30% of undiscounted DHC. Costs associated with ReA play only a minor role, but it has to be noted that these costs are rather underestimated. Hardly any information was available here. There was no useful information available with respect to drug and medicine use, and also nothing with respect to potential sickness leave. We had only some useful information with respect to medical service use. We therefore opt for a conservative cost estimate. Including economic questions in ReA epidemiological studies questionnaires would be a great help to close this gap.

Similar as for Campylobacter, the assumption about the part of Salmonella-associated GE cases at risk for ReA had a large impact on the estimated disease burden. The estimated total disease burden would increase from 670 DAYLs per year to about 880 DALYs when every person infected with Salmonella would be at an 8% risk, compared to the assumed 8% of GE cases visiting a GP. Whereas assuming that only 8% of laboratory-confirmed cases would be at risk, lowered the disease burden only slightly to about 650 DALYs per year. The same holds for the ReA associated costs, although with respect to the total costs-of-illnesses associated with Salmonella GE and sequelae, this increase (decrease) is negligible.

There was only one very recent (February 2006) publication available that links a previous Salmonella infection with the onset of IBD within one year after infection (adjusted odds ratio: 24.58) [61]. Given that we had in a previous study[12] estimated the disease burden and related costs for Campylobacter-associated IBD cases, an update and recalculation of the Salmonella model, including IBD was quickly done. But apart from IBD, these authors found also an increased risk for developing IBS (adjusted odds ratio: 6.68). However, for IBS no information was available with respect to incidence in general population, disease burden and costs. We therefore decided that in the current study IBS would not be considered. It is foreseen to gather and include information on IBS in a following update of the current model.

6. Norovirus

In the SENSOR study[34] Norovirus (NV), formerly known as Norwalk-like viruses or SRSV, was observed to be the most frequent pathogen of community-acquired GE cases. Apart from GE, no other illnesses are known to be related to a NV infection in humans. Most NV cases are acquired in the community, but NV is also a common source of nosocomial infections acquired during a stay in health-care institutions, such as hospitals, nursing homes and homes for elderly[67]. The aim of the current study was to develop a model to prioritize foodborne pathogens in the community. Programs to reduce foodborne pathogens in the population, however, would have no or only an indirect impact on nosocomial infections acquired in health-care institutions. We therefore considered in the current study only community-acquired NV cases.

6.1 Outcome tree, incidence and duration of illness

6.1.1 Outcome tree and incidence

Based on SENSOR[34] the estimated incidence of community-acquired NV cases in the population was estimated to be 472,000 cases per year, with an uncertainty range ranking from 359,000 (low estimate) to 643,000 (high estimate), see Table 25. Of these approximately 11,000 cases would visit a GP[44], both hospitalised and not hospitalised cases. The hospitalization rate for community-acquired NV patients in the Netherlands is unknown. Based on studies from England/Wales[68] and the US[69] we assumed that *most likely*, but also at *maximum*, 0.33%, and at a *minimum* 0.22%, of the NV cases in the population would be hospitalized. Mead *et al*. [69] estimated for the US that NV would be fatal in 0.001% of the entire population of ill patients. However, a one year study of outbreaks of gastroenteritis in the Netherlands showed that only residents (about 0.3%) of nursing homes or homes for the elderly died because of an NV infection[67]. From the affected individuals in all other settings (households, restaurants/catering, schools, and day-care centers), nobody died[67]. In the current study we assumed, for the *low estimate*, that community-acquired NV cases would never be fatal. In our *most likely estimate* we considered that 0.001% of all NV cases in the population would be fatal. This figure was multiplied by two for the *high estimate*, resulting in the assumption that 0.002% of all NV cases in the population to be fatal. In Table 25 we have summarized the most likely estimates, and the attendant uncertainty, for the incidence of community-acquired NV GE in the total population and split up according to the different disease severity states related to this pathogen.

The outcome tree for NV as considered in this study is shown in Figure 11.

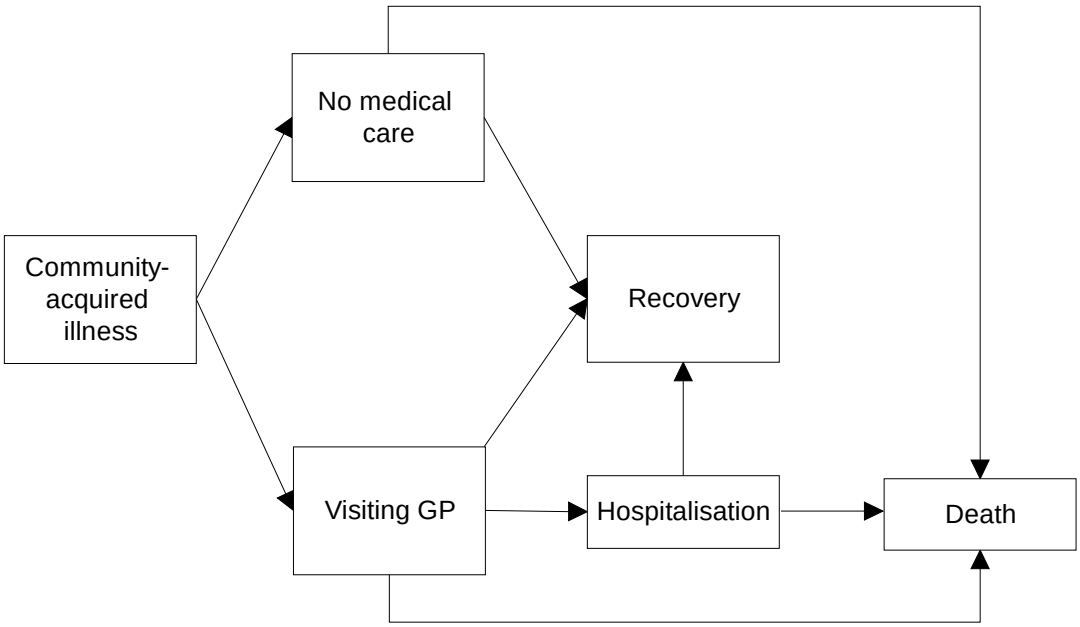


Figure 11. Outcome tree Norovirus-associated GE.

6.1.2 Duration of illness and age distribution

When estimating disease burden and cost-of-illness, information on duration of illness was required. Given that in most cases no doctor visit is required, we assume that the number of days of illness as found in community-cohort studies is representative for NV cases not visiting a GP. Based on medical diaries completed by participants of the SENSOR study with NV GE, Rockx *et al*. [70] estimated a median duration of illness of 6 days, 4 days, 5 days and 3 days, for patients aged <1 year, patients aged 1-4 years, patients aged 5-11 years and patients aged ≥ 12 years, respectively. No averages were reported. Multiplying these figures with the age distribution of community-acquired NV-GE cases, as shown in Table 26, we estimated that community-acquired NV cases not visiting a GP would be sick for 3.8 days (*most likely and high estimate*). This is slightly higher than the 3.32 days found in the community cohort of the English IID study[42] for SRSV (small rounded structured viruses), which was used as a *low* estimate for the number of days of illness. No information on duration of illness was available in the Netherlands for NV cases visiting a GP, hospitalized or not. The Food Standards Agency[42] reports an overall duration of illness for SRSV of 5.78 (range 0 -21), for all GP cohort cases, whereof an overall length of 0.048 days in hospital. We assumed that patients visiting a GP, hospitalized or not, would have the same overall mean for the period 'at home because of the illness' and the period 'feeling ill but able to do normal daily activities (work/school/shops)', which was 5.73 days (5.78-0.05). Hospitalized patients would on average have spent an additional 1.5 days in hospital[42] before recovering. This resulted in an average illness duration of 5.73 days for NV patients visiting only a GP and 7.23 days for hospitalized NV patients (see Table 25).

The age distributions of community-acquired NV-GE cases for the different disease severity states as used in the current study are shown in Table 26. Less than 3% of all NV cases would consult a GP. We therefore used for community-acquired NV-GE cases not visiting a GP the observed age distribution as found in the SENSOR study[34] for the entire population. For NV-GE cases visiting a GP the observed age distribution of the NIVEL[44] study was used. No information was available with respect to age distribution for specifically community-acquired hospitalised NV cases, or for community-acquired fatal NV cases, both severe disease states. Given that patients visiting a GP have on average more severe symptoms than an average case from the entire population, we assumed that the age distribution found in the GP case-control study (NIVEL) would be a better proxy for hospitalised cases than the one observed in SENSOR. However, from the outbreak study[67] it can be assumed that fatal cases will be almost excusively elderly individuals. But probably also for other immunity-compromised individuals, such as for example children younger than 5 years, an NV infection might be fatal. We therefore assumed that fatal cases would be in 95% elderly persons (> 64 years) and 5% would be children younger than 5 years. Using the age distribution for fatal cases, as given in Table 26, we estimated the age-specific incidences for all NV cases in the population, which were multiplied by the expected life span as reported in standard life tables by Statistics Netherlands for the year 2004. No distinction between men and women was made.

Table 25. Incidence and duration of illness of community-acquired NV-associated GE for 2004a

	Incidence estimate (cases per year)			No. of days of illness
	Most likely	Low	High	
Gastroenteritis	470,000	360,000	645,000	-
No GP	460,000	350,000	625,000	3.8
GP	10,000	7,000	16,000	5.7
Hospitalisation	1,000	790	2,100	7.2
Fatal	5	0	13	-[b]

[a)] Summations might not necessarily tally because of rounding errors.

[b)] Not shown as we used here the expected individual life span at the age of death.

Table 26. Age distribution of community-acquired NV-associated GE.

	Age classes				
	0-4 years	5-9 years	10-14 years	15-64 years	> 65 years
Gastroenteritis					
No GP	33,2%	14,4%	8,0%	34,9%	9,5%
GP	66,4%	5,3%	5,3%	20,5%	2,5%
Hospitalisation[a]	66,4%	5,3%	5,3%	20,5%	2,5%
Fatal	5%	0%	0%	0%	95%

[a)] No information available. We used the NIVEL age distribution as a proxy.

6.2 Disease burden

Incidence, used disability weights, and estimated results for YLD, YLL and DALY, discounted (4%) and undiscounted (0%), of community-acquired NV-associated GE are shown in Table 27 for the most likely estimate only. In Figure 12 results of community-acquired NV-associated GE are summarized for the most likely estimate and the attendant uncertainty. Discounting or not discounting the disease burden of non-fatal cases has no impact given that non-fatal gastroenteritis cases always recover within a few days. Years of life lost due to premature death, however, spreads out over several years. Consequently, discounting the disease burden of fatal cases does have an impact, see Figure 12.

Table 27. Incidence and disease burden of community-acquired NV-associated GE for 2004 (most likely estimates) [a]

	Incidence	Disability weight per case/year	YLD (0%)	YLL (0%)	DALY (0%)	DALY (4%)
Gastroenteritis	470,000	-	390	55	450	430
No GP	460,000	0.0007	320	-	320	320
GP	10,000	0.0062	65	-	65	65
Hospitalisation	1,000	0.0078	8	-	8	8
Fatal	5	1	-	55	55	35

[a)] Summations might not necessarily tally because of rounding errors.

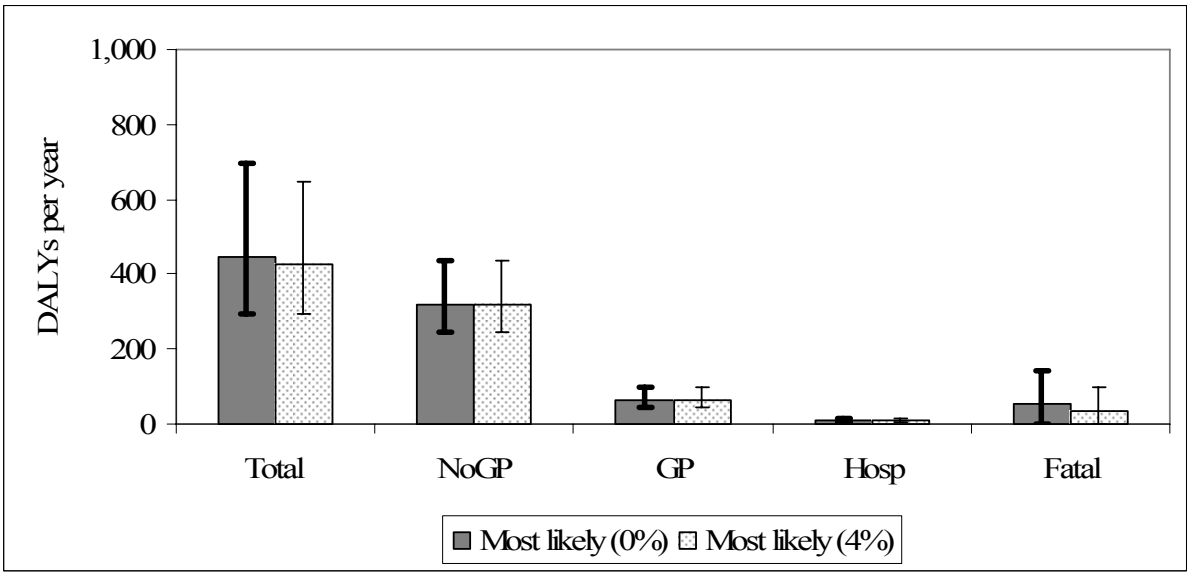


Figure 12. Disease burden of community-acquired NV-associated GE for 2004, using most likely estimates, undiscounted (0%) and discounted 4%). Error bars express an uncertainty interval that results from using low and high estimates.

6.3 Cost-of-illness

Based on the incidence and the duration of illness shown Table 25, and following in general the assumptions described in section 2.3.1, we estimated the direct health care costs for the different non-fatal health states as described in section 2.3.2. Hospitalized community-acquired NV patients were assumed to spend on average 1.5 days in hospital[42]. Dehydration remains the most common complication of disease, especially in young children and elderly persons, and no other severe sequelae have been reported[71]. The required medications were assumed to be included in the daily hospitalization fee, which included also staff costs and some basic medications. Although laboratory-confirmed NV cases are not reported in a national surveillance scheme, we assumed that at least for community-acquired hospitalised NV patients' laboratory testing would occur. We did not calculate the direct health care costs for fatal cases separately. These patients were already considered in one of the other sub-groups of community-acquired NV patients. DHC results of community-acquired NV cases are summarized in Table 28 for the most likely estimate only.

Table 28. DHC of community-acquired NV-associated GE in million € for 2004 (most likely estimates) [a]

	Drugs & medicine	GP consultations	Hospitalization	Other [c]	Σ DHC
Gastroenteritis [b]	0.73	0.44	0.74	-	1.9
No GP	0.27	-	-	-	0.3
GP	0.42	0.34	-	-	0.8
Hospitalisation	0.04	0.10	0.74	-	0.9

a) Summations might not necessarily tally because of rounding errors.

b) Direct health care costs of fatal cases are included in the other non-fatal health states.

c) For NV cases, apart from costs for drugs and medicine, GP consultations and hospitalization, no other direct health care costs were made.

DNHC considered in the current study were travel costs and additional diapers used for children of 3 years and younger, following the method and the assumptions described in section 2.3.1 and section 2.3.2. DNHC are only of minor importance with a total of € 0.3 million (most likely estimate), see Table 30.

Paid employment lost was considered in the current study due to work absence of patients as well as due to work absence of third persons taking care of sick persons, according to the method and assumptions described in section 2.3.1 and section 2.3.2. The estimated average work absence of 0.33 days of adult NV patients not visiting a GP was similar to the work absence reported for SRSV cases in the English community-cohort study[42]. However, for NV cases visiting a GP, our *most likely* estimate and *minimum* estimate of 0.9 days paid employment lost was lower than the 1.32 days reported by the Food Standards Agency [42]. This latter was considered in the *high* cost estimate. In Table 29 we have summarized the estimated number of days paid employment lost for adult patients and for third persons taking care of sick person. We further do present in Table 29 the most likely estimate of INHC.

Table 29. Number of days paid employment lost and INHC of community-acquired NV-associated GE in € million for 2004 (most likely estimates)[a]

	No. of days paid employment lost		Productivity losses		Σ INHC
	Patient	3rd person	Patient	3rd person	
Gastroenteritis	-	-	16.1	6.7	22.8
No GP	0.33	0.88	15.4	6.4	21.8
GP	0.80 [a]	1.33	0.5	0.3	0.8
Hospitalisation	2.56	1.68	0.2	0.03	0.2
Fatal	154	n.a [b]	0	n.a [a]	0

a) Summations might not necessarily tally because of rounding errors.
b) Not applicable (n.a.)

In Table 30 and Figure 13 we have summarized the most likely estimate and the most likely estimate with attendant uncertainty, respectively, for the total costs of community-acquired NV GE. The INHC are by far the dominant cost category within the cost-of-illness estimate. Given that all costs occur within one year, discounting the costs is not an issue.

Table 30. Cost-of-illness of community-acquired NV-associated GE in € million for 2004 (most likely estimates) [a,b]

	DHC (0%)	DNHC (0%)	INHC (0%)	Σ Costs (0%)	Σ Costs (4%)
Gastroenteritis	1.9	0.33	22.8	25.0	25.0
No GP	0.3	0.29	21.8	22.4	22.4
GP	0.8	0.03	0.8	1.5	1.5
Hospitalisation	0.9	0.01	0.2	1.1	1.1
Fatal	0	0	0	0	0

a) Summations might not necessarily tally because of rounding errors.
b) No discounting required as costs were all made within one year.

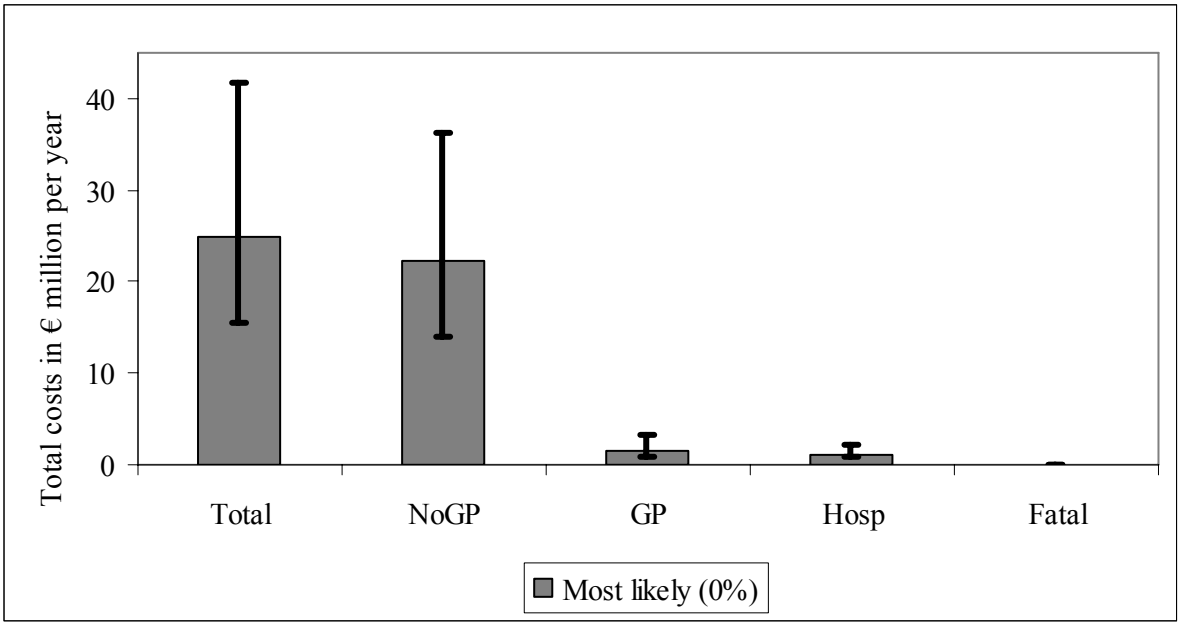


Figure 13. Cost-of-illness of community-acquired NV-associated GE, using most likely estimates. Error bars express an uncertainty interval that results from using low and high estimates. Discounting was not required as all costs occur within the first year.

6.4 Discussion

With about 470,000 NV cases occurring each year in the entire population, Norovirus outnumbers, with respect to incidence, by far any other foodborne pathogen. Despite the relatively high number of annual NV cases, the associated disease burden is about 450 DALYs per year, with an uncertainty range of 300 DALYs to 700 DALYs per year. The majority of NV cases (~ 97%) require no medical services. The disease burden associated to NV cases not visiting a GP, - approximately 97% of all NV cases -, accounted for 80% to 83% of the total disease burden associated to non-fatal NV cases. Less than 3% of all non-fatal NV cases were assumed to consult a GP or any other medical service. Resulting in a total of 70 DALYs (range: 50 DALYs -120 DALYs). NV was estimated to be fatal for about five NV cases (range: 0 – 13), mostly elderly persons. YLL accounted than also only for about 12% (range: 20% - 0%) of the total estimated disease burden, which was far lower compared to bacterial foodborne pathogens, such as Campylobacter or Salmonella. Total costs associated with community-acquired NV-associated GE totalled to € 25 million, with an uncertainty range of € 16 million to € 42 million. Despite the fact that we had not explicitly considered opportunity costs for the number of days lost for unpaid jobs, the indirect non-health care costs accounted for 90% of all costs associated to community-acquired Norovirus gastroenteritis.

Norovirus is each year responsible for numerous outbreaks in health care institutions[67]. But in the current study, nosocomial infections were not included. By including also nosocomial infections estimated disease burden and estimated costs-of-illness would have been higher.

7. Rotavirus

Rotavirus (RV) is a major cause of gastroenteritis. Specific sequelae such as for example ReA, GBS or HUS, occurring after an RV-associated GE are unknown. But RV is one of the major pathogens triggering nosocomial infections in paediatrics[72 73]. But given the aim of the current study, which was the prioritisation of foodborne pathogens in the community, nosocomial infections acquired in hospitals were not considered in the current study.

7.1 Outcome tree, incidence and duration of illness

7.1.1 Outcome tree and incidence

Based on the SENSOR study[34], and corrected for the trend observed in laboratory-confirmed cases[37], we estimated the number of community-acquired RV GE cases in the entire population to be 190,000 cases per year (range: 110,000 - 325,000). About 7% of all RV cases searched medical help[44]. Medical help was either a GP consultation, or a GP consultation with afterwards a transfer to hospital. About 1,000 cases of RV cases are each year reported to the Dutch surveillance system[37], which is according to van den Brandhof *et al*. [74] only 38% of all reported RV cases. In 2000-2004 about 94% of all laboratory-confirmed RV cases in the Netherlands were children younger than five years[37]. This was in line with the results of De Wit *et al*. [72], who reported for 1998 that of all community-acquired hospitalized RV cases 95% were younger than five years, and only 5% were five years or older. By combining data from the National Disease Registry on hospitalizations for gastroenteritis and laboratory surveillance data in a linear regression model, Van Pelt *et al*. [37] indirectly estimated the incidence and proportion of hospitalizations attributable to RV infection, but only for children younger than five years for the years 1996 to 2004. Taking the average over these years, we estimated that an average of 6,160 children younger than five years were hospitalized each year for gastroenteritis, whereof on average 54% (number = *most likely* estimate) was attributable to RV; ranging from 36% (number = *low* estimate) to 66% (number = *high* estimate). According to De Wit *et al*. [72], who conducted a similar study for the years 1996-1998, only 86.6% of these estimated hospitalized RV cases would be acquired in the community. The other 13.4% were so-called nosocomial RV cases that were acquired in hospital. In the current study, only community-acquired RV cases were considered. No information was available for children and adults older than 5 years, in total 5% of all hospitalized RV cases. We therefore considered them as being all in the age class five to nine years. In some rare cases RV infections can be fatal. No information was available on the occurrence of deaths due to RV within the Netherlands. We therefore based our estimate on Chang *et al*. [75], who reported the death of two children with RV as the potential primary cause in a total of 4,181 hospitalized children with RV as primary diagnosis in the New York State from 1989 to 2000, all children younger than five years. With an average 2,880 community-acquired hospitalized RV cases younger than five years each year in the Netherlands, a total of 1.4 would be fatal. Results are summarized in Table 31.

The NV outcome tree as considered in the current study is shown in Figure 14.

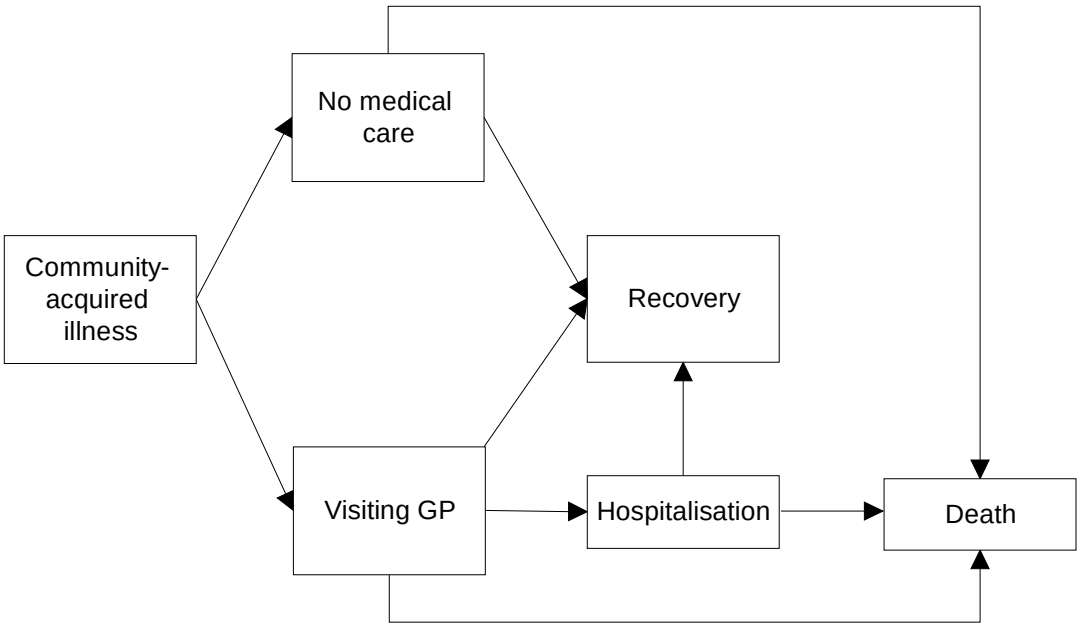


Figure 14. Outcome tree Rotavirus-associated GE

7.1.2 Duration of illness and age distribution

Information on duration of illness was required for both, the disease burden and the costs calculations. The only available information in the Netherlands with respect to duration of illness was for hospitalised children. According to De Wit *et al*. [72] the average stay in hospital of community-acquired RV cases was 4 days, with an average duration of 3.7 days of symptoms before admission to hospital. For RV patients not visiting a GP and RV patients visiting a GP but not being hospitalized, we used the overall duration of illness as reported by the Food Standards Agency[42] in the community-cohort and in the GP case-control component, respectively, but subtracting the overall mean time spent in hospital. Results are reported in Table 31.

Table 31. Incidence and duration of illness of community-acquired rotavirus-associated GE for 2004 [a]

	Incidence estimate (cases per year)			No. of days of illness
	Most likely	Low	High	
Gastroenteritis	190,000	110,000	325,000	-
No GP	170,000	100,000	305,000	4.9
GP	11,000	6,900	17,000	7.1
Hospitalisation	3,000	2,000	3,700	7.7
Fatal	1.4	0.9	1.7	-[b]

[a] Summations might not necessarily tally because of rounding errors.

[b] Not shown as we used here the expected individual life span at the age of death.

The age distribution of community-acquired Rotavirus-associated GE for the different health states is summarized in Table 32. Given that the majority of RV cases would not need a doctor, we assumed that the age distribution of RV cases as found in SENSOR [34] would be representative for RV cases not visiting a GP (No GP). The age distribution of RV cases visiting a GP was based on NIVEL [44]. The age distribution for hospitalised RV cases was based on a study on RV hospital admissions in 1998, where 95.2% were children below five years of age[72]. Whereas for fatal cases, we assumed that 100% of the RV cases would be in children younger than five years.

Table 32. Age distribution of community-acquired RV-associated GE.

	Age classes				
	0-4 years	5-9 years	10-14 years	15-64 years	> 65 years
Gastroenteritis					
No GP	31.8%	3.8%	1.8%	51.8%	10.9%
GP	81.5%	1.5%	1.5%	10.3%	5.2%
Hospitalisation	95%	5%	-	-	-
Fatal [a]	100%	-	-	-	-

[a)] Assuming that RV infection would be only fatal in children younger than five years.

7.2 Disease burden

Most likely values for incidences, used disability weights per case per year, and estimated YLD, YLL and DALYs, undiscounted and discounted at 4%, are shown in Table 33 for the different health states associated with RV. Most likely estimates and attendant uncertainty for disese burden, undiscounted (0%) and discounted (4%), are shown in Figure 15. Given that the years of life lost due to premature death would be spread over several years, discounting the disease burden had an impact on fatal cases. No discounting of the disease burden of non -fatal RV cases was required, as these cases recovered within a few days.

Table 33. Incidence and disease burden of community-acquired RV-associated GE for 2004 (most likely estimates) [a]

	Incidence	Disability weight per case/year	YLD (0%)	YLL (0%)	DALY (0%)	DALY (4%)
Gastroenteritis	190,000	-	260	110	370	290
No GP	170,000	0.0009	160	-	160	160
GP	11,000	0.0076	80	-	80	80
Hospitalisation	3,000	0.0083	25	-	25	24
Fatal	1.4	1	-	110	110	33

[a)] Summations might not necessarily tally because of rounding errors.

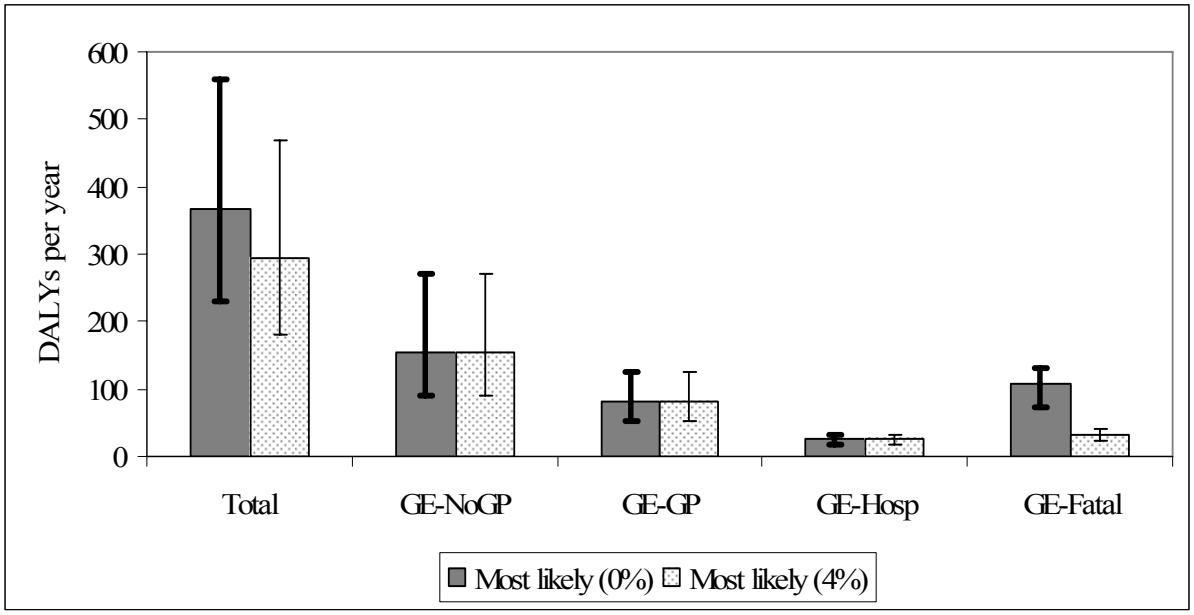


Figure 15. Disease burden of community-acquired RV-associated GE for 2004, using most likely estimates, both, undiscounted (0%) and discounted (4%). Error bars express an uncertainty interval that results from using low and high estimates.

7.3 Cost-of-illness

Following the method and the assumptions described in section 2.3.1 and in section 2.3.2, we estimated the direct health care costs for the different non-fatal health states for RV-associated GE cases. The used incidence numbers and duration of illness are shown Table 31. Assuming that only 38% of all laboratory-confirmed RV cases[74] would be reported to the Dutch RV surveillance system, the number of positive laboratory tests for RV were estimated to be above 2,700 per year. An average hospital stay of 4 days was assumed for community-acquired RV cases[72]. This is in line with other European studies[73 76], who estimated the average length of hospitalisation of RV infected children to be 3.8 days and 4.2 days, respectively. The required medications for dehydration, the most common complication of disease, were assumed to be included in the daily hospitalisation fee, which included also staff costs and some basic medications. DHC for fatal cases were not considered separately. These patients were already considered in one of the other sub-groups of community-acquired RV patients. DHC results of community-acquired RV cases are summarized in Table 34 for the most likely estimate only.

Table 34. DHC of community-acquired RV-associated GE in million € for 2004 (most likely estimates) [a,]

	Drugs & medicine	GP consultations	Hospitalization	Other [c]	Σ DHC
Gastroenteritis	0.68	0.62	5.8	-	7.1
No GP	0.13	-	-	-	0.1
GP	0.43	0.34	-	-	0.8
Hospitalisation [b]	0.12	0.28	5.8	-	6.2

[a)] Summations might not necessarily tally because of rounding errors.

[b)] Direct health care costs of fatal cases are included in the hospitalisation health state.

[c)] In the case of RV cases, apart from costs for drugs and medicine, GP consultations and hospitalization, no other direct health care costs were made.

DNHC considered in the current study were travel costs and additional diapers used for children of 3 years and younger, following the method and the assumptions described section 2.3.1 and in section 2.3.2. DNHC are only of minor importance with a total of € 0.2 million (most likely estimate), see Table 36.

Paid employment lost was considered in the current study due to work absence of patients as well as due to work absence of third persons taking care of sick persons, according to the method and assumptions described in section 2.3.1 and in section 2.3.2. The estimated overall work absence for RV patients not visiting a GP and RV patients visiting a GP only were estimated to be 0.43 days and 1.0 days, respectively. For RV cases visiting a GP, the Food Standards Agency [42] observed an overall mean of 1.33 days paid employment lost, if adult. This latter figure was considered in the high cost estimate. In Table 35 we have summarized the estimated number of days paid employment lost for adult patients and for third persons taking care of sick person. We further do present in Table 35 the most likely estimate of INHC.

Table 35. Indirect non-health care costs of community-acquired rotavirus-associated *gastroenteritis in € million for 2004 (most likely estimates)* [a]

	No. of days paid employment lost		Productivity losses		Σ INHC
	Patient	3rd person	Patient	3rd person	
Gastroenteritis	-	-	11.4	2.9	14.3
No GP	0.43	1.13	11.1	2.5	13.6
GP	1.00	1.65	0.3	0.3	0.7
Hospitalisation	2.73	1.79	0 [a]	0.1	0.1
Fatal	154	n.a [b].	0 [a]	n.a.	0

[a)] Summations might not necessarily tally because of rounding errors.

[a)] No productivity losses as only children younger than 5 years.

[b)] Not applicable (n.a.)

In Table 36 and Figure 16 we have summarized the most likely estimate and the most likely estimate with attendant uncertainty, respectively, for the total costs of community-acquired

RV-associated GE cases. The INHC are by far the dominant cost category within the cost-of-illness estimate. Given that all costs occur within one year, discounting costs is not an issue.

Table 36. Cost-of-illness of RV-associated GE in € million for 2004 (most likely estimates) [a]

	DHC (0%)	DNHC (0%)	INHC (0%)	Σ Costs (0%)	Σ Costs [b] (4%)
Gastroenteritis	7.1	0.2	14.3	21.7	21.7
No GP	0.1	0.1	13.6	13.8	13.8
GP	0.8	0.04	0.7	1.5	1.5
Hospitalisation	6.2	0.02	0.1	6.4	6.4
Fatal	n.a [c]	n.a [c]	0	0 [d]	0 [d]

[a] Summations might not necessarily tally because of rounding errors.

[b] No discounting required as costs were all made within one year.

[c] Not applicable (n.a.)

[d] No productivity losses as RV is only fatal in children younger than 5 years.

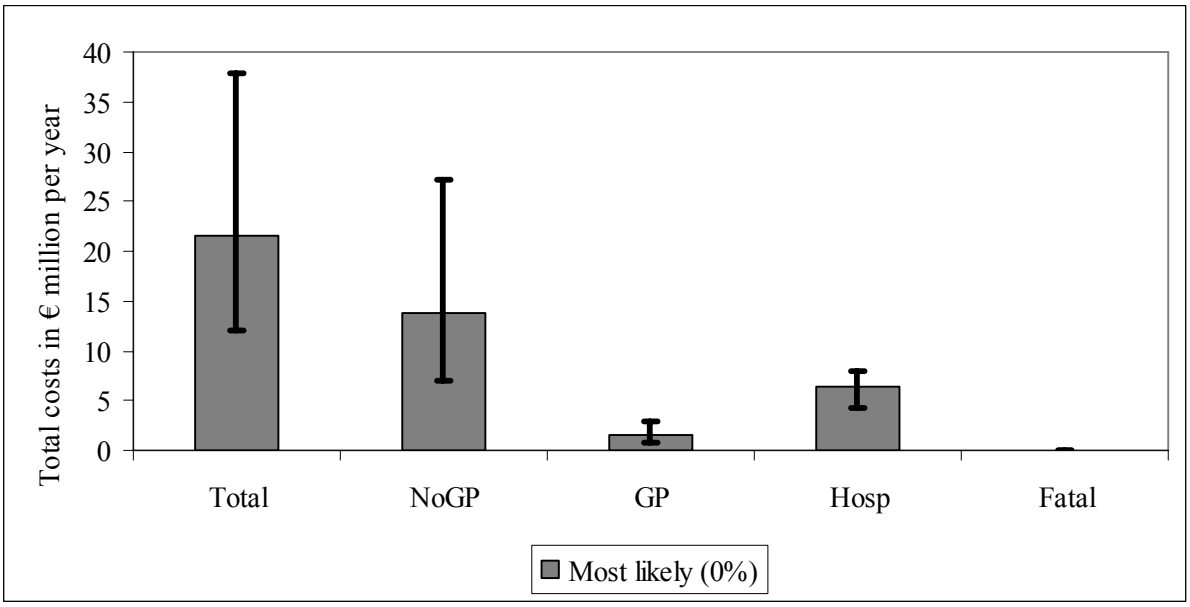


Figure 16. Cost-of-illness of community-acquired RV-associated GE, using most likely estimates. Error bars express an uncertainty interval that results from using low and high estimates. Discounting was not required as all costs occur within the first year.

7.4 Discussion

About 190,000 community-acquired RV cases occur each year in the entire population. Severe community-acquired RV cases are mainly found in children younger than five years. A total of 3,000 community-acquired RV cases in children younger than five years result in hospital admission each year (range: 2,000 – 3,700). Community-acquired RV cases results each year in 370 DALY, with an uncertainty range of 230 DALYs to 560 DALYs per year (undiscounted). The majority of RV cases (~ 93%) required no medical services. Total costs associated with community-acquired RV-associated GE totalled to € 21.7 million, range: € 12

million to € 38 million. Despite the fact that we had not explicitly considered opportunity costs for the number of days lost for unpaid jobs, INHC accounted for about 65% of all costs associated to community-acquired RV-associated GE cases. Of the € 7 million DHC, more than 80% of the costs are related to hospitalized RV cases.

Rotavirus is a major source for hospital acquired GE, mainly in hospitalised children. But similar as for Norovirus, nosocomial infections were not included in the current study. By including also nosocomial infections estimated disease burden and estimated costs-of-illness would have been slightly higher.

8. Listeriosis

Listeriosis, caused by the Gram-positive bacterium *Listeria monocytogenes* is a relatively rare disease with an incidence rate typically in the range of 2 to 8 cases per 1,000,000 individuals[77,78]. *L. monocytogenes* causes listerioses, an illness that is potentially life-threatening for riskgroups like neonates, elderly (especially with co-morbidity) and patients with impaired cell-mediated immunity[79]. Infections in previously healthy individuals may cause febrile gastroenteritis and are usually mild and self-limiting[80 81]. There can be a substantial delay (one to six weeks) between the time of ingestion of a contaminated food and the onset of serious symptoms. Listeriosis may lead to severe illnesses, like meningitis and septicemia[79,.82].

L. monocytogenes is commonly found in soil and water, and it has been isolated from a wide range of domestic and wild animals. Vegetables and fruit can become contaminated from the soil or from manure used as a fertilizer. Animals can carry the bacteria without apparent illness, and can contaminate foods of animal origin such as meats and dairy products. *L. monocytogenes* has been found in raw foods, such as uncooked meats, vegetables, fruits, and dairy products made from unpasteurised milk. However, contamination after pasteurization can occur because the microorganism can readily adapt to and live in the environment of food processing, distribution, and retail facilities. Unlike most foodborne pathogens, it can grow at refrigeration temperatures in many foods. It can also tolerate and grow in relatively acid foods, in foods with relatively low moisture content, and in foods with high salt concentration. This ability to persist in the food environment makes *L. monocytogenes* a particularly difficult micro-organism to control[83]. On the other hand, Goulet *et al.* suggested that there is a causal relationship between prevention measures by the food industry (i.e. control measures implemented at the food production level) reduction in *L. monocytogenes*-contaminated foodstuffs, and reduction in listeriosis incidence[84].

8.1 Perinatal listeriosis

8.1.1 Outcome tree and incidence

The perinatal group consists of pregnant women and their foetuses or newborns (see Figure 17). About two-thirds of *L. monocytogenes*-infected pregnant women will present with a prodromal influenza-like illness, which includes fever, chills and headache. About three to seven days after the onset of prodromal symptoms, a woman may abort the foetus or have premature labour[85]. In the first trimester, listeriosis may result in spontaneous abortion. In later stages of pregnancy the result may be stillbirth or a critically ill newborn. Listeriosis is rarely severe or life-threatening to the mother and is not known to cause increased risk in subsequent pregnancies[86]. Neonates may present with an early-onset or late-onset form of listeriosis. Early-onset (infected *in utero*) is defined as a case of listeriosis in a neonate less than 7 days old. Most early-onset cases develop sepsis and 20% have meningitis [87], which may lead to long term sequelae[88]. Late-onset (infection as a result of acquisition of the

organism during passage through the birth canal, although late-onset can also occur following caesarean delivery[89]) is defined as listeriosis in a neonate between 8 to 28 days of life. Usually, late-onset neonates are born healthy and at full term, but are at higher risk to develop meningitis during their first weeks of life[87]. The mothers of babies with late-onset listeriosis usually had an uneventful pregnancy without prodromal illness[86]. Most likely, the disease burden for the health outcomes of early- and late-onset infections will not differ from each other. Therefore we decided to combine these two categories.

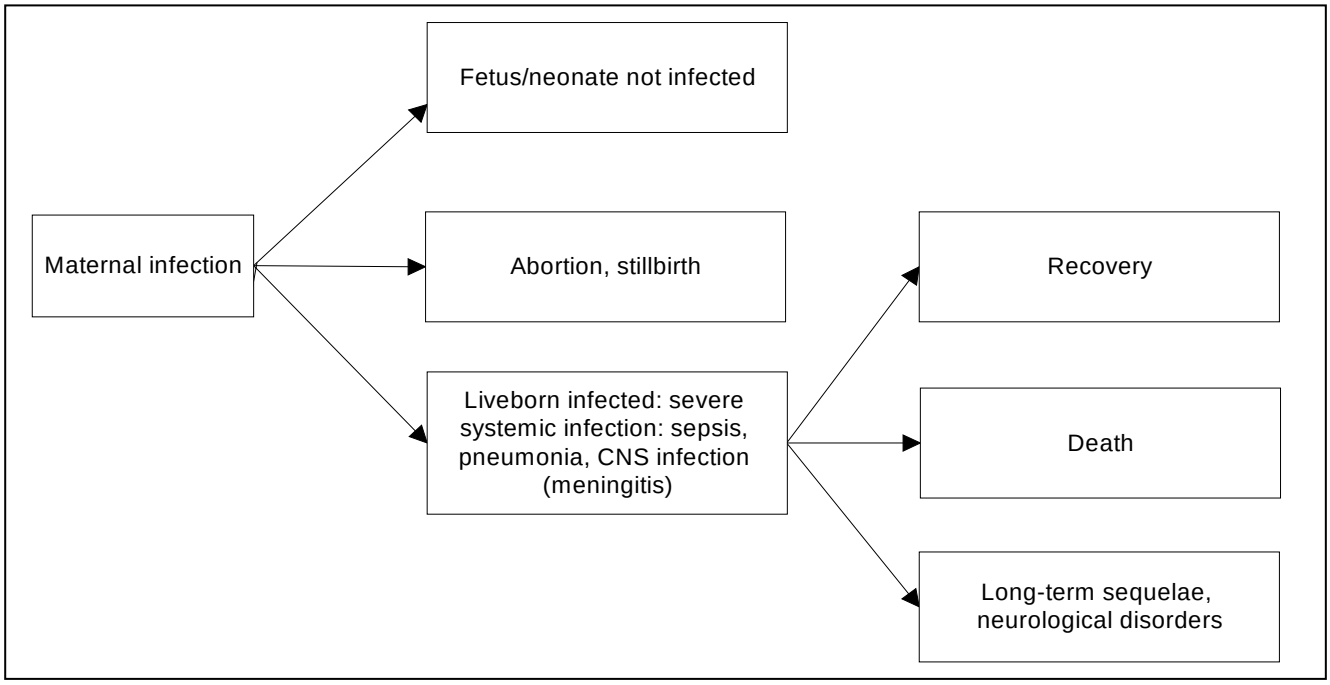


Figure 17. Outcome tree for perinatal listeriosis.

Incidence in the Netherlands

In the Netherlands the incidence of pregnancy-related listeriosis is recently estimated to range from 1.3 and 2.4 per 100,000 pregnancies over 24 weeks of gestation[90], although these incidences not only included children with perinatal listeriosis but also included pregnant women with listeriosis. Another Dutch study[91] showed a mean annual incidence of neonatal invasive infections of 1.3 per 100,000 live born children.

In January 2005, an enhanced surveillance of *Listeria monocytogenes* was implemented in the Netherlands. All laboratories were requested to report positive cases to the public health services and submit *Listeria* isolates of patients with meningitis or septicaemia to the Netherlands Reference Laboratory for Bacterial Meningitis (RBM). All isolates of the RBM were also forwarded to the RIVM for typing. In the first half of 2005, 2 pregnancy-related cases of listeriosis were detected, so the estimated incidence of perinatal listeriosis would be 4 per year.

Incidence of health outcomes

Results from several studies showed that about 15-25% of the perinatal infections will lead to abortion or stillbirth, and 55-70% of the infections result in a severe systemic infection like sepsis, pneumonia, or CNS infection[88,77]. In 5-25% of the affected pregnancies, the infant was born alive and without evidence of listeriosis[88,77]. Sixty-three percent of the live-born infected neonates recovered completely, 25% died, and 13% had neurological sequelae or other long-term complications[88]. A retrospective study in the Netherlands showed that 56% of the pregnancies with a maternal infection resulted in premature birth of an ill child (of which 20% died as a consequence of listeriosis), 22% resulted in intrauterine death, 17% resulted in a full-term child with meningitis and 6% resulted in a premature birth of a healthy child[92]. A review study from the same authors showed that 11% of the infected children suffered from sepsis[92].

In the disease burden calculation we used the results from the enhanced surveillance. Results from the retrospective and review study were considered in a scenario analysis.

In the first half of 2005, two newborns with a perinatal infection were found in the enhanced surveillance. Both children died; one at 28 weeks. Hence, the uncertainty of the incidence rate of fatal cases is Gamma (2,2) distributed with low - most likely –high values of 0.7 - 4 - 9.5 fatal cases per year, respectively (see Table 37).

Table 37. Incidence and duration of illness of perinatal listeriosis for 2005.

	Incidence estimates (cases per year)			No. of years
	Most likely	Low	High	of illness
Death in perinatal period	4	0.7	9.5	79
Long term sequelae	n.a.	n.a.	n.a.	n.a.

8.1.2 Disease burden

Table 38 presents the incidence, severity weight, duration and burden of disease per health outcome for a perinatal listeria infection. The calculated number of DALYs is 320. Taking the discount factor of 4% into account reduced the disease burden to 90 DALYs. The disease burden for perinatal listeriosis was calculated with data from the enhanced surveillance in the Netherlands. Since this surveillance has started in January 2005 and the incidence of perinatal listeriosis is very low, no surviving children were included. Therefore, the percentage of children developing long-term sequelae is not known, and the number of DALYs is fully contributed by the fatal cases.

Table 38. Incidence and disease burden of perinatal listeriosis for 2005 (most likely estimates).

	Incidence	Duration (years)	YLD	YLL	DALY (0%)	DALY (4%)[a)]
Death in postnatal period	4	79	0	320	320	90
Long term sequelae	na	na	na	na	na	na
TOTAL					320	90

[a] Discounted disease burden

Uncertainty analysis

Figure 18 shows the uncertainty in disease burden for perinatal listeriosis. In this calculation we choose the lowest and highest incidence rates, which was 0.7 and 9.5 for postnatal death, respectively (see Table 37). The minimum and maximum disease burden for perinatal listeriosis then appeared to be 60 and 750 DALYs, when we did not take the discount factor into account. Including the discount factor of 4%, the disease burden ranged from 20 to 220 DALYs.

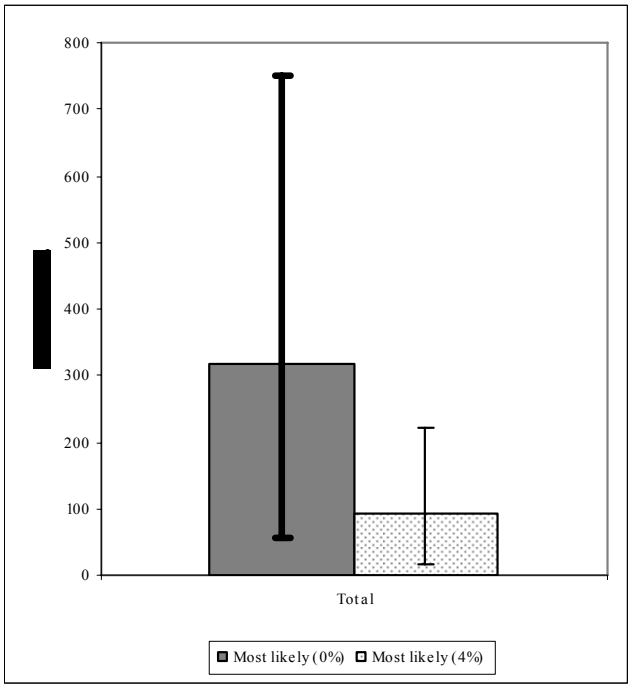


Figure 18. Disease burden of perinatal listeriosis for 2005, using most likely estimates. Error bars express an uncertainty interval that results from using low and high estimates.

Scenario analysis

Information on the incidence of *L. monocytogenes* infections in the Netherlands is limited. Therefore, the enhanced surveillance started in 2005 to get more inside in the incidence, risk factors and symptoms of this disease. However, up till now, this surveillance includes just a small number of patients, and therefore, no data are available about the incidence of several health outcomes. Using data from a retrospective study to the incidence of (severe) diseases

due to infection with *L. monocytogenes* in the Netherlands[92]showed a disease burden of 70 DALYs. This low number compared to the number of DALYs from the results of the enhanced surveillance (i.e. 320 DALYs) is mainly caused by the lower incidence of deaths (25% vs. 100%). Besides that, other health outcomes like meningitis, sepsis and long-term sequelae did not contribute to the disease burden.

The Dutch Public Health and Forcasts Report do not include perinatal deaths in their disease burden calculations. Using the same policy in our DALY calculation means excluding one child who died three days after it was born at 28 weeks of gestation. In this scenario the total number of DALYs for perinatal listeriosis decreased to 160.

8.2 Acquired listeriosis

8.2.1 Outcome tree and incidence

Acquired listeriosis is a relatively rare disease in North America en Western Europe, with an incidence rate typically in the range of 1.7 to 7.4 cases per 1,000,000 individuals per year[77,78]. Most individuals infected with *L. monocytogenes* do not experience obvious symptoms. In the first half of 2005, the Dutch enhanced surveillance reported 34 acquired cases, so the extrapolated estimated incidence rate is then 68 cases per year, i.e. 4.3 cases per 1,000,000 individuals per year.

Figure 19 shows the outcome tree for acquired listeriosis. In the enhanced surveillance, septicaemia was the most common sign (37%), followed by meningitis (22%), gastroenteritis (22%) and pneumonia (15%)[92]. In a retrospective study of 207 cases of *L. monocytogenes* meningitis in the Netherlands over a 20-year period, Aouaj *et al.* showed that fourteen percent of the adults with listeria meningitis will develop neurological sequelae[93]. The enhanced surveillance showed that eighteen percent of the cases with sepsis, meningitis or gastroenteritis will die[92].

Listeriosis most often occurs in people with increased susceptibility (75%). This included people with pre-existing illness that reduces their immune system function or an impaired immune system resulting from age or immunosuppressive treatments.

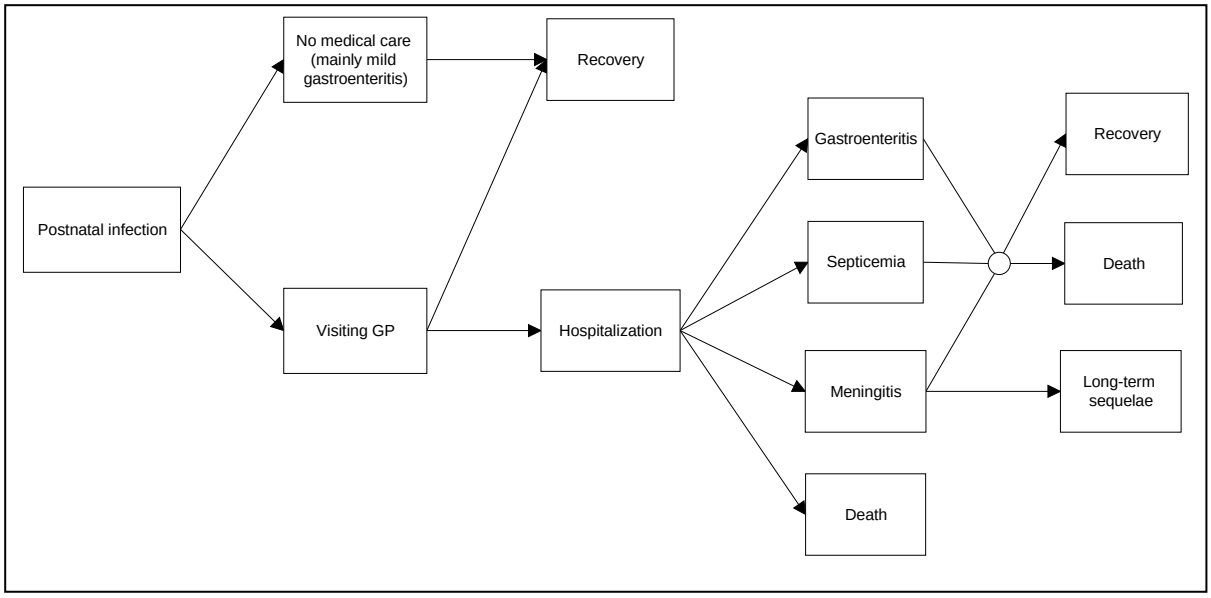


Figure 19. Outcome tree for acquired listeriosis.

In the uncertainty analysis we assumed that the observed cases resulted from a Poisson process. Then, the uncertainty of the incidence rate can be expressed as a Gamma (35, 2) distribution[49]. The most likely estimate for the incidence rate was 68 cases per year, corresponding with the median of this distribution. Low and high estimates correspond with the 5- and 95-percentile: 50-88 cases per year.

Additional information on health outcomes was available from 27 of the 34 acquired cases. Therefore, the uncertainty in the incidence of the health outcomes can be expressed as a Gamma (n/ 0.5) * 34/27 distribution. The uncertainty in the long-term sequelae can be expressed as a Gamma (n/0.5) * Beta (15;92) distribution.

The enhanced surveillance reported a median age of people who died of 75 year (Doorduyn, personal communication). The life expectancy at the age of 75 year is 11 years. However, all these cases had predisposing conditions for listeriosis, which will reduce the expected life span. Therefore, we assumed that their illness would reduce their life expectancy with 50% (i.e. 5 years), which we used as the most likely estimation. Furthermore, we assumed a minimum expected life span of 2.5 years (50% of the most likely estimation) and a maximum of the total 11 years. The median age of cases who did not die was at the time of diagnosis 70 years. The expected life span for people of 70 year of age is 14 years. Making the same assumptions compared to people who died, the most likely duration of long-term sequelae is 7 years, with a minimum and maximum of 3.5 and 14 years, respectively.
The low and high estimates are given in Table 39.

Table 39. Incidence and duration of illness of acquired listeriosis for 2005.

	Incidence estimates (cases per year)			No. of years of illness
	Most likely	Low	High	
Sepsis	25	14	40	0.02
Meningitis	15	7	30	0.5
Gastroenteritis	15	7	30	0.02
Pneumonia	10	3	20	0.02
Death	10	5	25	2.5 – 5 – 11[b]
Long term sequelae[a]	2	1	4	3.5 – 7 – 14[b]

[a] mainly neurological disorders as a result of meningitis (i.e. 14% of all meningitis cases)

[b] minimum – most likely – maximum estimation, respectively

8.2.2 Disease burden

Table 40 shows the results of the disease burden calculation for an acquired listeria infection per health outcome. The estimated disease burden is 70 DALYs. Death from meningitis, gastroenteritis or sepsis mainly contributes to the number of DALYs. Long-term sequelae accounts only for 6% in the disease burden, and meningitis itself for 3%. The influence of sepsis, gastroenteritis and pneumonia were negligible. Using a discount factor of 4%, reduced the number of DALYs to 60.

Table 40. Incidence and disease burden of acquired listeriosis for 2005 (most likely estimates).

	Incidence	Duration (years)	YLD	YLL	DALY (0%)	DALY (4%)[b)]
Sepsis	25	0.02	0	0	0	0
Meningitis	15	0.5	2	0	2	2
Gastroenteritis	15	0.02	0	0	0	0
Pneumonia	10	0.02	0	0	0	0
Death	10	5	0	60	60	50
Long term sequelae[a]	2	7	4	0	4	3
TOTAL					70[c]	60[c]

[a] Mainly neurological disorders as a result of meningitis (i.e. 14% of all meningitis cases)

[b] Discounted disease burden

[c] Summations do not necessarily tally because of rounding errors

Uncertainty analysis

Figure 20 shows the uncertainty in the disease burden for acquired listeriosis. Taking the lowest and higher parameter values (see Table 3) changed the number of DALYs from 70 (most likely estimation) to 15 (minimum estimation) and 270 (maximum estimation) respectively. Taking the discount factor of 4% into account resulted in a disease burden range from 15 to 220 DALYs.

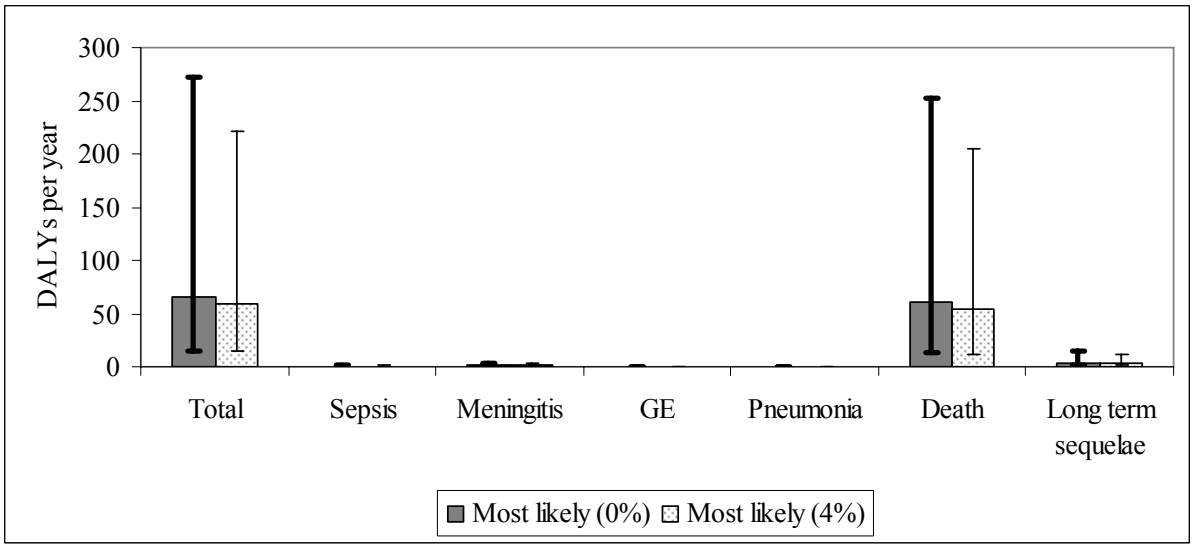


Figure 20. Disease burden of acquired listeriosis for 2005, using most likely estimates. Error bars express an uncertainty interval that results from using low and high estimates.

8.3 Discussion

In the present study we present the results of an inventory of the disease burden of perinatal and acquired listeriosis. We estimated that in total approximately 390 DALYs per year are lost (see Figure 21). This is larger than the disease burden for STEC O157, which was estimated at 120 DALYs[48]. Although the total number of DALYs is not very high, since the incidence of the disease is very low, on a case per case basis, listeriosis has a high health impact. The relatively high mortality rate is mainly responsible for the lost DALYs. Although the DALY concept provide a flexible and robust tool to estimate the impact of infectious illness on public health, the quality of a DALY calculation depends on the quality of the data, and some comments can be made about the data we used in the present study.

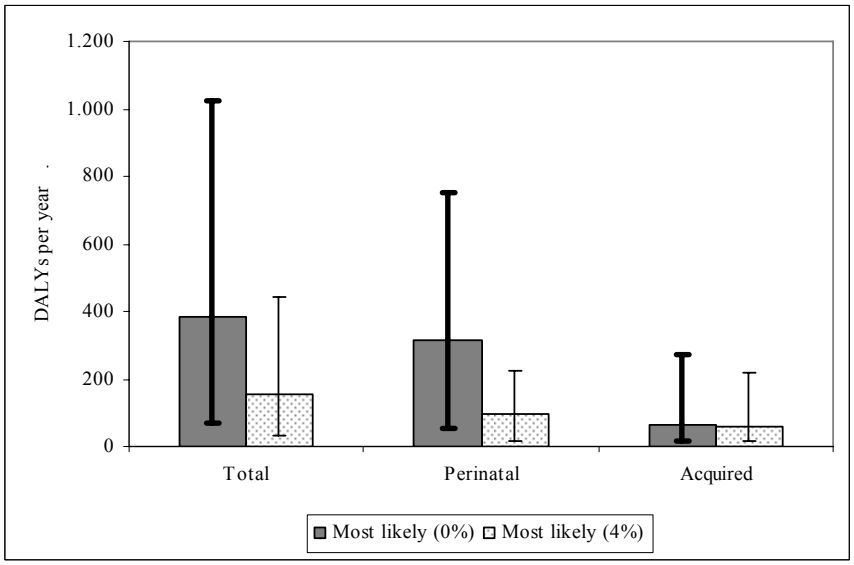


Figure 21. Disease burden of listeriosis for 2005, using most likely estimates.Error bars express an uncertainty interval that results from using low and high estimates.

Incidence of listeriosis

The incidence of listeriosis varies between countries. In North America en Western Europe, the incidence rate varies typically in the range of 4-8 cases per 1,000,000 individuals per year[83]. In the Netherlands the most recent estimated incidence rate was comparable: 4.3 cases per 1,000,000 individuals per year in 2005[92]. In previous years the estimated mean annual incidence of listeriosis was 2.0 per 1,000,000[92]. This higher incidence was estimated from the enhanced surveillance. This surveillance started in January 2005 and therefore the data were still scarce and the results are highly uncertain. In the coming years, when the surveillance will include more patients, more stable estimates can be generated.

Incidence of the health outcomes

Foodborne infection with *L. monocytogenes* can cause febrile illness with gastroenteritis.

The proportion of listeriosis cases with gastroenteritis in the enhanced surveillance was 22%, which were laboratory-confirmed (mainly hospitalized) cases. In two outbreak studies, the incidence of gastroenteritis was 72-79%[80 81]. From the differences in these incidences it can be assumed that many patients with a mild gastroenteritis will not visit a general practitioner or hospital and are therefore not registered. However, the disease burden will not change by this.

For both perinatal and acquired listeriosis, the number of DALYs was mainly caused by the number of deaths. These numbers were derived from the enhanced surveillance which started in January 2005. However, the number of identified cases is small because of the low incidence of listeriosis. Consequently, especially for perinatal listeriosis we may be did not have enough data to fill in the complete outcome tree. Therefore, in a scenario-analysis we also calculated the disease burden with data from a retrospective study[92]. This disease burden was considerable lower compared to the disease burden calculated with data from the enhanced surveillance. This was mainly caused by a lower number of deaths. In the coming years, when the surveillance will include more patients, it should generate more stable estimates.

From 28 of the 34 acquired cases we had additional information on health outcomes. However, this information was collected 2 weeks after diagnosis, so possibly some health outcomes were not apparent at that time. The impact on the disease burden is most likely low, because the impact of most of the health outcomes is negligible. Only when cases would have died after the information was collected, the disease burden is underestimated.

Disability weights and duration of the disease

Many patients with listeriosis had predisposing conditions for listeriosis. It can be assumed that people experience the presence of a health outcome due to listeriosis as less severe when suffering already from another severe disease, like cancer and diabetes. So, in that case, the disability weight for a specific health outcome due to listeriosis will be less high compared to disability weight for the same health outcome in cases who do not suffer from another

disease. We did not adjust for this phenomenon, and therefore the disability weights we used were probably too high. However, in the disease burden calculation for listeriosis this effect will be negligible because of the low incidence of the different health outcomes.

As mentioned before, all non-perinatal deaths were cases with predisposing conditions for listeriosis. The life-expectancy for these cases is not known. Using the expected life span at the age of death from the general population will overestimate the results. Therefore, we arbitrarily took 50% of this expected life span as the most likely estimation for the lost life years of individuals dying from listeriosis. For a more valid disease burden estimation, specific information is needed but may be difficult to obtain. Besides that, the necessity of this determination can be questioned since an uncertainty analysis (with a low and high estimation in the life-expectancy of 2,5 and 11 years, respectively) resulted in a relatively small DALY range of 40 to 140.

Uncertainty analysis

The uncertainty analysis for perinatal listeriosis showed that the disease burden ranged from 60 to 750 DALYs. For acquired listeriosis the number of DALYS ranged from 15 to 270. A more valid estimation can be given within a few years when the enhanced surveillance has collected more data.

9. Toxoplasmosis

Although *Toxoplasma gondii* infects a large proportion of the world's human population, it is an uncommon cause of manifest disease. Infection may be congenitally (i.e. congenital toxoplasmosis) or postnatally acquired (i.e. acquired toxoplasmosis).

9.1 Congenital toxoplasmosis

9.1.1 Outcome tree and incidences

Congenital infection occurs when a woman becomes infected during pregnancy. The parasite enters the foetal circulation by infection of the placenta[94]. The severity of disease depends on the stage of pregnancy at the time of infection. There is an inverse relationship between the frequency of transmission and the severity of disease. Infants born from mothers who acquire their infection in the first and second trimester, more frequently shown severe congenital toxoplasmosis or the infection may cause abortion / stillbirth. In contrast, the majority of children born of women who acquire their infection during the third trimester are born with the subclinical form of the infection.[95,96,94 97 98]

Clinical manifestations of congenital toxoplasmosis in the first year of life vary from signs of the classic triad of toxoplasmosis (chorioretinitis, intracranial calcifications, and hydrocephalus) to CNS abnormalities and neonatal death (see Figure 22). The surviving infants may suffer from neurological deficiencies. Other signs of congenital toxoplasmosis include a number of non-specific illnesses (like anaemia, jaundice, rash, petechiae, encephalitis, pneumonitis, diarrhoea etc.)[96]. However, the incidence of these health outcomes is low and most of these disorders are self-limiting. So, their influence on the disease burden is negligible. Therefore, we decided not to include these illnesses in the outcome tree.

Infants with subclinical infection in the first year of life may develop clinical signs and deficiencies later in life (most affecting the eyes)[99,100,101 102]. For a long time it was thought that children with asymptomatic congenital toxoplasmosis will develop CNS abnormalities later in life. However, this conclusion was based on case series or other studies which had not included appropriate comparison groups[103,104]. A recent study, which prospectively studied a cohort of children identified by screening, suggests that there is no evidence that impaired development or behaviour were more common in infected children[105]. This health outcome is therefore not included in the outcome tree.

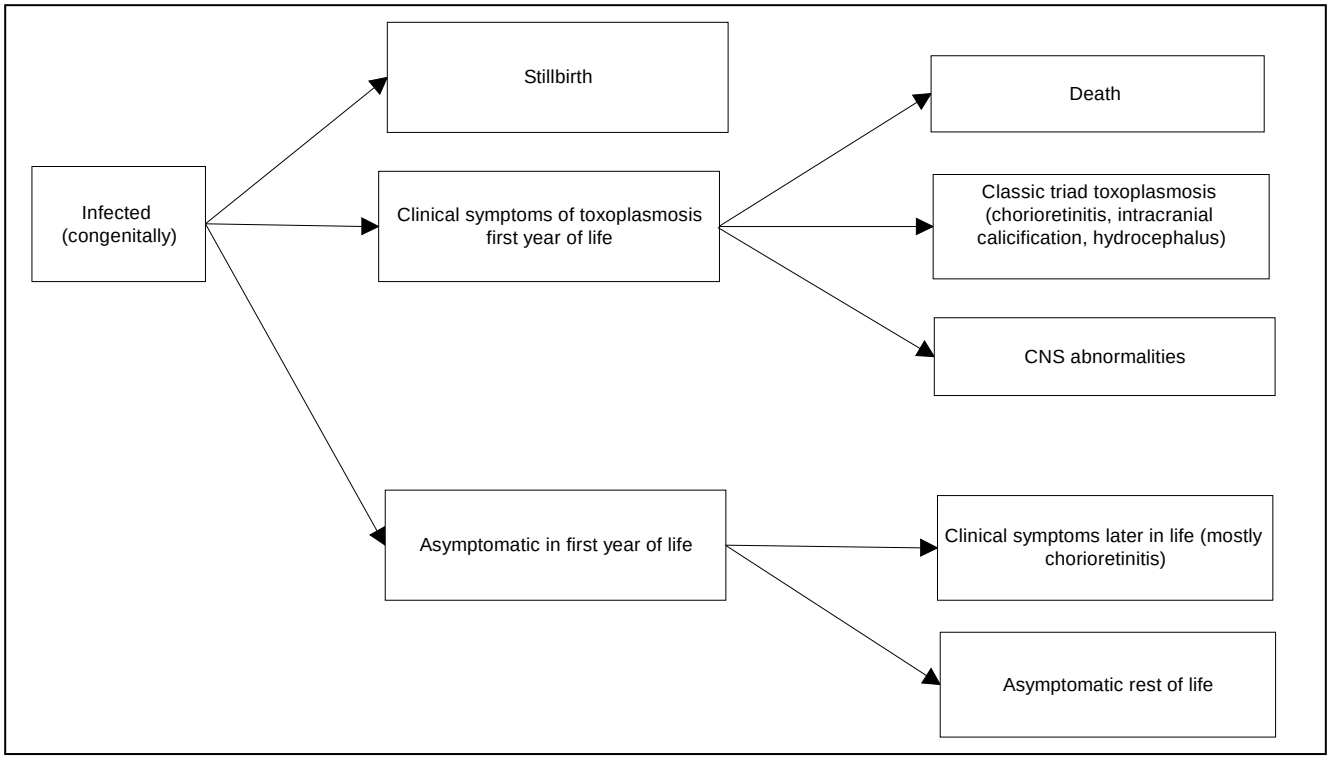


Figure 22. Outcome tree for congenital toxoplasmosis.

Incidence of congenital toxoplasmosis in the Netherlands

Little is known about the incidence of congenital toxoplasmosis. Recent estimates based on serological studies suggested incidences of primary maternal infection during pregnancy to range from about 1 to 310 per 10,000 pregnancies in different populations in Europe, Asia, Australia, and the Americas. Incidences of prenatal infection with *T. gondii* in the same or similar populations have been estimated to range from about 1 to 120 per 10,000 live births[95]. In the Netherlands, there is no regular screening of pregnant women for primary toxoplasmosis infection, so valid incidence data are unavailable. Therefore, we estimated the incidence from two incidental studies in the Netherlands i.e. the TIP and Pienter study[106,107] The TIP project was a prospective cohort study that started in 1987 among 28000 pregnant women in the South-West of the Netherlands. It was performed to compare the effects of primary and secondary prevention of congenital Toxoplasma infections[107]. Based on the results of this study, we calculated the incidence of a congenital infection as 8.2 per 10,000 births:

> In 15,170 seronegative women, 43 were infected during their pregnancy (= 0.28%, 90% confidence interval 0.21-0.36%). 12 newborn children had a congenital infection; this represents a transmission rate of 29% (18-41%).
>
> With the transmission rate of 29%, in 1987 an estimated number of 153 (90-229) children were congenitally infected. The estimated incidence rate of congenital toxoplasmosis is 0.28% * 29% * 10,000 = 8.2 (4.9-12.2) per 10,000 live births from women who seroconverted during their pregnancy.

In 1996, a seroprevalence study was performed in the Netherlands (Pienter study)[106]. Based on these results, we estimated the incidence of infection in the mothers by taken women aged 15 to 44 years as a proxy for pregnant women. We combined this incidence with data from Montoya *et al.*[94]on the transmission of infection from the mother to the foetus to estimate the incidence of a prenatal infection as 23 per 10,000 births:

In the age-range of 15-50 years, the observed seroprevalence for toxoplasmosis increases linearly with age and regression analysis indicates that the increase in seroprevalence is 1.4% per year (see Figure 23)[106].

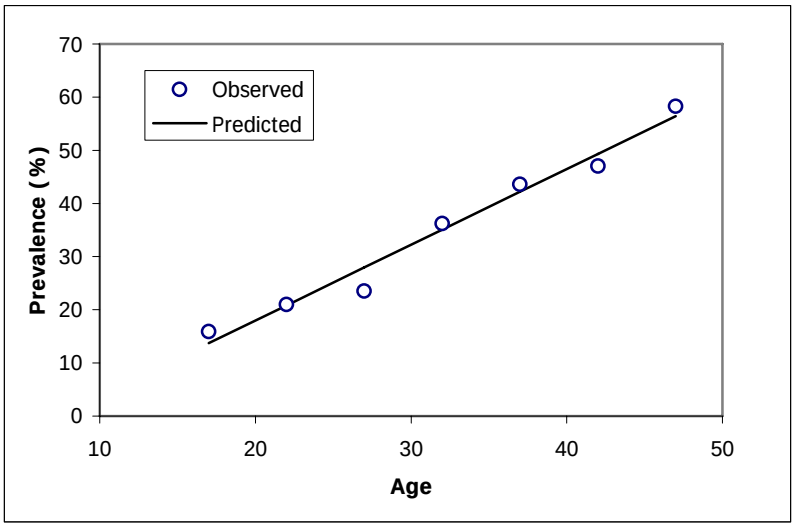


Figure 23. Seroprevalence for toxoplasmosis in relation to age, the Netherlands, 1996, and linear regression model (r^2 = 0.97; increase = 1.42% (se 0.10% per year).

If a mother is seropositive at the onset of pregnancy, she and her child are protected against Toxoplasma infection. However, if a seronegative mother is infected during pregnancy, there is a risk of transmission to the child. Assuming that the risk of infection of pregnant women is the same as for the general population, the risk of infection during pregnancy is 9/12 x 1.42% = 1.07%. In 1996, there were 189,521 live births of which 90% from mothers between 23 and 38 years of age (median age 29 years and 10 months). Combining these data leads to an estimated incidence of 1360 infections during pregnancy in 1996.

After maternal acquisition of *T. gondii* for the first time during gestation, the parasite enters the foetal circulation by infection of the placenta. The frequency of congenital transmission varies considerably according to the time during gestation at which the mother became infected: 9% in the first trimester, 27% in the second, and 59% in the third.[94]

Assuming an equal distribution of maternal infections during pregnancy, the frequency of foetal infection per trimester is then:

1st trimester:	454 x 9%	=	41
2nd trimester:	454 x 27%	=	123
3rd trimester:	454 x 59%	=	268
Total			432 per year

So, in 1996 the overall frequency in newborns with congenital toxoplasmosis was 432, which means an incidence rate of 23 per 10,000 births.

The estimated incidences of both studies differ markedly. In the present study, we used the incidence calculated from the TIP-study, which means that we use in the DALY calculation an incidence of congenital toxoplasmosis of 8.2 per 10,000 births from women who seroconverted during their pregnancy. In a scenario analysis we will use the higher estimate from the Pienter study. With an estimated number of live births of 129,000 from pregnancies at risk (i.e. women who were at the start of their pregnancy seronegative) in 2004, this implies 106 cases of congenital toxoplasmosis in the Netherlands, i.e. 5.5 per 10,000 births (total).

Incidences of health outcomes

To estimate the incidence of stillbirths and other health outcomes due to congenital toxoplasmosis, we overviewed relevant studies (see Table 41). In this overview we stratified the results for pre- and postnatal treatment of mother and/or child. However, after pooling these results, it turned out that all separate results fell within the uncertainty interval of the pooled result. So, we found no evidence that the results of the separate studies differed significantly from each other, and used therefore the pooled estimation as the most likely value. For the pooled estimations only studies were included which identified cases by screening because it can be assumed that the incidence of health outcomes in referred cases is per definition higher and not representative for all children with congenital toxoplasmosis.

Pooling the results of studies with information about stillbirths showed a total number of prenatal fatalities of 75 / 1863 (4%). We used this incidence as the most likely estimation. To calculate the number of stillbirths we assessed the total number of pregnancies in the Netherlands in 2004 (i.e. number of life born children[108] + number of stillbirths after 24 weeks[109] + number of spontaneous abortions up till 20 weeks[110] = 230,545). The number of women with a primary infection is 230,545 * 67% (percentage of women at risk at the start of their pregnancy; based on Pienter data) * 0.28% (based on TIP-data) = 432. In the DALY calculation we took only still births from 24 to the end of the pregnancy into account. We assumed that the number of still births over time of pregnancy is equally divided, resulting in an inclusion of 16 (i.e. 40-24 weeks) / 40 of the cases. So, the number of stillbirths was estimated to be 433 * 4% * 16/40 = 7.

The incidences of the health outcomes for congenital toxoplasmosis in the first year of life (i.e. chorioretinitis, intracranial calcifications, hydrocephalus, CNS abnormalities, and death in first year) were also estimated from pooled data from several studies on this topic (see Table 41). In the disease burden calculation we used this pooled estimation as the most likely value.

For both the incidence of stillbirths and all other health outcomes, the lowest and highest result from the studies included in the pooled estimation were used to calculate the attendant uncertainty (see Table 42).

Table 41. Overview of studies to the health effects of congenital toxoplasmosis.

	Stillbirth	Chorioretinitis	Hydrocephalus	Intracranial calcifications	CNS abnormalities	Death
m+[a] (%)	3.5[3], 11[8], 7[11], 5[12]					
pooled estimation (%)	4					
0-1 year[b](%)						
m+ c+[a]		23[1], 12[3+4] 9[2], 10[11]	2[3], 1[11] 0[2]	9[3], 8[11] 0[2]	0[2]	0[2], 0.3[3], 0.6[11], 0.7[12], 1.0[13]
m+ c-[a]		5[8]	5[8]		0[8]	0[8]
m? c-[a]		11[7]	4[7]	7[7]	7[7]	0[7]
m? c+[a]		19[6]		20[6]	29[6]	0[6]
m- c-[a]		15[10], 33[5]	2[10]	21[10]		0[5]
pooled estimation (%)		14	2	10	15	0.5
> 1 year[b](% increase per year)						
m+ c+[a]		0.9[1], 2.4[3], 2.1[11]	0.3[3]	0.1[11]		
m- c-[a]		3.3[5]		0[5]	0[5]	
m? c+[a]		1.7[6]			0[9]	
pooled estimation		2.1	0.3	0.05	0	

[a] m+ = mother is treated during pregnancy, m- = mother is not treated during pregnancy, m? = unknown whether or not mother is treated, c+ = child is treated in first year of life, c- = child is not treated in first year of life

[b] 0-1 year of age: denominator is infected children
> 1 year of age: denominator is children with congenital toxoplasmosis but asymptomatic in first year of life

1 = Peyron *et al.* (n = 121; mean follow-up = 12 (5-22) years) [100]
2 = Jenum *et al.* (n = 47) [111]
3 = Binquet *et al*. (n = 327; median follow-up = 6 (3-10) years) [112]
4 = Wallon *et al.* (n = 327) [102]
5 = Koppe *et al.* (n = 11; follow-up = 20 years) [99]
6 = Guerina *et al.* (n = 50; follow-up = 6 (1-6) years) [113]
7 = Lebech *et al.* (n = 27) [114]
8 = Gratzl *et al.* (n = 9) [115]
9 = Freeman *et al*. (n = 178; follow-up = 3 years) [105]
10 = Schmidt *et al*. (n=47, follow-up = 3 years) [116]
11 = Gras *et al.* (n= 181; follow-up 3-7 years) [101]
12 = Foulon *et al.* (n=140; follow-up 1 year) [117]
13 = Couvreur *et al*. (n = 210) [116]

The probability of chorioretinitis later in life of asymptomatic children at birth was 74 / 571, based on pooled data from several studies. The uncertainty in the incidence rate can be expressed as a Beta (74, 497) distribution. The most likely estimate for the incidence rate is 13%, corresponding with the median of this distribution. Low and high estimates correspond with the 5- and 95-percentile: 11 – 15%. The most likely estimate of developing chorioretinitis later in life was 2% per year, based on the relatively large studies of Binquet *et al.* and Gratzl *et al.*[112 115]. The proportion of subjects who were symptom-free at an age of 1 year who have developed chorioretinitis at an age i was calculated as $1 - e^{-\lambda(i-1)}$, with λ =

hazard rate (per year). Follow-up in these studies was up to 14 and 10 years, respectively, which resulted in a risk of developing chorioretinitis later in life of 2% per year. The reported rate in other studies varied between 1% and 3%, which we applied as low and high estimates, respectively. The studies of Binquet *et al.* and Gratzl *et al.* suggested that the incidence rate was constant throughout the years and did not level off at later ages. A study by Koppe *et al.* indicated that new cases can arise up to at least an age of 20 years, albeit that the number of observations was relatively small[99]. Furthermore, we concluded that the risk of developing chorioretinitis is constant over the years, and therefore we assumed that in this period of 20 years the mean age of developing chorioretinitis was 10 years. So, the duration of this disorder is the life expectancy of the general population minus the mean age of developing chorioretinitis (79 – 10 = 69; see Table 42). We used this as our most likely estimate and also used this as our low estimate. As a high estimate, we arbitrarily doubled the period to 20 years.

Table 42. Proportion and duration of illness of congenital toxoplasmosis for 2004.

	Proportion			No. of years
	Most likely	Low	High	of illness
Still birth	4.0	3.5	11	79
Clinical symptoms in first year of life				
Chorioretinitis	14	5	33	79
Intracranial calcifications	10	0	21	79
Hydrocephalus	2	0	5	79
CNS abnormalities	15	0	29	79
Death	0.5	0	1	79
Asymptomatic at birth				
Chorioretinitis later in life	19	6	54	69

9.1.2 Disease burden

Table 43 presents the burden of disease per health outcome for congenital toxoplasmosis. It shows a total disease burden of 1200 DALYs per year. This number is mainly caused by stillbirths (46%) and chorioretinitis (35%). Taking a discount factor of 4% into account reduced the number of DALYs to 360 per year.

The disease severity weights used in the DALY calculation are described in section 1.2.1.

Table 43. Incidence and disease burden of congenital toxoplasmosis for 2004 (most likely estimates).

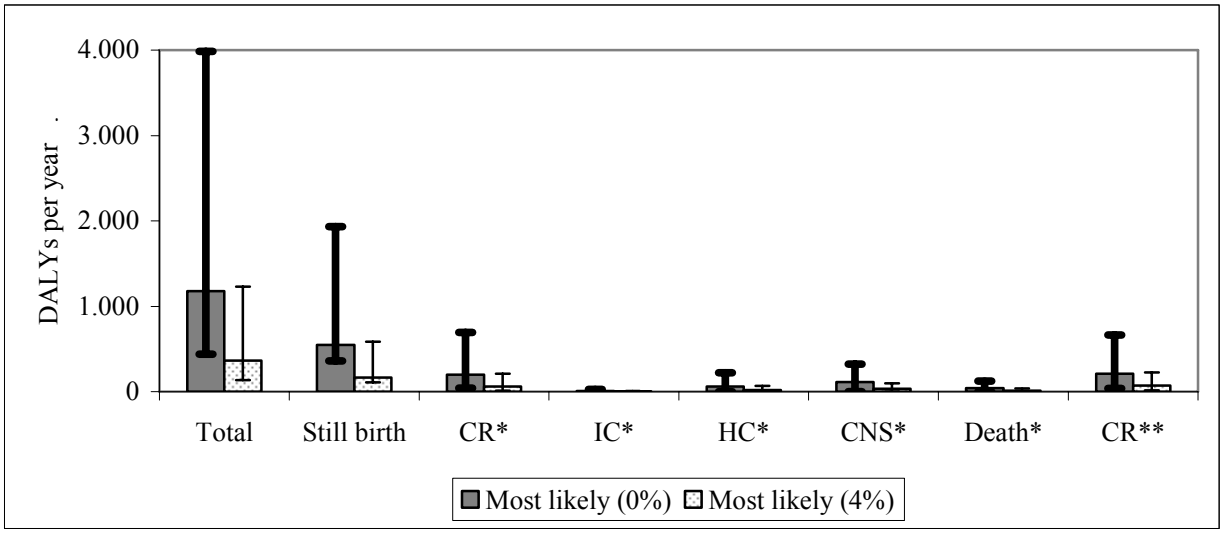
	Incidence	Duration (years)	YLD	YLL	DALY (0%)	DALY (4%)[a]
Still birth	7	79	0	550	550	170
Clinical symptoms in first year of life						
Chorioretinitis	15	79	200	0	200	60
Intracranial calcification	11	79	8	0	8	3
Hydrocephalus	2	79	60	0	60	20
CNS abnormalities	16	79	110	0	110	30
Death	1	79	0	40	40	10
Asymptomatic at birth						
Chorioretinitis later in life	18	69	210	0	210	70
TOTAL					1200[b]	360[b]

[a] Discounted disease burden

[b] Summations do not necessarily tally because of rounding errors

Uncertainty analysis

There are many uncertainties in the incidence estimation of congenital toxoplasmosis and its health outcomes. An uncertainty analysis was performed to see how the outcome changes when we choose for all parameters the lowest and highest values from the literature (see Table 41 and Table 42). Figure 24 shows a minimum disease burden for a congenital toxoplasma infection of 440 and a maximum disease burden of 4000 DALYs per year, when not taking the discount factor into account.



* symptoms occurring in first year of life: CR = chorioretinitis, IC = Intracranial calcifications, HC = Hydrocephalus, CNS = Central Nervous System abnormalities

** symptoms occurring after first year of life: CR = Chorioretinitis

Figure 24. Disease burden of congenital toxoplasmosis for 2004, using most likely estimates. Error bars express an uncertainty interval that results from using low and high estimates.

Scenario analysis

Not only the incidences of the different health outcomes are uncertain, as stated earlier the incidence of congenital toxoplasmosis itself is also largely unknown. We estimated the incidence from the TIP-study, and used this estimation as the most likely incidence. However, when we used the estimated incidence calculated from the Pienter study, the disease burden increased to 2300 DALYs per year (range 870-5800).

Another scenario is to exclude the number of stillbirths from the DALY calculation, since many women will become pregnant again soon after their stillbirth ('replacement pregnancy'). In this scenario the number of DALYs decreased to 630 per year (range 140-1500).

Different scenarios are also possible for the severity weight for CNS abnormalities. In the present study we used for CNS abnormalities a disability weight factor of 0.09. However, the severity weight for congenital anomalies after meningitis (0.25)[25] might be valid as well. Using this higher disease weight increased the most likely disease burden to 1400 DALYs per year (range 620-3400).

9.2 Acquired toxoplasmosis

9.2.1 Outcome tree and incidences

Human beings can be postnatally infected with *T. gondii* by ingestion or handling of undercooked or raw meat containing tissue cysts or water, food or soil containing oocysts excreted in the faeces of infected cats[94]. The great majority of postnatal *T. gondii* infections in immunocompetent humans are asymptomatic (see Figure 25). Occasionally, mild symptoms may be observed of which lymphadenopathy is the most significant clinical manifestation. Severe manifestations, such as encephalitis, sepsis/shock, myocarditis, or hepatitis may occur, but are very rare in immunocompetent humans[95]. Only chorioretinitis may be an important consequence. This disorder has long been regarded as a result of a prenatal infection which manifests later in life. However, there are now several recorded cases in which the development of ocular symptoms was convincingly associated with acquired toxoplasmosis in humans.[95]

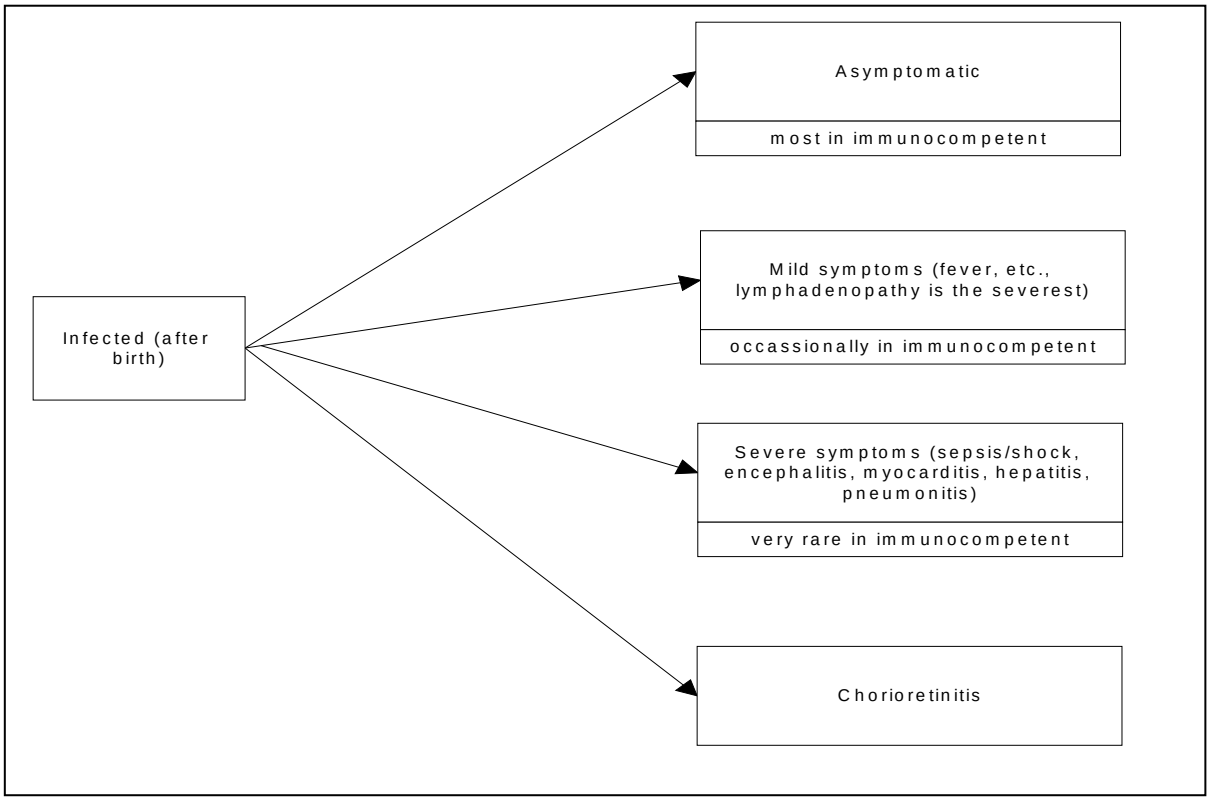


Figure 25. Outcome tree for acquired toxoplasmosis.

Incidence of acquired toxoplasmosis

Little is known about the incidence of acquired Toxoplasma infection. In the United States and the United Kingdom, it is estimated that 16-40% of the population is infected with *T. gondii* during their lifetime, whereas in Central and South America and continental Europe, estimates of infection prevalence range from 50-80%[97]. In the Netherlands, the seroprevalence in 1996 was estimated to be 40.5%[106]. This seroprevalence varied with age: less than 17% among those < 20 years, 21% in the 20-24 years age group, 47% among the 40-44 years age group, and at least 70% for those aged 60-64 years or over. These prevalence data show that the disease is contracted through the entire lifespan. The prevalence increase is steepest among the 25-45 years group compared to both younger and older age groups. No differences are found between men and women[106].

To estimate the incidence in the Netherlands, we applied back calculation, that is we start with the final complication ocular toxoplasmosis which is known, and by introducing the complication rate per acquired case, an estimate of the incidence is deduced.

It is estimated that in the Netherlands 200 new cases develop ocular toxoplasmosis (chorioretinitis) annually[118]. Burnett *et al*. reported that at least 0.3% of the people with Toxoplasma infection acquired during an outbreak in Vancouver presented with sypmtoms to opthalmologists[119]. From these data it follows that 200/0.3*100, that is 67,000 cases contract an acquired toxoplasma infection per year, which means an incidence rate of 41 cases per

10,000 person years. In the Pienter study, the lifetime risk of infection was approximately 70% or in the order of 1.4% per year (see Figure 23)[106]. With a population of approximately 16 million, this would imply 227,000 infections per year (3.4 times higher than the estimate based on ocular toxoplasmosis). The effect of these two different incidences is shown in a scenario analysis.

Incidence of health outcomes

It is estimated that only 10-20% of cases of *T. gondii* infection in adults and children are symptomatic[96]. In the DALY calculation we used the mean of these estimations as our most likely estimate, with a proportion of 14% for mild symptoms, 0.7 % for severe symptoms and 0.3% for chorioretinitis[118]. In the uncertainty analysis we arbitrarily used as low estimates 10% for mild symptoms and 0% for severe symptoms and chorioretinitis. Burnett *et al*. estimated that at most 0.7% of the infected individuals will develop chorioretinitis[119]. Therefore, our high estimates are arbitrarily supposed to be 17% for mild symptoms, 2.3% for severe symptoms, and 0.7% for chorioretinitis (see Table 44).

Table 44. Probability and duration of illness of acquired toxoplasmosis for 2004.

	Probability			No. of years
	Most likely	Low	High	of illness
Mild symptoms	14	10	17	0.04
Severe symptoms (chorioretinitis excluded)	0.7	0	2.3	0.04
Chorioretinitis	0.3	0	0.7	34

We estimated from the Pienter study that the median age of an acquired toxoplasma infection is 45 years[106]. Therefore we included for the duration of symptoms 34 years (life expectancy – median age = 79 – 45 = 34 years).

In most cases the clinical course of toxoplasmosis in the immunocompetent patient is benign and self-limited. However, it may be a life-threatening disease in immunodeficient patients. In 2004, 1 patient was reported to die in the Netherlands due to a toxoplasmosis infection[120]. The effect of this death on the disease burden is shown in a scenario analysis.

9.2.2 Disease burden

Table 45 shows the results of the disease burden calculation for acquired toxoplasmosis per disease outcome. It shows a disease burden of 1200 DALYs per year, which is dominated by the presence of chorioretinitis. If discounting was applied it decreased to 640 DALYs per year. Especially the long duration of the illness and the relatively high severity weight are responsible for the relatively high disease burden.

Table 45. Incidence and disease burden of acquired toxoplasmosis for 2004 (most likely estimates).

	Incidence	Duration (years)	YLD	YLL	DALY (0%)	DALY (4%)[a]
Mild symptoms	9300	0.04	4	0	4	4
Severe symptoms (chorioretinitis excluded)	470	0.04	2	0	2	2
Chorioretinitis	200	34	1200	0	1200	640
TOTAL					1200[b]	640[b]

[a] Discounted disease burden

[b] Summations do not necessarily tally because of rounding errors

Uncertainty analysis

Figure 26 shows the uncertainty in the disease burden for acquired toxoplasmosis. The minimum and maximum disease burden for acquired toxoplasmosis then appeared to be 3 and 2700 DALYs per year. With discounting these were 3 and 1500, respectively.

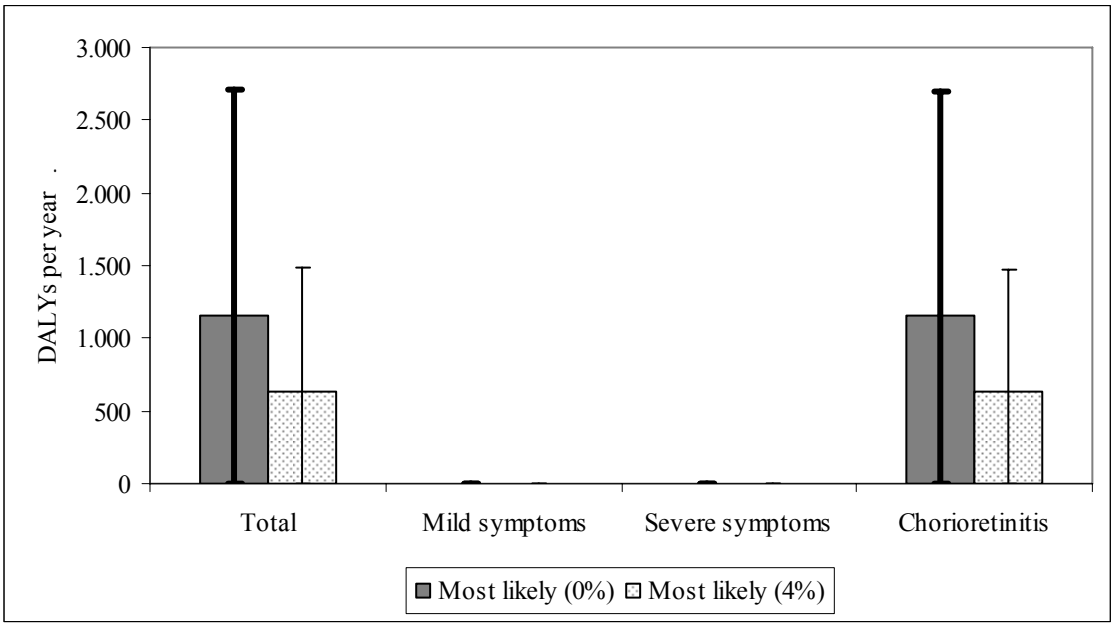


Figure 26. Disease burden of acquired toxoplasmosis for 2004, using most likely estimates. Error bars express an uncertainty interval that results from using low and high estimates.

Scenario analysis

The incidence of acquired toxoplasmosis is estimated from expert estimates. When we used the assessed incidence from the Pienter study in the disease burden calculation, the number of DALYs increased to 4000 per year (range 9-9200).

In 2004 one person was reported to die from acquired toxoplasmosis[120]. Because of this low incidence, including this case into the disease burden calculation showed no significant

change in the number of DALYs (1200 DALYs; range 40-2700). Herewith we assumed that this person had a normal expected life span at the time of death (i.e. 34 years). When it turned out that this case was an immunodeficient patient, the increase in DALYs would even be less.

9.3 Discussion

The results of this study show a cumulative disease burden of congenital and acquired toxoplasmosis of approximately 2400 DALYs per year (see Figure 27). This disease burden is somewhat larger than the burden of infectious diseases like bacterial meningitis and tuberculosis and more than twofold that of a major foodborne pathogen *Campylobacter* spp.. The disease burden of congenital toxoplasmosis is 1200 DALYs per year, just as high as that of toxoplasmosis acquired later in life. Factors with an important contribution to the burden of congenital toxoplasmosis are death (still birth, at birth), chorioretinitis, and CNS abnormalities. Although the DALY concept proved a flexible and robust tool to estimate the impact of infectious illness on public health, the quality of a DALY calculation depends on the quality of the data. Some comments can be made about the data we used in the disease burden calculation.

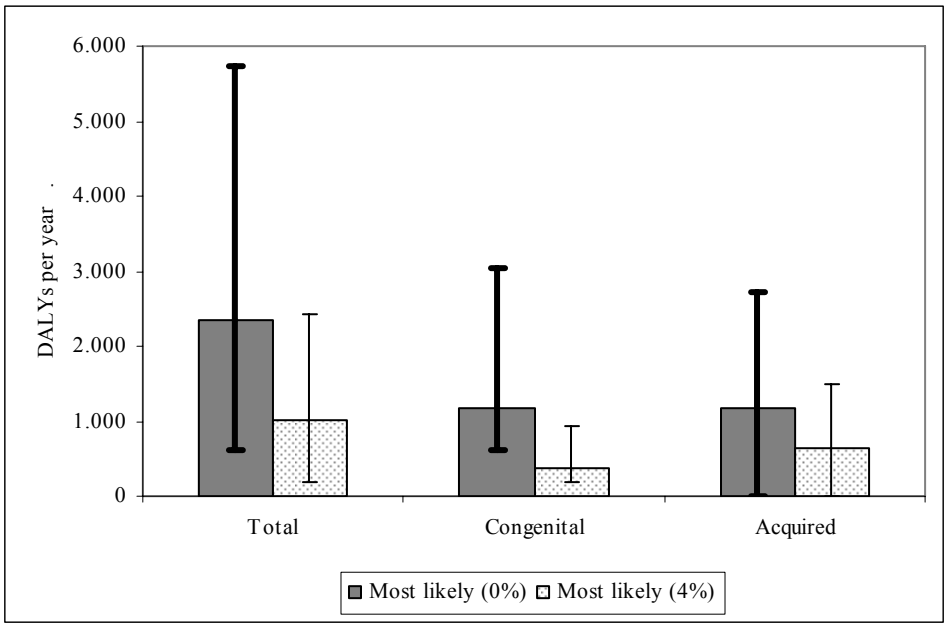


Figure 27. Disease burden of toxoplasmosis for 2004, using most likely estimates. Error bars express an uncertainty interval that results from using low and high estimates.

Incidence of toxoplasmosis

Incidences of prenatal infection with *T. gondii* have been estimated to range from about 1 to 120 per 10,000 births. The wide range of these numbers may reflect the use of different tests and different cut-offs for test positivity, but may also reflect genuine regional differences in infection frequency, maybe due to differences in exposure.

The incidence of congenital toxoplasmosis in the Netherlands is not known. Therefore we estimated this incidence from two different studies[106 107]. In the TIP-study, about 15,000

women in the province South Holland were followed during their pregnancy because of their risk for a primary Toxoplasma infection[107]. From the results of this study we calculated an incidence of 8.2 infected newborns per 10,000 births from women at risk at the start of their pregnancy. This estimate is comparable to the incidences found in countries around the Netherlands. In the United Kingdom and Germany incidences of 3-16 per 10,000 births were found[95], whereas in France and Belgium the incidence lies between the 10-30 per 10,000 births[121]. It is suggested that the incidence in the Netherlands is in the same order of magnitude of the incidence in Finland and Denmark (15 per 10,000 births)[95]. However, it is not known whether the incidence in South-Holland is representative for the whole country, since no adjustments could be made for the in the Pienter study identified confounding factors like education level, urbanization, and marital status.[106] The representativeness of this estimate for the whole country and for the number of DALYs is therefore unclear.

From the seroprevalence Pienter study carried out in 1996, combined with data from the literature about transmission rate per trimester, we estimated an incidence of 23 per 10,000 births[94 106]. This estimate is rather high, compared to the incidence in our neighbouring countries. Kortbeek *et al*. compared data on the seroprevalence of women in the TIP and Pienter study. On average, the data of the Pienter study showed a lower level of seropositivity (e.g. 44% vs. 24% in the 25-29 years age group). However, the increase of seroprevalence in women of child-bearing age was the same in both studies, suggesting that the risk of a primary toxoplasma infection during pregnancy did not change between 1987-1989 and 1995-1996. It must be noted that in the TIP project, the participating women received intensive counselling. On the other hand, in the time period between 1987 and 1996 the median age of pregnancy has increased from 28 to 30 years[122], which would slightly decrease the proportion of pregnant women at risk.

We did not calculate the incidence of congenital toxoplasmosis from data of LMR (the national medical registration), since this data source does not register stillbirths and neonatal deaths, the main factor in the DALY calculation. Besides that, most of the cases in this registration are included in a-specific groups, like ‘toxoplasmosis nec’ (not elsewhere classified) and ‘toxoplasmosis nno’ (not further specified). Therefore, the reliability of these data is doubtful.

Besides the incidence of congenital toxoplasmosis, the incidence of acquired toxoplasmosis is not known either. Burnett et al. reported that 0.3-0.7% of the people with a toxoplasma infection acquired during an outbreak in Vancouver presented with symptoms to ophtalmologists[119]. If the same risks applied to the Netherlands we estimated in a backward calculation that at least 67000 individuals contract an acquired toxoplasma infection per year. However, the validity of these data is unclear and therefore the estimation can be questioned.

Incidence of health outcomes

Not only the incidence of the disease is unknown, also the incidence of several health outcomes caused by a congenital or acquired toxoplasmosis infection varies between different studies. For example, the estimate of developing chorioretinitis in infected newborns

varies between 5-33% in the first year of life[115,99] to 85% later in life[99,123]. To estimate an overall incidence we pooled the results of the specific studies weighted for study size and used this pooled estimation as the most likely incidence. For chorioretinitis, however, the calculated disease burden may be overestimated since not all laesions will lead to vision loss. Laesions located peripherally probably do not have an effect on the disease burden. However, most studies do not give information on the location of the laesions and therefore we did not stratify for this factor.

Another problem to estimate incidences of health outcomes is that in some countries pregnant women are screened for the presence of a primary toxoplasma infection. It is not known whether this strategy is more effective in prevention of a congenital infection compared to counselling only. However, in the overview of studies to the health effect of congenital toxoplasmosis (see Table 41) it seems that there is no evidence that prenatal treatments have a clinically important effect on the risk of transmission. Besides that, there is a lack of evidence on the effect of postnatal treatment in children. This opinion was also shared by members of the Eurotox Conference recently (Bordeaux, 2005). Therefore, we pooled all appropriate studies.

Furthermore, we decided to take only stillbirths of a viable foetus into account (is recently lowered to 24 weeks in the Netherlands). However, it is not known how many pregnancies due to toxoplasma infection end in the last part of the pregnancy. We assumed that this number is equally divided over the weeks of pregnancy, but no data are available to support this assumption. Probably this frequency is overestimated since infections acquired in the first and second trimester are more severe compared to infections acquired in the third trimester. Therefore these pregnancies probably may end more frequently before the viable state has been reached. This could have led to an overestimation of the disease burden. Unfortunately this is not verified because from most of the stillbirths foetal tissues were not available for parasitic examination. It could therefore not be ascertained whether these stillbirths were due to foetal *T. gondii* infection or to other causes.

Some newborns with a congenital toxoplasma infection will suffer from more than one disorder. Therefore, it may be possible that the disability weights we used were a little too high, because it can be assumed that people experience the presence of a disorder as less severe when already suffering from another disorder. So, in that case, the disability weight for certain health outcomes will be lower when suffering from two or more health outcomes rather than when suffering from only one disorder. However, because of the low incidence we suppose that this effect is rather small and did not adjust for it, although it could have led to some overestimation of the disease burden.

Just like the incidences of the health outcomes for congenital toxoplasmosis, the incidences of health outcomes for acquired toxoplasmosis are uncertain. As a low estimate in the uncertainty analysis we only took the presence of mild symptoms into account. However, it seems not realistic that none of the cases with an acquired infection would develop

chorioretinitis, especially since it became clear that chorioretinitis may be both a result of a prenatal infection or an infection that was acquired postnatally[95].

Therefore it can be assumed that the incidence of 0.3% that we used in our most likely estimation is a conservative estimation, which in spite of that resulted in a disease burden of 1200 DALYs.

Disability weights

The disability weights used in the present study were mostly derived from the Dutch Public Health Status and Forecast study. For intracranial calcifications and hydrocephalus these severity weights are satisfactory. However, for CNS abnormalities many severity weights are available, depending on the severity level and disease stage (which ranges from 0.09 for mentally subnormal to 0.76 for serious mentally handicapped). It is questionable which disability weight is most valid for CNS abnormalities caused by a toxoplasma infection. In the present study we used for CNS abnormalities a disability weight factor of 0.09. However, the severity weight for congenital anomalies after meningitis (0.25) might be valid as well. Field experts have to go into this question and additional data collection is necessary.

Also, for ocular toxoplasmosis the validity of the severity weight is not clear. In 2004, this disability weight was assessed in a panel study, which provided us a better estimate. However, the vignette with the description of ocular toxoplasmosis was based on preliminary data without clinical investigations, which made it less valid. In the future this disability weight will be reassessed with a more valid vignette.

Uncertainty and scenario analyses

To measure the impact of the different incidence rates on the disease burden, we performed uncertainty and scenario analyses. The uncertainty analysis for congenital toxoplasmosis showed that, using the lowest and highest incidence rates for the different health outcomes, the disease burden will range between 440 and 4000 DALYs, with 1200 DALYs as the most likely outcome (incidence based on the TIP-study). So, due to the differences in incidences of several health outcomes in the literature, there is a substantial uncertainty. For acquired toxoplasmosis the uncertainty was even higher.

In different scenarios we assessed the influence of using the incidence rate of congenital toxoplasmosis estimated from the Pienter study, the influence of excluding the number of stillbirths, and using different disease severity weights for CNS abnormalities. We suppose that the number of DALYs based on the Pienter study will be the upper limit, because the incidence rate calculated from this study is very high compared to our neighbouring countries and other literature. Furthermore, the number of DALYs calculated when we excluded all stillbirths may be the lower limit, assuming that all will become pregnant soon after their stillbirth. The influence of using other disease severity weights for CNS abnormalities is limited in the disease burden calculation.

Using incidence data for acquired toxoplasmosis assessed from the Pienter study did increase the disease burden considerably. Since no valid incidence data are available we suppose that the disease burden for acquired toxoplasmosis will lie between 1200 (incidence based on the TIP study) and 4000 (incidence based on the Pienter study).

10. General discussion

Priority setting is a complex process that involves consideration of many different factors and there is no generally accepted single process that will lead to unequivocal conclusions. It is therefore not expected, nor desirable, that a project on priority setting will lead to a single list of priorities. Rather, the process of priority setting should help to integrate complex information in a structured framework so that it is easily accessible to decision makers, and can easily be updated if new information is available. This report presents one step in this direction, by integrating a large body of evidence on the social impact of several infectious diseases that can (also) be transmitted by food in two indicators: disease burden and cost of illness. The choice for these indicators is based on experience from other projects on priority setting and is consistent with general trends in public health research. In contrast to other studies on priority setting, a quantitative approach was chosen rather than a qualitative or ranking approach. One advantage of a quantitative approach is that the end result is less dependent on arbitrary choices such as the choice of the type and number of indicators. Also, all factors are weighed in proportion to their true values, instead of on some simplified scale. A disadvantage is that the process is very resource intensive, requiring careful consideration of a large volume of data while many data gaps may exist. Such data gaps result in uncertainties about the final results, but the quantitative approach also helps to prioritise among data needs and to identify key research questions.

Disease burden and cost of illness estimates are data-based indicators of social impact of illness, but it must be realised that in order to complete the calculations, many choices must be made that include value judgements. In that sense, these estimates are not objective but are subjective and need to reflect societal values. The methods used to calculate both indicators are based on a large body of theoretical and practical studies and where possible we have followed existing guidelines. These guidelines reflect choices made in the Netherlands, and may not be directly applicable in other countries. For example, in the Netherlands the economic costs of fatalities are estimated using the friction method, assuming that after a certain period of time the deceased person will be replaced on the labour market. Other countries prefer to use the human capital method, in which all foregone earnings in an individual's life span are assigned to the cause of death.

Figure 28 shows a summary of disease burden estimates of seven pathogens that were evaluated in this report. *Toxoplasma gondii* is the pathogen associated with the highest disease burden. Although it was already known that an infection with *T. gondii* may have serious consequences for individual patients, the disease burden on a population level has not been calculated before. However, the results are also very uncertain. In particular, the incidence of both congenital toxoplasmosis and toxoplasmosis acquired later in life is highly uncertain. The results presented in the baseline model are a conservative estimate. Scenario analyses has indicated that the incidence of congenital toxoplasmosis and hence the true disease burden might be considerably higher. Likewise, the health impact of toxoplasmosis

acquired later in life has not been included in the baseline model but it is not unlikely that including the impact of the resulting chorioretinitis at least doubles the disease burden.

This report also presents the first results of disease burden estimates for *Listeria monocytogenes*. The incidence estimates were based on data from the enhanced surveillance project, which started in 2005. Hence, the results are still highly uncertain, but the data suggest that the number of reported cased is higher than observed earlier with passive surveillance. Although the number of cases of listeriosis is relatively small in the Netherlands, it is a serious illness, particularly due to the high mortality rate. As a consequence, the disease burden is still appreciable.

Among the pathogens that mainly cause gastroenteritis, noro- and rotaviruses are the agents that cause most incident cases in the general population. Yet, the disease burden is somewhat lower than that of Salmonella and less than half of that of Campylobacter. This is related to the fact that most cases of viral gastroenteritis are mild, of relatively short duration, and have a low case-fatality ratio. About 97% of community-acquired norovirus cases and 93% of community-acquired rotavirus cases recover without requesting medical services. Recently, complications of norovirus infections in hospitalised patients have been reported[124], mainly affecting patients with underlying disease. Consideration of such complications is of importance for hospital hygiene, but is of limited significance from an overall public health point of view. In the case of bacteria triggered gastroenteritis, the request for medical services is far higher, namely more than 20% for Campylobacter, and about 15% for Salmonella and STEC O157. Also, in contrast to bacterial infections, viral gastroenteritis rarely results in sequelae. Often, sequelae associated with bacterial infections are long-lasting and/or chronic, resulting in a considerable disease burden.

Another point is that severity weights used for the calculation of the disease burden of acute GE were based on acute profiles, using illness specific length of symptoms for each pathogen. In 2005, severity weights for acute GE were determined based on annual profiles, resulting in much higher disease burden estimates for these illnesses. So, panel members weighed for example ‘a healthy year with 10 days of mild GE’ different from ‘10 days with mild GE’. Furthermore, in the severity weights no threshold values were included, i.e. all illnesses related to GE were included, even the very mild ones. So, 180 people with a disease for 2 days weigh just as much as 1 person with this disease throughout a whole year. Including a threshold value (for example excluding of cases who do not visit the GP for their illness), would probably give more valid estimations. This possibly would have resulted in different ranking of the evaluated pathogens.

Figure 27 also shows the effects of discounting on the disease burden estimates. Discounting reflects the fact that an immediate profit is generally preferred over a profit at a later moment in time; see Chapter 2.4 for further details. The figure shows that discounting stringly affect the disease burden estimates for Listeria and Toxoplasma, because for both illnesses pre- or perinatal death is an important component. The effect of discounting is related to a difficult choice that needed to be made to complete the disease burden calculations: what is the burden

of the death of an unborn or newborn child? In our baseline model, we assumed that any death beyond a gestation period of 24 weeks would be considered as the loss of a human life. This assumption does not account for effects of possible substitution pregnancies, which might lead to a lower burden estimate. On the other hand, the impact of a child's death on the quality of life of the parents was not included and this might lead to a higher burden estimate. The Dutch Public Health Status and Forecasts Report do not take any prenatal death into account in their disease burden calculations. As mentioned, in the present study we decided to take all stillbirths after 24 weeks of gestation into account. However, no guidelines on this subject could be identified.

The disease burden of virus gastro-enteritis causing pathogens is hardly affected by discounting, because they are mainly associated with acute effects and only few fatal cases. Whereas for bacteria gastro-enteritis causing pathogens, apart from acute effects and a few fatal cases, a relatively important compontent of chronic residual disabilities of Guillain-Barré syndrome and of IBD, for Campylobacter and life-long persistent IBD symptoms for Salmonella are included in the disease burden estimate. Based on discounted disease burden, Toxoplasma would still rank as the pathogen that causes the highest disease burden, but the difference with Campylobacter would be much smaller. The burden of Listeria would rank lower than that of noro- and rotavirus and *Salmonella* spp.

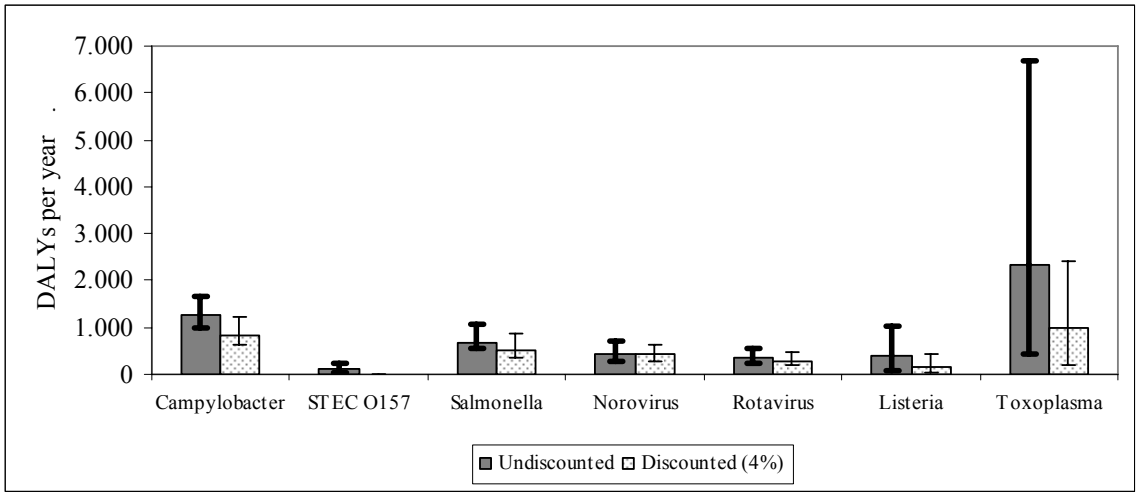


Figure 28. Disease burden of infectious diseases that can (also) be transmitted by food. The figure shows the total disease burden associated with different pathogens, undiscounted and discounted at 4%, and the uncertainty around the most likely estimate.

Figure 29 shows a summary of cost of illness estimates of four pathogens that were evaluated in this report. Using this indicator, the impact of viral gastroenteritis is greater than that of bacterial gastroenteritis. In all cases, the indirect non-health care costs (mainly temporary absence from work) were much higher than the direct on indirect health care costs. For chronic and long-lasting diseases, such as those associated with bacterial infections, the direct health care costs do contribute to the total cost and are often far higher than the estimated indirect costs for these diseases by using the friction cost method. The effects of discounting are limited because most costs relate to acute effects.

The relative importance of different cost categories differs per pathogen. For example, 26% of all costs related to rotavirus infections were due to hospitalisation, or 80% of all DHC. In contrast, more than 90% of all costs related with norovirus infections were due to indirect non-health care costs (sickness leave). For Campylobacter, a high proportion (50%) of all costs is related to sequelae (and more than 75% of all direct health care costs). These results show that costs associated with foodborne pathogens may have an impact on very different sectors of the society and all relevant sectors must be considered in a realistic comparison.

The cost estimates as presented in this report are not exhaustive. In particular, outbreak related costs and the opportunity costs associated with sickness leave from unpaid work have not yet been considered. Also, costs related to nosocomial infections and preventive measures in hospitals and other health care institutions have not been included as they are not relevant for priority setting in the food safety domain. From other perseptvies, e.g. vaccine evaluation, these costs may well be important. Furhtermore, some costs such as those of reactive arthritis were underestimated because of a lack of information.

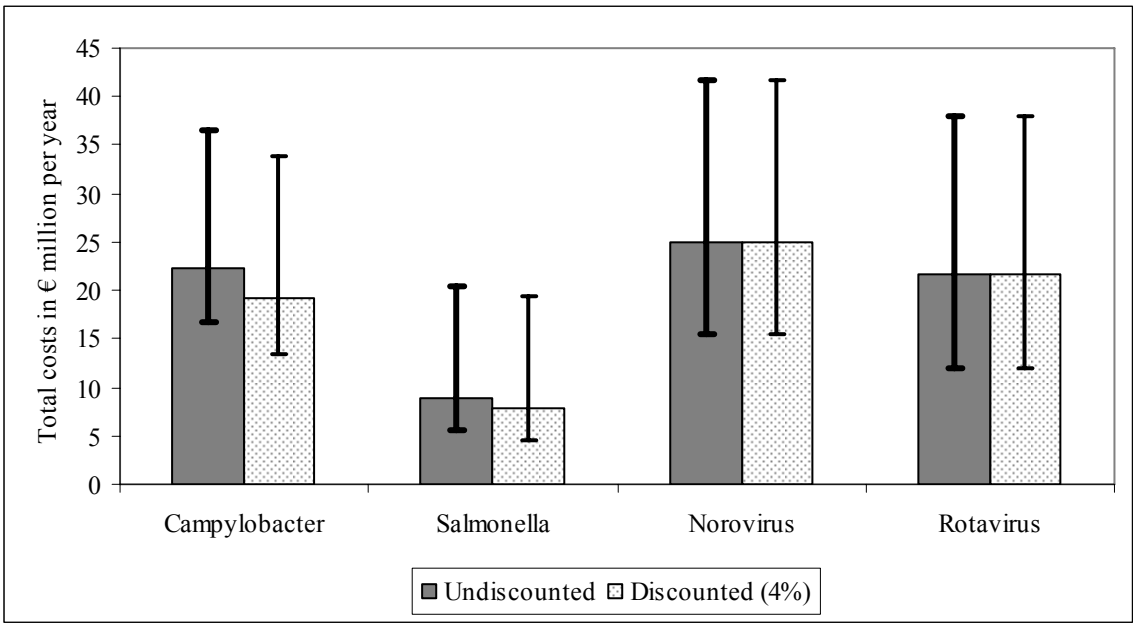


Figure 29. Cost of illness of infectious diseases that can (also) be transmitted by food. The figure shows the total cost of illness associated with different pathogens, undiscounted and discounted at 4%, and the uncertainty around the most likely estimate.

Figure 30 and Figure 31 compare the disease burden for the different pathogens on an individual rather than on a population basis. Note the difference in scale between the two figures. Congential toxoplasmosis and listeriosis cause the highest individual disease burden (11 and 80 DALYs per case respectively), but there is a major impact of discounting. In contrast, the disease burden of pathogens that primarily cause gastro-enteritisis is much lower. Bacteria, particularly STEC O157 rank highest (90 DALYs per 1000 cases), whereas the individual burden of viral gastroenteritis is very low (up to 2 DALYs per 1000 cases).

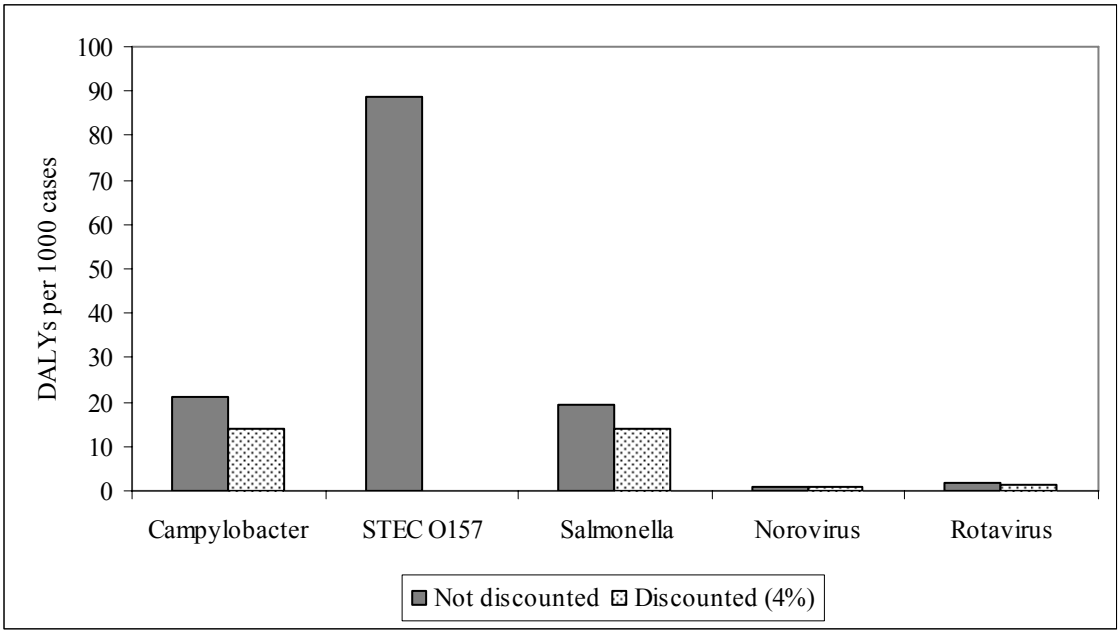


Figure 30. Individual disease burden of enteric infectious diseases that can (also) be transmitted by food in the Netherlands, 2004. Data are presented as average burden per 1000 cases of gastro-enteritis in the total population.

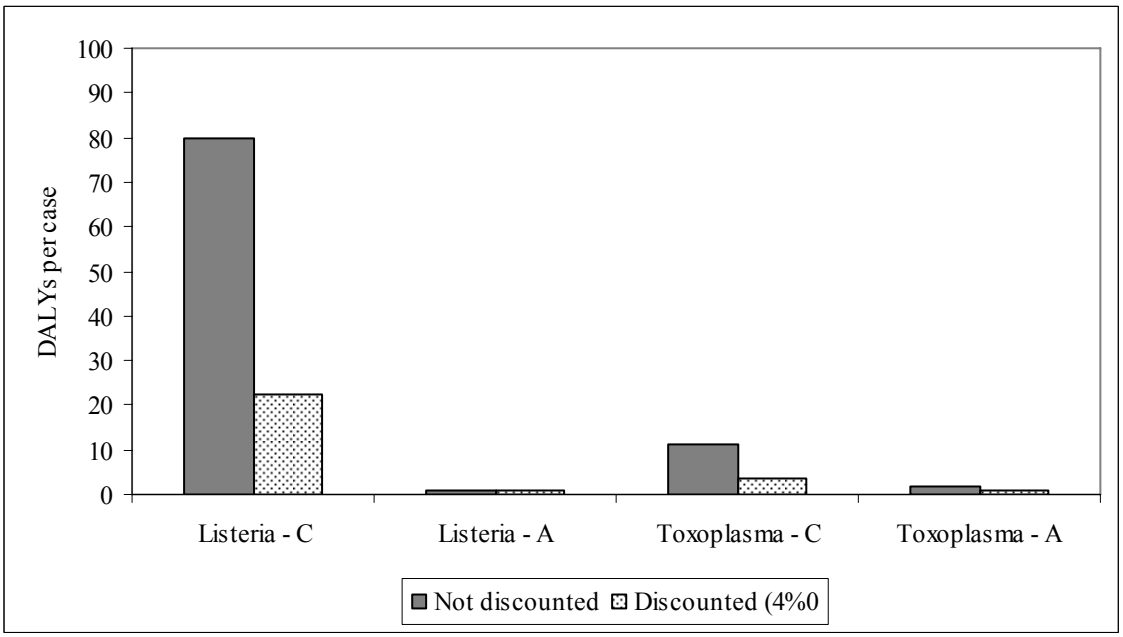


Figure 31. Disease burden of non-enteric infectious diseases that can (also) be transmitted by food in the Netherlands, 2004 (toxoplasmosis) and 2005 (listeriosis). Data are presented as average burden per case of reported congenital or acquired listeriosis, per case of congenital Toxoplasma infection or per case of severe acquired toxoplasmosis. Note the difference in scale with Figure 30.

Figure 32 shows the costs of four pathogens on an individual basis. The costs of the two bacterial pathogens Campylobacter and Salmonella are somewhat higher (200-400 euro per case) than the costs of noro- and rotavirus (50-100 euro per case).

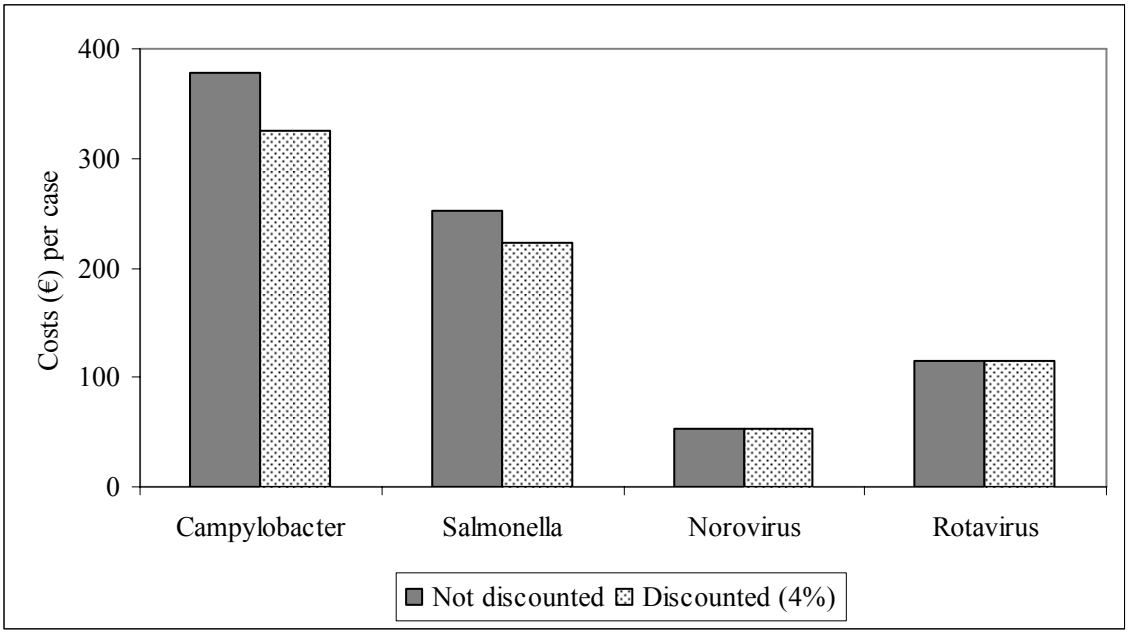


Figure 32. Individual cost of illness of enteric infectious diseases that can (also) be transmitted by food in the Netherlands, 2004. Data are presented as average cost per case of gastro-enteritis in the total population.

11. Research recommendations

As discussed in previous chapters of this report, there are many uncertainties attending the estimated disease burden and cost-of-illness of the described pathogens. In many cases, representative quantitative data are scarce. In this study we used the best information available and asked experts for the correctness of this information, especially when adequate data were lacking.

To decrease the uncertainty, more research is necessary and data collection should be focused on quantitative data. Specific research recommendations per pathogens and the follow-up of the present study will be discussed below.

GE pathogens in general

Severity weights for acute GE were based on Havelaar *et al*.[28], who determined weights for the acute-phase profile of Campylobacter-associated GE. In the current study it was assumed that NV, RV, Campylobacter and Salmonella-associated GE had the same severity weights during the acute-phase, using illness specific length of symptoms for each pathogen. In 2005, severity weights for GE stratified for severity, were determined, but now based on annual profiles[26]. However, these estimations seemed less accurate for mild diseases. More work is needed on deriving severity weights for acute, short-term illnesses like gastro-enteritis.

Within SENSOR and NIVEL some information was collected with respect to work absence. Information with respect to unpaid work and informal care were mostly lacking. We therefore considered in the current study only productivity losses due to work absence from paid work, knowing that we will probably underestimate the total costs. We therefore would recommend for future observational studies to distinguish between paid and unpaid work and informal care, both for patients as well as for third persons taking care of a sick person.

For future studies we would highly recommend to include, apart from epidemiologically relevant questions, also relevant questions for economics such as the use of medical services; sickness leave; costs of outbreak and costs of surveillance.

Reactive arthritis

Especially for ReA, independent of the etiological agent, a few crucial assumptions had to be made due to data limitations. Information available with respect to ReA incidence was mainly based on laboratory-surveillance. However, according to experts, also non-laboratory confirmed cases might be at risk to develop ReA. Therefore longer follow-up studies of community or GP-cohort studies, and/or outbreaks might help to clarify this point. Detected ReA cases should then also be observed for a longer period than only 6 months or 1 year, in order to define the risk that the acquired ReA symptoms might develop into a chronic form, the so-called anklyosing spondylitis. Apart from incidences and symptoms length, information is needed with respect to disability weights, use of medical services, informal care and work absence for ReA associated with various gastro intestinal pathogens.

Norovirus

Norovirus is the most common community-acquired gastro intestinal pathogen. But apart from a registration of outbreaks, no surveillance of community-acquired norovirus infections is in place, so no information on trends or up-to-date incidence estimates are available.

STEC O157

Given the informal nature of the current system, a more permanent surveillance for HUS is recommended. Especially the role of STEC O157 and other STEC serotypes in the development of HUS is relevant to study.

Listeriosis

The incidence estimates of listeriosis are highly uncertain since these were based on data from the enhanced surveillance which started in 2005. Therefore the observed number of cases with listeriosis is still small. However, it is a matter of time that more data will become available and more precise estimates can be calculated. A necessary condition for this purpose is the continuation of the enhanced surveillance. In the future, the same data set will enable us to provide more stable estimates of the incidences of stillbirths, neonatal death, and sequelae due to perinatal infections. Besides that, it is recommended to follow infected individuals in time to get more information about the incidence of long-term sequelae. In addition, the Dutch data may be combined with the results of international studies to get more valid estimations. This will be meaningful for both perinatal and acquired listeriosis.

Toxoplasmosis

Little is known about the incidence of both congenital and acquired toxoplasmosis in the Netherlands. We estimated the incidence from the TIP and Pienter study, but, these estimates are highly uncertain. The same applies for the different health outcomes of congenital toxoplasmosis (especially the incidence of stillbirth and its distribution about the weeks of pregnancy, the incidence of neonatal deaths, and the incidence of chorioretinitis and CNS abnormalities) and acquired toxoplasmosis (i.e. chorioretinitis and the number of deaths). However, better estimates are very important because from the evaluated pathogens, *Toxoplasma gondii* is the one with the highest disease burden.

One possibility to get more insight in the incidence of congenital toxoplasmosis is analysing eluates from PKU cards which are obtained within a few weeks after birth[114 116]. To provide a better estimate of the incidence of acquired toxoplasmosis, a one-year follow-up study can be performed with seronegative individuals at the start of the study. Longitudinal data are necessary to get more reliable information about the incidence of different health outcomes, although the necessary cohort size may be quite large because of the low incidence. Another approach to estimate the incidence of especially chorioretinitis is by modeling, attributing the incidence of chorioretinitis to congenital toxoplasmosis and acquired infections. This would also require better surveillance of chorioretinitis.

Follow-up of the present project

In the present report we calculated the disease burden and/or cost-of-illness for seven pathogens. To make the developed tool useful for future decision making, it is recommended that new data will be integrated in the calculations. Development of appropriate software applications and data management for this purpose is required. Following this project, the disease burden and cost-of-illness will be calculated for other pathogens that meet the inclusion criteria (see section 2.3). Furthermore, the uncertainties in the estimations have to be analysed in a more structured way, and a number of severity weights for several health outcomes will be assessed by the Amsterdam Medical Centre.

Besides that, there are more indicators for priority setting, like food attributive fraction, trends in incidence of foodborne pathogens, involved food products and effectiveness of preventive measures, and risk perception among the general population. So, the next step is to also consider these indicators in the project.

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Acknowledgements

The study described in this report would not have been realised without the help of a number of persons who are gratefully acknowledged for their contribution:

Wilfrid van Pelt (RIVM) for the epidemiologic data on rotavirus, CaSa, labsurveillance, rotavirus hospitalisation and trends, and critical advice concerning the chapters about gastroenteric pathogens;

Yvonne Doorduyn (RIVM) for listeria data and critical advice concerning this chapter;

Titia Kortbeek (RIVM) and Joke van der Giessen (RIVM) for their critical advice concerning the chapter about toxoplasmosis;

Marion Koopmans (RIVM) and Erwin Duizer (RIVM) for their critical advice concerning the chapters about norovirus and rotavirus;

Ardine de Wit (RIVM) for her critical advice concerning the cost-of-illness calculations;

Nancy Hoeijmans (RIVM) and Gouke Bonsel (AMC, Amsterdam) for the DALY methodology and severity weight estimations;

Morten Helms and Kåre Mølbak (SSI, Copenhagen, Denmark) for access to detailed information on the results of their registry-based studies on mortality and sequelae of gastro-enteritis.

Appendix 1 – Incidence of gastroenteritis, 2004

This Appendix presents updated incidence estimates for gastroenteritis per pathogen in the Netherlands for the year 2004. For this purpose, incidence rates for the general population in 1999 (from the Sensor study) and for visits to a general practitioner in 1996-1999 (from the NIVEL study) were applied to the population of 2004. The population increase from 1999-2004 was 3.2% with a slight shift towards older ages (source Statistics Netherlands). Incidence estimates for specific pathogens increased by 1.5 – 4.4%, reflecting the effect of different age-specific morbidity rates. The data in this Appendix were not corrected for trends in data from laboratory surveillance. Such data are only available for a limited number of pathogens and are presented in the main text. Note that no corrections were made for subtyping of pathogens (e.g. none of the yersiniae isolated in the original studies belonged to a known pathogenic serotype) or for isolation of pathogens from healthy controls (e.g. S. aureus and G. lamblia were isolated in approximately the same frequencies from patients and controls).

Table 46. Incidence of gastroenteritis per pathogen in the Netherlands, 2004.

	Incidence[a]	
Pathogen	General population	General practitioner
All causes	**4,800,000** **4,400,000-5,200,000**	**220,000** **15,000-34,000**
Bacteria – infectious		
Campylobacter	65,000 27,000-160,000	18,000 10,000-31,000
STEC – all serotypes	10,000 2,700-45,000	1,500 480-3,600
STEC O157	1,300 80-7,200	180 10-860
Salmonella	46,000 12,000-140,000	9,300 5,600-15,000
Yersinia	690 50-2,000	100 10-450
Shigella	1,400 100-6,000	560 100-1,800
Bacteria – toxin-producing		
B. cereus	42,000 22,000-86,000	-
C. perfringens	140,000 64,000-290,000	-
S. aureus	260,000 150,000-450,000	
Viruses		
Adenovirus (40/41)	61,000 40,000-100,000	7,800 4,800-12,000
Astrovirus	77,000 37,000-170,000	4,100 2,000-7,800
Norovirus	470,000 360,000-640,000	12,000 7,700-18,000
Rotavirus	220,000 130,000-360,000	16,000 11,000-22,000
Sapovirus	110,000 78,000-160,000	5,100 2,700-9,500
Protozoa		
C. parvum	71,000 34,000-165,000	5,200 2,900-8,800
G. lamblia	140,000 90,000-230,000	12,000 7,200-20,000

a) median
5-95 percentile