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Disease burden and costs of selected foodborne pathogens in the Netherlands, 2006

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Abstract

Disease burden and costs of selected foodborne pathogens in the Netherlands, 2006

The RIVM studies the disease burden and cost-of-illness caused by six foodborne pathogens in 2006. These pathogens are toxin-producing bacteria *Clostridium perfringens*, *Staphylococcus aureus* and *Bacillus cereus*, *Listeria monocytogenes* and hepatitis A and E virus. Additionally, the disease burden of irritable bowel syndrome following infectious intestinal disease was included in the calculation. This increased the disease burden due to the selected pathogens that may cause irritable bowel syndrome by forty percent (an increase of 1,400 DALYs per year to almost 5,000).

The disease burden of the toxin-producing bacteria *Clostridium perfringens* and *Staphylococcus aureus* are in the range of 500 and 700 DALYs per year. This is comparable to the burden of disease of protozoon Giardia and rotavirus. The disease burden of *Bacillus cereus* and Hepatitis A and E virus are with less than 140 DALYs per year low in comparison to other foodborne pathogens.

This study examined the pathogens as well as the transmission routes by which they spread to humans. The most important route is food, and within this category poultry, beef and mutton proved to be the major source of pathogen transmission.

Key words:
foodborne illness, priority setting, disease burden, cost-of-illness, gastroenteritis

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Rapport in het kort

Ziektelast en kosten van geselecteerde voedsel-overdraagbare micro-organismen in Nederland, 2006

Het RIVM heeft voor het eerst de ziektelast en de kosten onderzocht die zes ziekteverwekkende micro-organismen in 2006 veroorzaakten. Het gaat om de toxinevormende bacteriën *Clostridium perfringens, Staphylococcus aureus* en *Bacillus cereus, Listeria monocytogenes* en het hepatitis A- en E-virus. De bacteriën veroorzaken bij mensen darminfecties met diarree en buikgriep als gevolg. Hepatitis leidt tot leverinfecties. Behalve deze infecties is de ziektelast van het prikkelbare darmsyndroom na een voedselinfectie in de berekening opgenomen. Deze ziekte kan onder andere worden opgelopen door een besmetting met de Salmonella bacterie en het norovirus en leidt tot aanhoudende buikklachten. Door deze toevoeging stijgt de totale ziektelast als gevolg van micro-organismen die het prikkelbare darmsyndroom kunnen veroorzaken met veertig procent (een toename met 1400 DALYs per jaar tot bijna 5000).

De ziektelast van de toxinevormende bacteriën *Clostridium perfringens* en *Staphylococcus aureus* zijn tussen de 500 en 700 DALY's per jaar (Disability-Adjusted Life-Years, oftewel het aantal gezonde levensjaren dat een bevolking verliest door ziekte of vroegtijdig overlijden). Deze ziektelast is daarmee vergelijkbaar met infecties als gevolg van de parasiet Giardia en het rotavirus. De ziektelast van *Bacillus cereus* en het hepatitis A- en E-virus zijn met minder dan 140 DALYs per jaar laag vergeleken met andere voedseloverdraagbare micro-organismen.

In het onderzoek zijn zowel de ziekteverwekkers onderzocht als de wijze waarop ze de mens bereiken. Van deze blootstellingroutes is voedsel de belangrijkste bron. Binnen deze categorie blijken kip en rundvlees de belangrijkste bronnen die de micro-organismen overdragen.

Het onderzoek is uitgevoerd in opdracht van het ministerie van VWS en helpt om prioriteiten te kunnen aanbrengen in maatregelen die voedselinfecties voorkomen. Het onderzoek is onderdeel van een reeks naar de gezondheidseffecten van ziekteverwekkende micro-organismen waarvan het merendeel via voedsel wordt overgedragen.

Trefwoorden:
voedselinfecties, prioritering, ziektelast, ziektegebonden kosten, gastroenteritis

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Summary

Human health is threatened by a wide variety of foodborne and zoonotic pathogens. The major objective of this project was to develop a model that helps the Dutch Ministry of Public Health, Welfare and Sports to prioritize pathogenic micro-organisms as a decision tool in their food safety policy.

In two preceding studies published in 2006 and 2007 the disease burden and/or costs of nine pathogens were estimated. In the current follow-up study, in which we applied the same methods as the previous studies, we estimated the burden of disease and/or costs of post-infectious irritable bowel syndrome, three spore-forming bacteria *Clostridium perfringens*, *Staphylococcus aureus* and *Bacillus cereus*, *Listeria monocytogenes* and hepatitis A and E virus.

A literature review showed that 9% of bacterial gastroenteritis cases and 2% of viral gastroenteritis cases go on to develop post-infectious irritable bowel syndrome, resulting in an annual disease burden of 1,400 DALYs for six pathogens, increasing the total disease burden of studied pathogens with 40%.

For the spore-forming bacteria *Clostridium perfringens* and *Staphylococcus aureus* the most likely undiscounted annual disease burden was 509 DALYs and 688 DALYs, respectively. Cost-of-illness of these two spore forming bacteria was approximately 10 and 18 million euros in 2006. The disease burden and associated costs of *Bacillus cereus* was relatively low compared to other pathogens, with a most likely undiscounted disease burden of 109 DALYs and a cost-of-illness of approximately 3 million euros in 2006.

Over 2005 and 2006 the most likely annual disease burden of perinatal listeriosis was 203 and 62 DALYs undiscounted and discounted, respectively. Over the same time period the annual disease burden for acquired listeriosis was 108 and 96 DALYs lost. The annual cost-of-illness of perinatal and acquired listeriosis was 0.2 and 2 million euros, respectively.

With 103 and 136 DALYs, the most likely undiscounted annual disease burden of respectively hepatitis A and E virus was also relatively low.

The pathogens studied in this report were compared to the nine pathogens from the two preceding studies. *Bacillus cereus* had the lowest disease burden and cost-of-illness compared to the other eleven pathogens. The cost-of-illness *of Listeria monocytogenes* was even lower than the costs of *Bacillus cereus*. The annual burden of disease of *Listeria monocytogenes* on the other hand was in de middle range. *Clostridium perfringens, Staphylococcus aureus* and hepatitis A and E virus disease burden and costs were in the middle range.

1 Introduction

1.1 Background

Human health is threatened by a wide variety of foodborne and zoonotic pathogens. In order to provide an objective basis for policy decisions the Dutch Ministry of Public Health, Welfare and Sports asked the National Institute for Public Health and the Environment (RIVM) to develop a model that helps them 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.

A first study was published in 2006, estimating the disease burden for five enteric and two non-enteric pathogens, and the related sequelae. The selected pathogens were norovirus (NV), rotavirus (RV), thermophilic *Campylobacter* spp., *Salmonella* spp., Shiga-toxin producing *Escherichia coli* O157 (STEC O157), *Listeria monocytogens* and *Toxoplasma gondii*. For four of these pathogens, namely norovirus, rotavirus, thermophilic *Campylobacter* spp. and *Salmonella* spp. the associated cost-of-illness were also estimated. Full details were reported by Kemmeren et al. [1]. A second study, published in 2007, applied the same methods to estimate the disease burden and cost-of-illness of *Giardia lamblia* and *Cryptosporidium spp*. [2]. Both studies focused on community-acquired infections (i.e. excluding infections caused in health-care settings).

The current report is a follow-up of this earlier work. In this report we describe the disease burden of post-infectious irritable bowel syndrome, a sequel to infectious diarrhea, and Hepatitis A and E virus. For the toxin-producing pathogens *Clostridium perfringens, Staphylococcus aureus* and *Bacillus cereus*, the burden of disease as well as the cost-of-illness is described. Also, an update of surveillance-based *Listeria monocytogenes* and associated costs are reported. All estimates are based on incidence data and cost estimates for the year 2006.

1.2 Outline of report

Adjustments regarding the incidence of gastroenteritis (GE) are described in chapter 2. The methodology applied for disease burden and cost-of-illness estimates is shortly described in chapter 3. In chapter 4 through 10 the results are described. Chapter 11 integrates the result of this report and earlier work. Chapter 12 ends with a general discussion.

2 Incidence of gastroenteritis, 2006

As mentioned before, the results presented in this report are a continuation of previous work on the burden of foodborne disease, published in 2006 and 2007 [1, 2]. In many respects, the approach to assess the burden of disease used in the current study is similar to the 2006 and 2007 studies; however, some important adjustments have been made regarding the incidence of gastroenteritis and the methodology to assess the non-fatal burden of disease. This chapter covers the update of the incidence of gastroenteritis. The methodological adaptations will be discussed in the next chapter.

The previous 2006 and 2007 burden of foodborne disease estimates were based on the incidence of gastroenteritis for the year 2004 [1, 2]. For the current study the GE incidence was updated to 2006. This update entailed both data on acute GE in the population and the fraction of cases consulting the GP. The GE incidence in the entire population of the Netherlands was based on data from SENSOR, a Dutch community based cohort study performed from 1998 through 1999 in order to estimate the incidence of GE and its pathogens [3]. NIVEL, a Dutch GP based cohort study from 1996 though1999, was used to assess the fraction of cases that consulted a GP [4]. For all enteric pathogens, the age-specific SENSOR and NIVEL cases were extrapolated to 2006, adjusting for population growth and age-composition of the Netherlands in the year 2006, and, where available, taking into account trends in reported cases to the Laboratory Surveillance System [5].

In Table 1 the updated incidence estimates for GE per pathogen in the Netherlands over the year 2006 is presented.

Table 1. Incidence of gastroenteritis per pathogen in general population of the Netherlands, 2006.

Pathogen	Incidence general population
All causes	4,800,000 †
	4,400,000 – 5,200,000 ‡
Bacteria – infectious	
(Thermophilic) *Campylobacter* spp.	79,000
	28,000 – 170,000
Shiga-toxin producing *Escherichia coli* (STEC) O157	1,800
Salmonella spp.	43,000
	8,600 – 110,000
Bacteria – toxin producing	
Bacillus cereus	47,000
	21,000 – 87,000
Clostridium perfringens	160,000
	65,000 – 290,000
Staphylococcus aureus	270,000
	150,000 – 450,000
Viruses	
Norovirus	640,000
	470,000 – 850,000
Rotavirus	300,000
	170,000 – 480,000
Protozoa	
Cryptosporidium parvum	56,000
	23,000 – 110,000
Giardia lamblia	110,000
	69,000 – 180,000

† mean
‡ 5-95 percentile

3 Disease burden and cost-of-illness methodology

In order to assess the burden of disease and the cost-of-illness for the various pathogens under study, information on clinical outcomes of infection was arranged in outcome trees. An outcome tree defines the possible health outcomes followed by infection. Details are given in the following chapters.

Disease burden, one of the two criteria considered, is expressed in Disability Adjusted Life Years (DALYs). By using the DALY methodology, morbidity, expressed in years lived with disability (YLDs), and mortality, expressed in years of life lost (YLLs), are summed up into one metric unit. Compared to the preceding Dutch burden of foodborne disease studies, two significant adaptations regarding the methodology to calculate YLDs were made.

The first adaptation concerns the disability weights used. The disability weight is a scaling factor that reflects the impact of a specific health outcome with a value ranging from 0, indicating best imaginable health state, to 1, indicating worst imaginable health state. In the previous two Dutch burden of foodborne disease studies disability weights were based on the so-called standard QALY/DALY disability model (SQM). This model assumes that each health profile is separated into a succession of independent health states with distinct severities and that the valuation of each of the health states is independent of the duration of the health state. For chronic disease these assumptions are valid, but in case of a disease with an acute onset and/or a complex pattern over time, like gastroenteritis, the SQM assumptions are not appropriate [6, 7]. To overcome the operational limitations of the SQM, the annual profile model (APM) was developed. The most important feature of the APM is that it describes the course of the health state over the period of one year [6]. Because the duration of the health state is incorporated into the APM disability weight, YLD is calculated by multiplying the incidence by the disability weight. The current study adopted APM disability weights derived from a Dutch population panel in order to estimate YLDs lost due to foodborne disease. For certain health states, APM disability weights were not available. For these health states, SQM disability weights were applied.

The disability weights that were used are summarized in Table 2.

The second adjustment of the methodology to calculate YLDs concerns the lack of a clear cut-off point for severity, the so-called relevance criterion. Foodborne disease encompasses a wide variety in possible health states, ranging from minor to severe, and using incidence data from population health surveys, like the SENSOR study, implies that cases of minimal disease are included in burden of disease estimates. Collectively these highly prevalent cases of minimal disease may amount to a large number of YLDs in the aggregate, which may get priority above severe, but less frequently occurring disease. As a result, the application of burden of disease estimates in prioritization discussion may be restricted. This can be overcome by including a criterion for relevant disease. In the current study, a preference-bases relevance criterion was applied. This is a relevance criterion that is based on the preferences of a Dutch population panel [8]. The preference-based relevance criterion is met if at least 50% of the panel members is willing to trade-off time in order to be restored from the health state. If the health state is regarded as not relevant, it is excluded from the burden of disease calculation.

Apart from these two methodological adaptations, the DALY methodology used in the current study was similar to the 2006 and 2007 studies. A detailed description of the DALY methodology and the general assumptions made with respect to disease burden are given in chapter 2 of Kemmeren et al. [1]. Details on the methodological choices made are summarized in the Appendix.

Table 2. Disability weights used in this report.

	Disability weight	Source
Death	1.00	
Gastroenteritis		
Not visiting GP	0[a]	Haagsma et al.[8]
Visiting GP	0.015[a]	Haagsma et al.[8]
Hospitalized	0.041[a]	Haagsma et al.[8]
Irritable bowel syndrome	0.042[a]	Bonsel et al.[9]
Meningitis	0.32	Melse et al.[10]
Neurological disorders	0.25	Melse et al.[10]
Pneumonia	0.04	Melse et al.[10]
Sepsis	0.93	Melse et al.[10]
Hepatitis, mild	0.011[a]	Haagsma et al. [11]
Hepatitis, moderate	0.058[a]	Haagsma et al. [11]
Hepatitis, hospitalized	0.353	Havelaar et al. [12]

a) annual profile disability weight

Cost-of-illness, the second valuation criterion, is calculated by accumulation of: a) direct health care costs (DHC), which are costs for example the consultation of general practitioners and specialists, hospitalization, drugs and rehabilitation; b) direct non-health care costs (DNHC), which include e.g. the travel costs by patients and other co-payments by patients; and c) indirect non-health care costs (INHC), such as the productivity losses of patients and/or care-givers. Productivity losses were estimated according to the friction method. In order to keep our results comparable with the earlier estimations, costs were estimated using cost prices of the year 2006. The cost vectors used in the current study are summarized in Table 3. Pathogen specific assumptions, if available/necessary, are given in the specific chapters hereafter.

Disease burden and costs are presented, both discounted at a rate of 4% and undiscounted.

Uncertainty analysis was restricted to using low, most likely and high values for uncertain parameters, and some scenario analyses. For details, see Kemmeren et al. [1].

Table 3. Cost vectors in the Netherlands for the year 2006 (in €), most likely point estimate and if applicable, minimum and maximum point estimate.

Cost vectors	Costs per unit (in €) Most likely point estimate (minimum and maximum)
Direct medical costs	
Over-the-counter medicine of patients not requiring medical help per day of illness	0.16
Over-the-counter medicine of patients requiring medical help per day of illness	0.53
Cost for medication incl. prescription charges	37.1
Cost per average GP visit	32.3 (20.4 – 32.3) [a]
Costs for pathogen diagnostic in feces/sample submitted	67
Hospitalization adults/day	367
Hospitalization child/day	461
Outpatient clinic/consultation	64[b]
Short subscription fee for internist	62
Short subscription fee for paediatrician	88
Direct non-medical services	
Travel cost per average GP consultation	0.8 (0.14 – 1.5) [c]
Travel cost per hospitalization	3.5
Cost per diaper	0.3
Indirect costs	
Average costs of absence from paid work/hour	36.5
Average costs of third person taking care of sick person/hour	22.5 (8.5 - 36.5) [d]

a) Of the considered GP consultations, approximately 90% were GP practice visits (€ 21/visit) and the remaining 10% were house calls from the GP to the patient (€ 41/visit). Furthermore, per registered GP consultation, an additional 0.97 GP telephone consultations of the doctors' assistant took place (€ 10/call). For the minimum estimate we assumed 100% GP practice visits and no phone calls.
b) Calculated as the weighted average of visiting a general hospital (84% of patients and €57 per consultation) and a university hospital (16% of patients and €101 per consultation).
c) Depending on the assumption made of an average GP consultation and depending of the travel form used (e.g. public transport, car or cycling/walking). For details see Kemmeren et al. [1].
d) It could not be assessed whether work absence was from paid work or from unpaid work. We therefore assumed as most likely point estimate that the average of productivity losses for an average working person, € 36.5/hour, and the opportunity costs for informal care, € 8.5/hour, which was equal to an average of € 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.

4 Post-infectious irritable bowel syndrome

Irritable bowel syndrome (IBS) is a chronic functional bowel disorder characterized by abdominal pain and intermittent diarrhea/constipation. It is a highly prevalent disorder, affecting an estimated 10 to 20% of the Western population at a certain point in time [13, 14]. Following the results from a community survey, the prevalence of IBS-like complaints in the Netherlands is 6.2%, with 2% meeting the diagnostic criteria of Manning, ROME I and ROME II [15]. Extrapolating this prevalence rate to the whole population of the Netherlands leads to a prevalence of 330,000 individuals with formally diagnosed IBS.

The cause of IBS is largely unknown; however several studies have found evidence that IBS is a sequel of a preceding episode of infectious gastroenteritis [16, 17]. Due to gastroenteritis the concentration of the serotonin-containing enteroendocrine cells within the gut may increase, resulting in higher gut motility [18]. Pathogens known to be associated with post-infectious IBS (PI-IBS) are *Salmonella spp.*, *Shigella spp.*, (thermophilic) *Campylobacter* spp, Shiga-toxin producing *Escherichia coli* (STEC) O157 and norovirus (see Table 5). Women suffer from PI-IBS more often compared to men [19, 20]. Other risk factors for the development of PI-IBS include severity and duration of the gastro-enteritis episode, age, smoking and co-occurring depression [19, 21, 22]. This section describes the estimated disease burden of PI-IBS due to pathogens Campylobacter, Salmonella, STEC, Shigella, norovirus and rotavirus in the Netherlands.

4.1 Outcome tree, incidence and duration of illness

4.1.2 Outcome tree and incidence

The outcome tree of PI-IBS is shown in Figure 1.

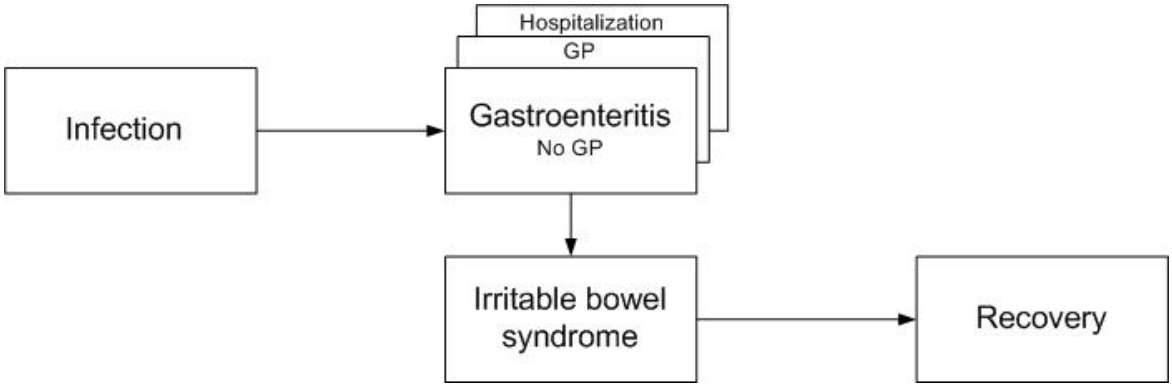

Figure 1. Outcome tree of post-infectious irritable bowel syndrome (PI-IBS).

We conducted a systematic literature review of published studies to date that explored PI-IBS following gastroenteritis (see Table 4). Firstly, we conducted a search of the database MEDLINE that was restricted to articles published in English from and including 1990, using the following search terms: irritable bowel syndrome, functional bowel disorder, post infectious, infectious, follow-up, gastroenteritis, diarrhea, incidence, and prevalence. The resulting articles were screened in order to identify articles that met the predefined selection criteria. Reference lists of the included articles were then examined to identify cited articles not captured by MEDLINE. Finally, full text articles that met the selection criteria were scrutinized to assess methodological quality.

Table 4. Overview of the systematic review on post-infectious irritable bowel syndrome (PI-IBS).

Database	MEDLINE
Keywords	irritable bowel syndrome, functional bowel disorder, post infectious, infectious, follow-up, gastroenteritis, diarrhea, diarrhoea, incidence, prevalence
Selection criteria	Written in English or Dutch, year of publication >1990

We found 19 studies that investigated the incidence of PI-IBS following gastroenteritis. Table 5 presents an overview of the findings of these 19 follow up studies. In these studies, the index group was a cohort of GE-patients, usually with confirmed bacterial or viral etiology. Controls were included in 8 studies and comprised of volunteers, patients from the same general practice, siblings or spouse of the patient. The PI-IBS incidence rate found in the 19 studies ranges from 4% up to 36%.

The data reported in the follow-up studies was pooled in order to estimate the incidence rate of PI-IBS. This resulted in an incidence rate of PI-IBS of 13.1%. If the pooled incidence was *weighted* for sample size of the study, the pooled PI-IBS incidence was 11.6%. This pooled incidence rate has not been corrected for background illness. For the case-control studies, the incidence rate can be adjusted by calculation of the attributable proportion (AP; see Table 6). The data do not suggest an increasing probability of PI-IBS for different levels of the surveillance pyramid. Neither do the data suggest that PI-IBS differs between pathogens, except for a lower risk following norovirus infections.

Table 5. Incidence rate of post-infectious irritable bowel syndrome (PI-IBIS).

Author	Year	Study design[a]	Pathogen	Subjects[b]	Follow up (months)	Rate PI-IBS (%)
Borgaonkar et al.[23]	2006	PC	Bacterial	Lab+ patients	3	4
Cumberland et al.[24]	2003	PCC	?	GP patients	3	3
Dunlop et al.[25]	2003	PCC	Campylobacter	Lab+ patients	3	14
Gwee et al.[20]	1996	PC	Mixed	Hosp. patients	3, 6, 9, 12	29, 27, 20, 12
Ilnyckyj et al.[26]	2003	PC	TD*	Travelers (no GP)	3	4
Ji et al. [27]	2005	PCC	Shigella	Hosp. employees	3, 6, 12	19, 11, 15
Kim et al.[28]	2006	PCC	Shigella	Lab+ patients	36	18
Marshall et al.[29]	2006	RC	E coli/ Campylobacter	Residents	24	36
Marshall et al.[30]	2007	PCC	Norovirus	Conference part	3, 6, 12, 24	24, 12, 15, 20
McKendrik et al.[31]	1994	RC	Salmonella	Lab+ patients	6	31
McKeown et al.[32]	2006	PC	Campylobacter	Hosp. patients	3, 6	17, 17
Mearin et al.[33]	2005	PC	Salmonella	Lab+ patients	3, 6, 12	7, 11,12
Neal et al.[19]	1997	PC	Bacterial	Lab+ patients	6	6
Okhuysen et al.[34]	2004	PC	E coli	Travelers (no GP)	6	11
Parry et al.[21]	2003	PCC	Bacterial	Lab+ patients	6	17
Rodriguez et al.[35]	1999	PCC	Bacterial	GP patients	12	4
Spence et al.[36]	2007	PC	Campylobacter	Lab+ patients	6	8
Thornley et al.[37]	2001	PC	Campylobacter	Lab+ patients	6	9
Wang et al.[38]	2004	PCC	Shigella	Lab+ patients	10	9
Total						13,1

a) PC = prospective cohort, PCC = prospective case control, RC = retrospective cohort
b) Lab+ patients = Laboratory confirmed cases of bacterial gastrointestinal pathogen
b) number of people with PI-IBS/total number of GE patients
* TD = traveler's diarrhea

Table 6. Attributive Risk (AR), per study.

Study	Pathogen	Cases	Controls	AP
Ji et al.[27]	Shigella	15/101	6/102	0.090
Kim et al.[28]	Shigella	17/95	4/105	0.141
Parry et al.[21]	Bacterial	18/108	4/206	0.147
Rodriguez et al.[35]	Bacterial	14/318	2027/584308	0.041
Wang et al.[38]	Shigella	24/235	2/243	0.094
Marshall et al.[30]	Norovirus	11/87	3/29	0.023

The APs were calculated as:

$P_{ge}^{*}(RR-1)/RR$;

where p_{ge} is the proportion exposed to acute gastroenteritis among cases and RR is the relative rate adjusted for developing IBS without exposure acute gastroenteritis. We employed data from five case-control studies in order to calculate the AP for bacterial infections [21, 27, 28, 35, 38]. The mean AP risk for bacterial infections weighted for sample size was 8.6% (most likely estimate) with a minimum of 5.5%, corresponding to the 5th percentile, and a maximum AP of 9.6%, corresponding to the 95th percentile of the Beta distribution. To determine the AP for viral infections, data from one case-control study performed by Marshall et al. was available [30]. This study measured incidence of PI-IBS at 3, 6, 12 and 24 months after infection. The diagnostic criteria for IBS suggest evident symptoms for at least three months, either continuously or recurrent, over a period of at least 6 months prior to the diagnosis. In accordance with the diagnostic criteria and the follow-up period regarding studies on PI-IBS following bacterial infection, we used the 6-month follow-up data for the AP calculation. This resulted in a best estimate of the AP for viral infections of 2.3% with a minimum of 0 and a maximum of 9.5% (95th percentile of the distribution). The estimated incidence of PI-IBS is shown in Table 7.

Table 7. Incidence of gastroenteritis and post-infectious irritable bowel syndrome per pathogen for 2006 [a].

	Incidence					
	Gastroenteritis			Post-infectious IBS		
Pathogen	Most likely	Low	High	Most likely	Low	High
Bacteria						
Campylobacter	79,000	28,000	170,000	6,600	2,300	14,000
STEC	15,000	2,700	44,000	1,300	220	3,800
Salmonella	43,000	9,100	110,000	3,600	730	9,000
Shigella	4,400	320	14,000	380	25	1,300
Viruses						
Norovirus	640,000	470,000	850,000	15,000	0	69,000
Rotavirus	300,000	170,000	480,000	6,900	0	35,000
Total	1,100,000	680,000	1,700,000	33,000	3,300	130,000

a) Summations might not necessarily tally because of rounding

4.1.2 Duration of illness

About the long-term course of IBS, little is known. Results from studies that did investigate the course of IBS indicated that symptoms do not change over one year time [39]. Spence et al. [36] as well as Parry et al.[21] found incidence rates that were similar at 3 months and 6 months follow up. Ji et al. [27], who sent a follow-up questionnaire at 3, 6 and 12 months, reported that 50% of the patients with PI-IBS did not recover within 12 months. Moreover, long-term follow-up studies showed that symptoms often lasted for several years. Owens et al. [40] performed a prospective review of the medical records of 112 IBS patients. The median follow time of this study was 40 years (range 1 to 80 years) and the median duration between diagnosis of IBS and last recorded IBS related visit to the clinic was 29 years (range 1 to 32 years). Results from a retrospective six year follow up showed that 31% of patients with IBS and 43% of patients with post-infectious (PI) IBS were recovered [19]. This suggests that the prognosis of patients with PI-IBS is slightly better compared to IBS [41]. A literature

search yielded 5 long-term PI-IBS follow up studies. The findings of these studies are summarized in Table 8.

However, it should be noted that the PI-IBS follow up studies relied on patient-reported questionnaires and that the validity of self-reported questionnaires to assess health has been disputed [42]. This means that the reported symptoms might not correspond to actual health. In clinical practice, the majority of patients (80-90%) do not consult a gastroenterologist after a period of one year (P. Siersema, University Medical Centre, Utrecht, personal communication). We assumed a median duration of symptoms in between these extremes of one year on the one hand and six years on the other hand, i.e. a median duration of one year, with a minimum duration of 6 months and a maximum duration of 6 years.

Table 8. Percentage of patients with persistent post-infectious irritable bowel syndrome symptoms at follow-up.

Study	Follow up	% with persistent PI-IBS symptoms
Gwee et al.[20], McKeown et al.[32]	6 months	91%; 100%
Ji et al.[27], Marshall et al.[30]	1 year	80%; 43%[a]
Marshall et al.[30]	2 years	41%[a]
Kim et al.[28]	3 years	75%
Neal et al.[43]	6 years	56%
Agrues et al.[39]	7 years	44% (note: IBS)

a) viral rather than bacterial pathogen.

4.2 Disease burden

The estimated YLD lost due to PI-IBS following infection with the selected pathogens was computed by combining incidence, duration of the illness and the disability weight for IBS. Minimum and maximum YLD estimates were calculated using the low and high incidence estimates of PI-IBS. The results are shown in Table 9.

Table 9. Incidence and YLD of post-infectious irritable bowel syndrome for 2006 (undiscounted) [a].

		YLD estimate		
Pathogen	Incidence	Most likely	Low	High
Bacteria				
Campylobacter	6,600	279	49	3,640
STEC all serotypes	1,300	54	5	954
Salmonella	3,600	151	15	2,258
Shigella	380	13	<1	320
Viruses				
Norovirus	15,000	613	0	17,434
Rotavirus	6,900	291	0	8,806
Total	33,000	1,401	69	33,412

a) Summations might not necessarily tally because of rounding

4.3 Scenario analysis

Because the data of the case-control studies on PI-IBS that were included in our analysis did not suggest an increasing probability of PI-IBS for different levels of the surveillance pyramid, we have calculated PI-IBS following gastroenteritis of six selected pathogens using all cases of gastroenteritis in the population, independent of the severity and duration of the episode. However, there is evidence that the probability of developing PI-IBS increases by level of severity and duration of gastroenteritis symptoms [19, 21, 22]. Therefore, the assumption that all cases in the population are at risk to develop PI-IBS, even the cases that do not seek medical advice, might not be correct. Symptoms severity and duration of the gastroenteritis episode are determinants of seeking medical advice [3]. Rather than using all cases in the population, perhaps only cases with that consult a GP or hospitalized cases should be used to estimate the number of patients that go on to develop PI-IBS. Table 10 shows the estimated number of cases of PI-IBS and DALYs lost based on the cases visiting the GP and hospitalized cases.

Table 10. Incidence and DALY of post-infectious irritable bowel syndrome for 2006 (undiscounted), using GP and hospitalized cases of gastroenteritis [a].

Pathogen	Incidence	DALY (most likely)
Bacteria		
Campylobacter	1,700	70
STEC all serotypes	140	6
Salmonella	620	26
Shigella	60	30
Viruses		
Norovirus	365	15
Rotavirus	470	20
Total	3,300	140

a) Summations might not necessarily tally because of rounding

4.4 Discussion

The findings of the systematic literature review indicate that 9% of patients with bacterial gastroenteritis and 2% of patients with viral gastroenteritis go on to develop PI-IBS. Annually, this amounts to an estimated 33,000 cases of PI-IBS following gastroenteritis of the six selected pathogens that occur in the Dutch population, with an uncertainty range of 3,300 and 130,000 cases per year. Each year the total number of PI-IBS cases results in a loss of 1,401 DALYs per year (undiscounted), increasing the total number of DALYs lost due to studied pathogens with 40%, assuming that all GE cases in the population are at risk to develop PI-IBS, even cases that do not consult the GP. If only cases that seek medical advice are included in the estimates, the total number of DALYs lost due to PI-IBS is 140 DALYs per year.

Including PI-IBS increases the annual burden of disease of *Campylobacter spp.* with 18% (from 1,564 to 1,843 DALYs). For *Salmonella spp*. this increase is 17% (from 905 to 1056 DALYs) and for STEC 46% (from 118 to 172 DALYs). Highest increase in burden of disease regards the viral pathogens noro-

and rotavirus. The burden of norovirus increases with 152% (from 404 to 1,017 DALYs) and rotavirus with 56% (from 521 to 812 DALYs). Figure 2 shows the disease burden of the five pathogens, both excluding and including PI-IBS.

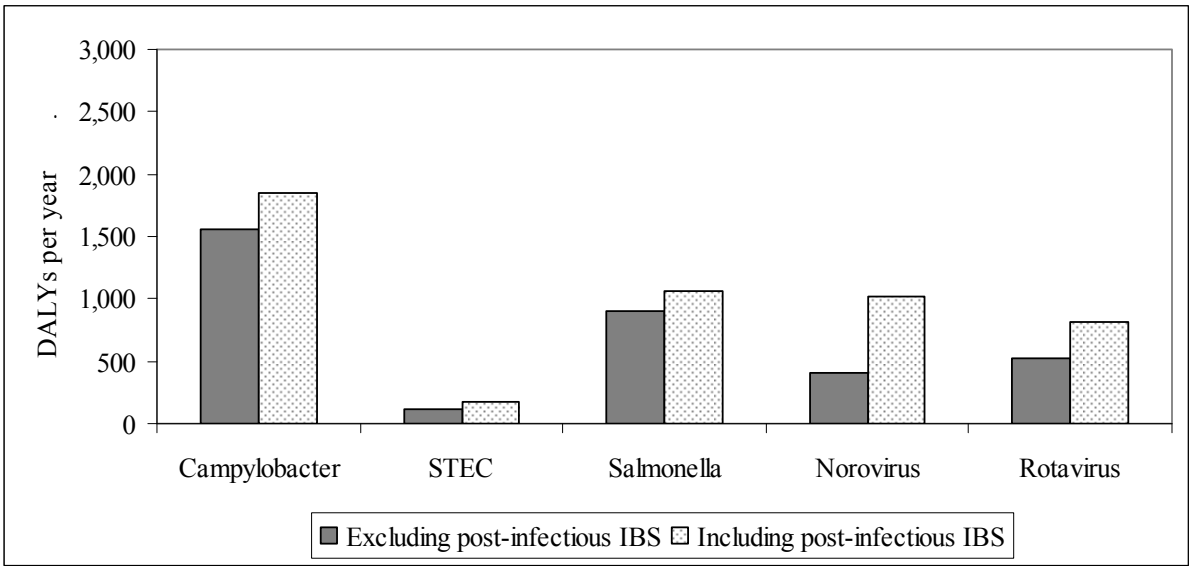

Figure 2. Disease burden of five pathogens for 2006, using most likely estimates, both excluding and including post-infectious irritable bowel syndrome. Error bars express an uncertainty interval that results from using low and high estimates.

5 Clostridium perfringens

Clostridium perfringens, previously known as *Clostridium welchii,* are anaerobic, Gram-positive, spore-forming bacteria. They are widely distributed in the environment, inhabiting soil and water, and also the intestinal tract and faeces of warm-blooded animals and humans [44]. In healthy humans the *C. perfringens* in the intestinal tract do not cause disease; however, if humans ingest food that is contaminated with large numbers of *C. perfringens*, food poisoning may occur [45, 46].
After ingestion *C. perfringens* multiply in the small intestines and release enterotoxin during sporulation [47, 48]. The enterotoxins cause food poisoning, of which the clinical signs occur 8 to 12 hours after ingestion. Usually *C. perfringens* food poisoning is characterized by a relatively mild self-limiting gastroenteritis with short duration. Due to these mild and short-term symptoms, many cases of *C. perfringens* food poisoning are undiagnosed [49].

In very rare cases, *C. perfringens* food poisoning causes necrotizing enterocolitis, a severe and often fatal disease that involves infection and necrosis of the intestinal wall and tissue [50]. This rare but severe sequel of food poisoning mainly involves *C. perfringens* type C strains which produce β-toxin as well as α-toxin, whereas the mild form of *C. perfringens* food poisoning is mainly caused by the α-toxin producing type A strains [45, 46, 50]. Cases with necrotizing enterocolitis have chiefly been reported regarding inhabitants of Papua New Guinea, although sporadic cases of enteritis necroticans have been reported from Western countries [51]. Because of its sporadical occurrence, we excluded the sequel necrotizing enterocolitis from the burden of disease estimate of *C. perfringens.*

C. perfringens are typically found in raw and processed meat products, especially beef and poultry [47]. Unlike most foodborne pathogens, *C. perfringens* survive cooking because of the ability to form spores that are heat-resistant. Additional factors that enhance *C. perfringens* outbreaks are improper cooling and long duration between preparation and consumption of the food [52]. Most cases of *C. perfringens* food poisoning are reported from restaurants, hospitals and old people's homes [44].

5.1 Outcome tree, incidence and duration of illness

5.1.2 Outcome tree and incidence

Food poisoning due to *C. perfringens* is not systematically registered in the Netherlands. Therefore, to estimate the incidence of *C. perfringens* food poisoning in the population we used data from the SENSOR-study [3]. SENSOR is a Dutch prospective population-based cohort study that was conducted from 1998 through 1999 in order to estimate the incidence of gastro-enteritis and its pathogens. The age-specific SENSOR-data on *C. perfringens* induced gastro-enteritis were adjusted for population growth and age composition of the Netherlands in the year 2006, resulting in an estimated incidence of *C. perfringens* food poisoning of 160,000 cases per year. The uncertainty of this estimation ranges from 65,000 (low estimate corresponding with the 5th percentile of the estimation) to 290,000 (high estimate corresponding with the 95th percentile of the estimation).

The number of cases that would visit a GP due to *C. perfringens* food poisoning is also unknown for the Netherlands. A large study from England/Wales reported that 53% of the cases would visit the GP [53]. This percentage seems rather high regarding the relative mildness and short duration of the symptoms. The reported high percentage of cases consulting the GP might be explained by the relatively high consultation rate of gastroenteritis patients in England, which is approximately three times higher compared to the consultation rate in the Netherlands [3]. Correcting for the differences in consultation rates between England and the Netherlands, we assumed that in the Netherlands 19% of the *C. perfringens* food poisoning cases would visit the GP. Consequently, the number of cases that would consult the GP due to *C. perfringens* food poisoning is estimated at 29,000 per year. This estimation includes both hospitalized and non-hospitalized cases. The minimum estimation of cases consulting the GP is 12,000, corresponding with the 5th percentile of the estimation. The maximum estimation of cases consulting the GP is 54,000, corresponding with the 95th percentile of the estimation.

The hospitalization rate of patients with *C. perfringens* food poisoning was calculated using data on *C. perfringens* cases reported by Dutch public health laboratories (PHL) that participate in the Infectious Diseases Surveillance System database (ISIS). In total, fourteen PHLs reported hospitalized *C. perfringens* cases. Taking the coverage rate of the PHLs into account, we estimated that the hospitalization rate of *C. perfringens* food poisoning is 0.002. This hospitalization rate is slightly lower compared to those reported by Adak et al. [53] and Mead et al. [54], who found *C. perfringens* hospitalization rates of 0.004 and 0.003, respectively. Using the calculated Dutch hospitalization rate of 0.002, we supposed that in 2006 most likely 270 cases of *C. perfringens* food poisoning were hospitalized, with a minimum of 120 cases, and a maximum of 510 cases.

Based on case fatality rates reported by Mead et al. [54], we assumed that most likely 4 people died due to *C. perfringens* food poisoning, with a minimum of 2 cases and a maximum of 8 cases. Figure 3 shows the outcome tree for C. perfringens food poisoning and Table 11 shows the estimated incidence of *C. perfringens* food poisoning.

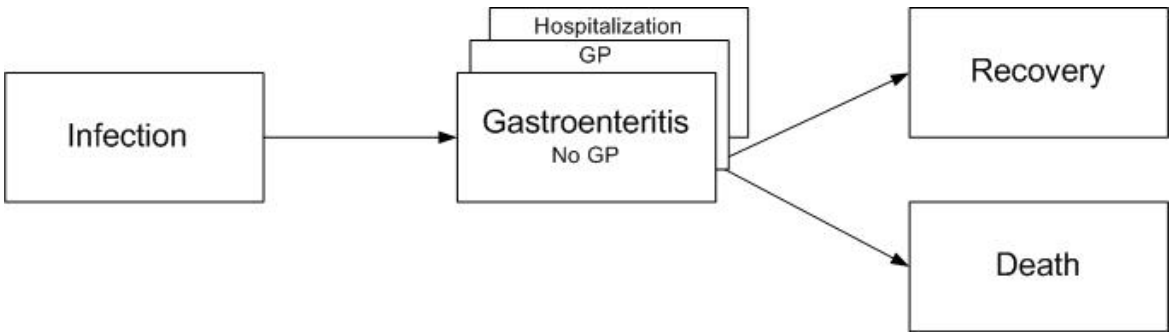

Figure 3. Outcome tree *C. perfringens*-associated gastroenteritis.

Table 11. Incidence of illness of *C. perfringens*-associated gastroenteritis for 2006.

	Incidence estimates (cases per year)		
	Most likely	Low	High
Gastroenteritis	160,000	65,000	290,000
No GP	130,000	53,000	230,000
GP	29,000	12,000	54,000
Hospitalization	270	120	510
Fatal	4	2	8

* Summations do not necessarily tally.

5.1.2 Duration of illness and age-distribution

C. perfringens food poisoning symptoms often last no longer than two days. This relatively short duration is endorsed by several *C. perfringens* outbreak studies reporting a median duration of symptoms lasting 16 through 24 hours [55-59]. Results from the IID-study showed that adults who did not visit the GP reported diarrhea for a median duration of 2 days and abdominal pain for 3 days, whereas adults that did visit the GP reported diarrhea for 4 days and abdominal pain for 6 days [60]. Taking into account both outbreak studies and the IID-study, we supposed that cases not visiting the GP had a duration of illness of 2.5 days and cases visiting the GP had a duration of illness of five days. Hospitalized patients from England/Wales were admitted to hospital for 10.5 days on average [53]. Taking this into account, we assumed that the duration of illness of hospitalized patients was 14 days.

The age distribution of *C. perfringens* induced food poisoning is summarized in Table 12. The age distribution of cases not visiting the GP is unknown for the Netherlands. We therefore supposed that the age distribution of cases not visiting the GP (no GP) is similar to the age distribution observed in the laboratory confirmed cases reported by the Dutch PHL participating in ISIS. To render the age distribution of cases that did visit a GP (GP) and cases that were hospitalized (hospitalization), we also used the cases reported by the PHLs. Data on the age distribution of fatal cases of *C. perfringens* food poisoning are lacking. However, it is suggested that death due *C. perfringens* food poisoning is mainly seen in elderly [44, 47]. This is supported by findings reported in several outbreak studies [61-63]. Therefore, we assumed that fatal cases only occurred in the age group of 65 years and older.

Table 12. Age distribution of *C. perfringens*-associated gastroenteritis.

	Age classes				
	0-4 years	5-9 years	10-14 years	15-64 years	> 65 years
Gastroenteritis					
No GP[a]	3%	1%	3%	33%	61%
GP[b]	4%	1%	8%	33%	54%
Hospitalization[b]	2%	1%	1%	27%	69%
Fatal[c]	-	-	-	-	100%

a) no information available. We used laboratory confirmed cases reported by PHLs from ISIS as a proxy.
b) based on C. perfringens cases reported by PHLs from ISIS.
c) no pathogen specific information available.

5.2 Disease burden

The estimated number of YLD, YLL and DALYs lost due to *C. perfringens* food poisoning are shown in Table 13. Both the discounted (4%) and the undiscounted number of DALYs lost are calculated. The incidence, duration and disability weights used for the estimations are also shown in Table 12. In Figure 4 the DALY estimates for the most likely estimate and the uncertainty (low and high estimate) are shown for the total estimation as well as for each health state separately, both discounted and undiscounted.

Table 13. Incidence, duration and disease burden of *C. perfringens* food poisoning for 2006 (most likely estimates).

	Incidence	Disability weight	YLD	YLL	DALY (0%)	DALY (4%)[b]
Gastroenteritis	160,000					
No GP	130,000	0	0	-	0	0
GP	29,000	0.015	441	-	441	441
Hospitalization	270	0.041	11	-	11	11
Fatal	4		-	58	58	45
Total			452	58	509	497

* Summations do not necessarily tally.

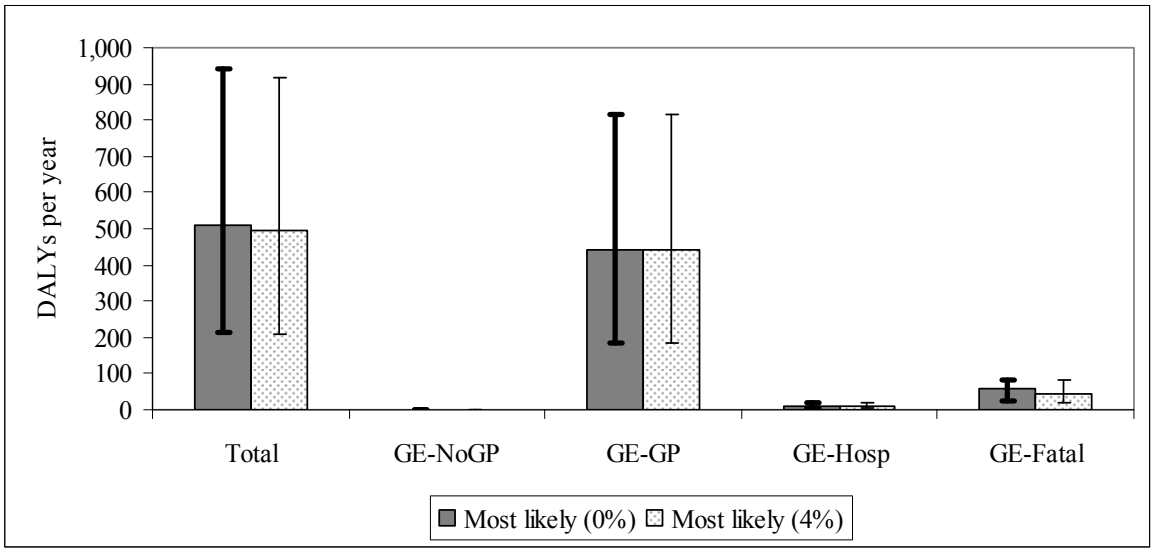

Figure 4. Disease burden of *C. perfringens*-associated gastroenteritis for 2006, using most likely estimates, discounted (4%) and undiscounted (0%). Error bars express an uncertainty interval that results from using low and high estimates.

5.3 Cost-of-illness

Based on the incidence and duration of illness shown in Table 11, and following in general the assumptions described in section 2 and in the previous report, we estimated the direct health care costs for the different health states. An average hospital stay of 10.5 days was assumed for *C. perfringens* cases. DHC results of *C. perfringens* cases are summarized in Table 14 for the most likely estimate only.

Table 14. DHC of *C. perfringens*-associated gastroenteritis in million euros for 2006 (most likely estimates).

	Drugs & medicine	GP consultations	Hospitalization	Other	∑ DHC
Gastroenteritis	1.2	1.1	1.5	-	3.8
No GP	<0.1	-	-	-	<0.1
GP	1.2	1.1	-	-	2.3
Hospitalization	<0.1	<0.1	1.4	-	1.5
Fatal	-	-	-	-	-

Productivity losses due to 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 assumptions described in section 2. The estimated overall work absence for *C. perfringens* patients not visiting a GP and *C. perfringens* patients visiting a GP only, were estimated to be a 0.22 days and 0.69 days, respectively. In Table 14 we have summarized the estimated number of days paid employment lost for adult patients and for third persons taking care of a sick person. We further present in Table 15 the most likely estimate of Indirect Non Health Care Costs (INHC).

Table 15. Number of days paid employment lost and INHC of community acquired *C. perfringens*-associated gastroenteritis in million euros for 2006 (most likely estimates).

	No. of days paid employment lost		Productivity losses		∑ INHC
	Patient	Third person	Patient	Third person	
Gastroenteritis	-	-	4.7	0.9	5.6
No GP	0.2	1	2.6	0.6	3.2
GP	0.7	1	1.9	0.3	2.2
Hospitalization	5.0	3	0.1	-	0.1
Fatal	154	-	-	-	-

In Table 16 and Figure 5 we present the cost-of-illness of community acquired *C. perfringens*-associated GE in detail for the different health states in million euros for 2006.

Table 16. Cost-of-illness of community acquired *C. perfringens*-associated gastroenteritis for the different health states in million euros for 2006 (most likely estimates).

(discounting)	DHC (0%)	DNHC (0%)	INHC (0%)	∑ Costs (0%)
Gastroenteritis	3.8	<0.1	5.6	9.4
No GP	<0.1	-	3.2	3.3
GP	2.3	<0.1	2.2	4.6
Hospitalization	1.5	-	0.1	1.6
Fatal	-	-	-	-

In Figure 5 we have summarized the most likely estimate and the most likely estimate with attendant uncertainty, respectively, for the total cost of community acquired *C. perfringens*-associated GE cases. Given that all costs occur within one year, discounting is not an issue.

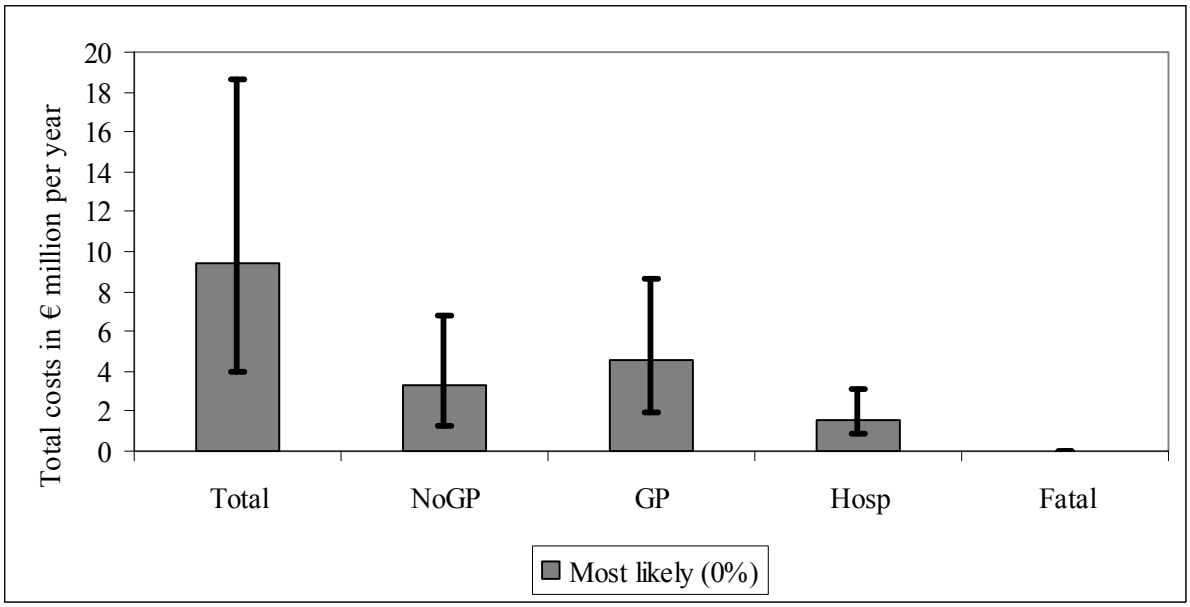

Figure 5. Total cost-of-illness of community acquired *C. perfringens*-associated *gastroenteritis*, using most likely estimates. Error bars express an uncertainty interval that results from using low and high estimates. Discounting was not required as all costs occur within the first year.

5.4 Scenario analysis

In the current study the number of cases with gastroenteritis due to *C. perfringens* that consulted a GP was based on data from study of Adak et al. who found a GP consultation rate of 0.53 for *C. perfringens* in the UK [53]. This rate was then adapted for the Dutch situation, resulting in a GP consultation rate of 0.19. This latter adaptation contains some uncertainties, since general differences in consultation rates between the Netherlands and the UK were used for the adaptation. It is unclear whether the differences in consultation rate between UK and the Netherlands hold true for the relatively mild symptoms of gastroenteritis caused by *C. perfringens*.

In Table 17 we have summarized the incidence and burden of disease if we apply the GP consultation rate of 0.53 rather than the adapted consultation rate. Using the UK GP consultation rate for *C. perfringens* increases the number of DALYs lost significantly by 154% from 509 to 1,293 DALYs and the cost-of-illness with 64% from 9.4 to 15.9 million euros.

Table 17. Incidence, DALY and cost-of-illness of community acquired *C. perfringens*-associated GE for the different health states [a].

Pathogen	Incidence	DALY (0%)	Cost (0%)
Gastroenteritis	160,000	1,293	15.9
No GP	73,000	0	1.9
GP	82,000	1,224	12.4
Hospitalization	270	11	1.6
Fatal	4	58	0

a) Summations might not necessarily tally because of rounding

5.5 Discussion

Each year about 160,000 cases of *C. perfringens* food poisoning occur in the Dutch population. Although the incidence is relatively high, the duration of the symptoms is short, often lasting no longer than 2 days. About one in five cases of *C. perfringens* food poisoning requests medical help and an estimated 4 people die annually due to *C. perfringens* food poisoning. *C. perfringens* food poisoning results in a loss of 509 DALYs per year, with an uncertainty range of 215 DALYs to 942 DALYs per year (undiscounted). Total costs associated with *C. perfringens*-associated gastroenteritis amounted to 9 million euros (uncertainty range 4 million euros to 19 million euros). INHC accounted for 59% of all costs associated with *C. perfringens* gastroenteritis cases, the majority from patients, or their caretaker, not requiring any medical services. DHC accounted for 40% of all costs.

On average, with each *C. perfringens* food poisoning case 0.003 DALYs are lost. The mean cost-of-illness of *C. perfringens* food poisoning is 61 euros per case.

A problem concerning the estimation of the burden of disease and cost-of-illness of *C. perfringens* is the lack of data. *C. perfringens* food poisoning is not systematically registered in the Netherlands, therefore estimations regarding the incidence in the population, mortality and age distribution had to be drawn from other sources, like literature. This adds to the uncertainty of the estimations of both valuation criteria.

Secondly, it should be noted that information on the duration of illness of *C. perfringens* food poisoning was based on the IID-study. The duration reported by the IID-study, however, seems quite long compared to the duration of illness reported in several outbreak studies. The main share of outbreak studies recorded a duration of illness of less than 24 hours, whereas the IID study reported a length of illness of 3 days. As a result, the most likely estimation of the burden of disease and cost-of-illness might be fairly high.

6 Staphylococcus aureus

Staphylococcus aureus (*S. aureus*) is an aerobic Gram-positive bacterium that can be found in the air, on dust, in sewage, water, milk, and food, as well as on animals and humans. Approximately 30-50% of the human population carries *S. aureus* on the skin, the throat or in the nose [64, 65]. Usually these *S. aureus* do not cause illness; however, they may cause skin infections, like folliculitis. Furthermore, *S. aureus* carried on the body of food handlers or other sources may contaminate food that comes in contact with their hands [64, 66]. Subsequent improper storage of the food may enhance multiplication of *S. aureus* and production of heat-stable protein toxins [67]. *S. aureus* may also originate from food-producing animals or from contaminated equipment.

If an individual ingests food with preformed staphylococcal enterotoxins, food poisoning may occur. The symptoms of staphylococcal food poisoning have a rapid onset (2 to 6 hours) and include nausea, vomiting, and abdominal cramping. The symptoms are self-limiting and resolve within 24 to 48 hours of onset [68]. In severe cases of *S. aureus* food poisoning headache, muscle cramping, changes in blood pressure and pulse rate may occur. The complications of *S. aureus* intoxication may be lethal, although this happens very rarely [69].

Because *S. aureus* cannot form spores, food contamination can be easily prevented by proper heating of the food [65]. In spite of this, *S. aureus* is one of the most common causes of food borne illness [52, 54, 61, 70].

6.1 Outcome tree, incidence and duration of illness

6.1.1 Outcome tree and incidence

To estimate the incidence of *S. aureus* food poisoning, we used data from the SENSOR-study [3]. By adjusting the SENSOR-data collected in 1998 and 1999 to the Dutch population growth and age composition of the year 2006, we estimated that the annual incidence of *S. aureus* food poisoning in Dutch population was 270,000, with an uncertainty ranging from 150,000 (low estimate corresponding to the 5th percentile) to 450,000 (high estimate corresponding to the 95th percentile).

For the Netherlands it is unknown how many cases of *S. aureus* food poisoning consult a GP. Adak et al. [53] estimated that in England/Wales 40% of patients with S. *aureus* food poisoning would visit a GP. However, due to differences in consultation rates between England/Wales and the Netherlands, this percentage is most probably higher than the percentage of cases consulting the GP in the Netherlands [3, 71]. Since the GP consultation rate in the Netherlands is about three times lower compared to England/Wales, we presumed that in the Netherlands 14% of S. *aureus* food poisoning cases consulted the GP, resulting in an estimated 39,000 cases consulting the GP due to *S. aureus* food poisoning in 2006, with a minimum estimation of 21,000 and a maximum estimation of 64,000.

Regarding hospitalization, rates ranging from 0.005 up to 0.18 have been reported [53, 54, 70-72]. Because of the rapid and often mild course of *S. aureus* food poisoning on the hand, and the improper sample collection and examination on the other hand, the total number of *S. aureus* food poisoning cases is often underestimated [64]. Therefore, we adopted a hospitalization rate of 0.005. Thus, most likely 1,400 cases of *S. aureus* food poisoning were hospitalized, with a minimum of 750 cases, and a maximum of 2,300 cases.

Fatal cases of *S. aureus* food poisoning are very rare; nevertheless fatal cases do occur among susceptible subjects, like elderly people. Using the fatality rate reported by Mead et al., we estimated that annually 3 fatal cases occur, with a minimum of 2 and a maximum of 5 cases [54].

The outcome tree of *S. aureus* is shown in Figure 6. Table 18 presents the estimated incidence of *S. aureus* food poisoning.

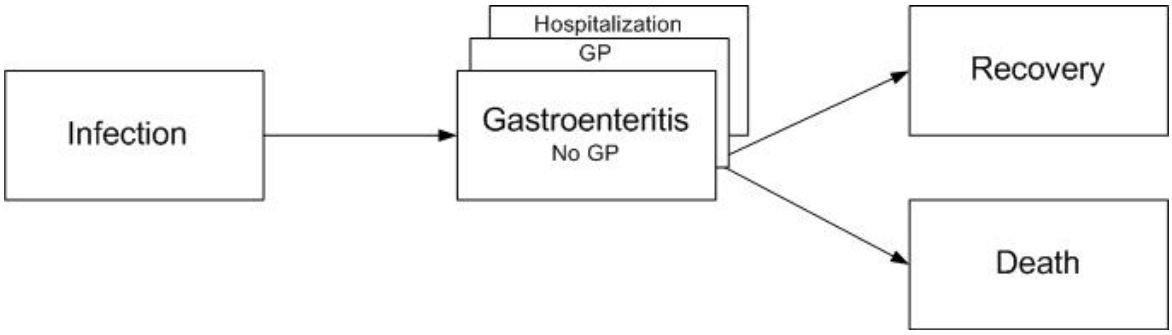

Figure 6. Outcome tree *S. aureus*-associated gastroenteritis.

Table 18. Incidence *S. aureus*-associated gastroenteritis for 2006.

	Incidence estimates (cases per year)		
	Most likely	Low	High
Gastroenteritis	270,000	150,000	450,000
No GP	230,000	120,000	380,000
GP	39,000	21,000	64,000
Hospitalization	1,400	750	2,300
Death	3	2	5

* Summations do not necessarily tally.

6.1.2 Duration of illness and age-distribution

S. aureus food poisoning symptoms usually abate within 24 hours [61, 65, 73]. We estimated that for cases not visiting the GP the duration of the symptoms was one day. For cases visiting the GP mean duration of symptoms was estimated at four days. A study on a massive *S. aureus* food poisoning incident affecting approximately 4,000 people reported a duration of hospitalization of 7-10 days [70]. We therefore assumed length-of-illness of symptoms of 12 days for hospitalized cases.

The age distribution of *S. areus*-associated gastroenteritis is summarized in Table 19. We assumed that the age distribution of gastroenteritis as found in the SENSOR study would be representative for *S. areus* cases not visiting a GP (no GP) [3]. The age distribution of cases visiting a GP and hospitalized cases are based on ISIS data. Fatal cases of *S. areus* food poisoning occur mainly among the elderly [61, 69, 71].

Table 19. Age distribution of *S. aureus*-associated gastroenteritis.

	Age classes				
	0-4 years	5-9 years	10-14 years	15-64 years	> 65 years
Gastroenteritis					
No GP[a]	33%	14%	8%	35%	10%
GP[b]	26%	7%	10%	46%	12%
Hospitalization[b]	23%	1%	3%	41%	32%
Fatal[c]	-	-	-	-	100%

a) no information available. We used laboratory confirmed cases reported by PHLs from ISIS as a proxy.
b) based on S. aureus cases reported by PHLs from ISIS
c) no pathogen specific information available.

6.2 Disease burden

The estimated number of YLD, YLL and DALYs lost due to *S. aureus* food poisoning are shown in Table 20, both undiscounted and discounted (4%). The incidence, duration and disability weights used for the estimations are also shown in Table 20. In Figure 7 the DALY estimates for the most likely estimate and the uncertainty (low and high estimate) are shown for the total estimation as well as for each health state separately, both discounted and undiscounted.

Table 20. Incidence, duration and disease burden of *S. aureus* food poisoning for 2006 (most likely estimates).

	Incidence	Duration	Disability weight	YLD	YLL	DALY (0%)	DALY (4%)[b]
Gastroenteritis	270,000						
No GP	230,000	1 day	0	0	-	0	0
GP	39,000	4 days	0.015	592	-	592	592
Hospitalization	1,400	12 days	0.041	57	-	57	57
Fatal	3	11,5 years		-	39	39	30
Total				649	39	688	667

* Summations do not necessarily tally.

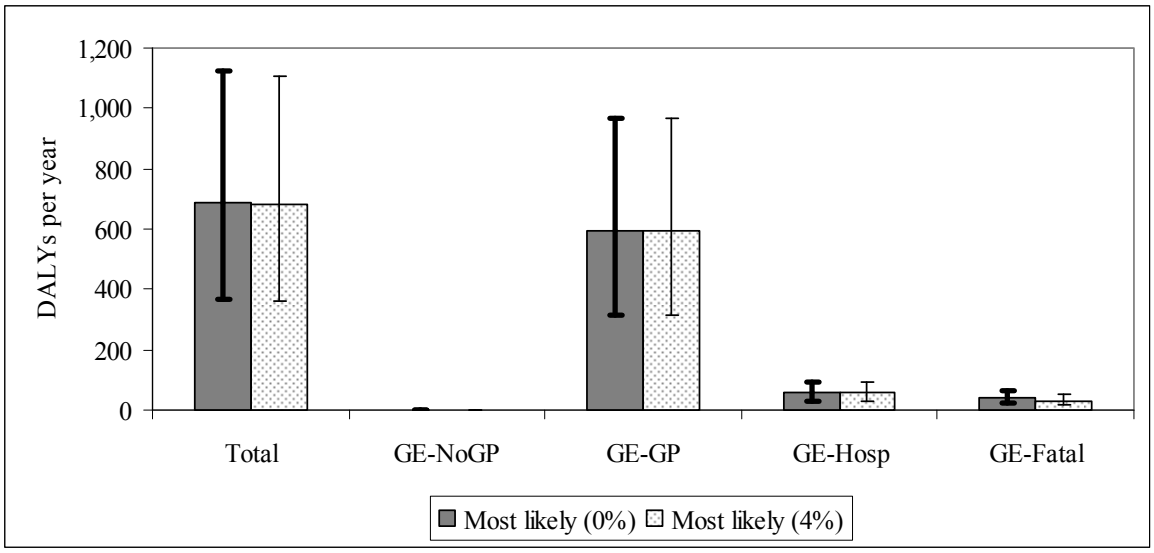

Figure 7. Disease burden of *S. aureus*-associated gastroenteritis for 2006, using most likely estimates, discounted (4%) and undiscounted (0%). Error bars express an uncertainty interval that results from using low and high estimates.

6.3 Cost-of-illness

Based on the incidence and duration of illness shown in Table 18, and following in general the assumptions described in chapter 2 and in the previous report, we estimated the direct health care costs for the different health states. An average hospital stay of twelve days was assumed for *Staphylococcus aureus* cases. DHC results of *S. aureus* cases are summarized in Table 21 for the most likely estimate only.

Table 21. DHC of *S. aureus*-associated gastroenteritis in million euros for 2006 (most likely estimates).

	Drugs & medicine	GP consultations	Hospitalization	Other	∑ DHC
Gastroenteritis	1.5	1.4	6.2	-	9.1
No GP	<0.1	-	-	-	<0.1
GP	1.4	1.3	-	-	2.7
Hospitalization	0.1	0.1	6.2	-	6.4
Fatal	-	-	-	-	-

Productivity losses due to 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 assumptions described in Chapter 2. The estimated overall work absence for *S. aureus* patients not visiting a GP and *S. aureus* patients visiting a GP only, were estimated to be a 0.09 days and 0.56 days, respectively. In Table 22 we have summarized the estimated number of days paid

employment lost for adult patients and for third persons taking care of a sick person. We further present in Table 22 the most likely estimate of Indirect Non Health Care Costs (INHC).

Table 22. Number of days paid employment lost and INHC of community acquired *S. aureus*-associated gastroenteritis in million euros for 2006 (most likely estimates).

	No. of days paid employment lost		Productivity losses		∑ INHC
	Patient	Third person	Patient	Third person	
Gastroenteritis	-	-	5.3	1.4	6.7
No GP	0.09	-	2.0	0.9	2.9
GP	0.56	-	2.6	0.5	3.1
Hospitalization	6.21	4	0.7	<0.1	0.7
Fatal	154	-	-	-	-

In Table 23 and Figure 8 we present the cost-of-illness of community acquired *S. aureus*-associated GE in detail for the different health states in million euros for 2006.

Table 23. Cost-of-illness of community acquired *S. aureus*-associated gastroenteritis for the different health states in million euros for 2006 (most likely estimates).

	DHC (0%)	DNHC (0%)	INHC (0%)	∑ Costs (0%)
Gastroenteritis	9.1	0.1	6.7	15.9
No GP	<0.1	<0.1	2.9	3.0
GP	2.7	<0.1	3.1	5.8
Hospitalization	6.4	<0.1	0.7	7.1
Fatal	-	-	-	-

In Figure 8 we have summarized the most likely estimate with attendant uncertainty, respectively, for the total cost of community acquired *S. aureus*-associated gastro-enteritis cases. Given that all costs occur within one year, discounting is not an issue.

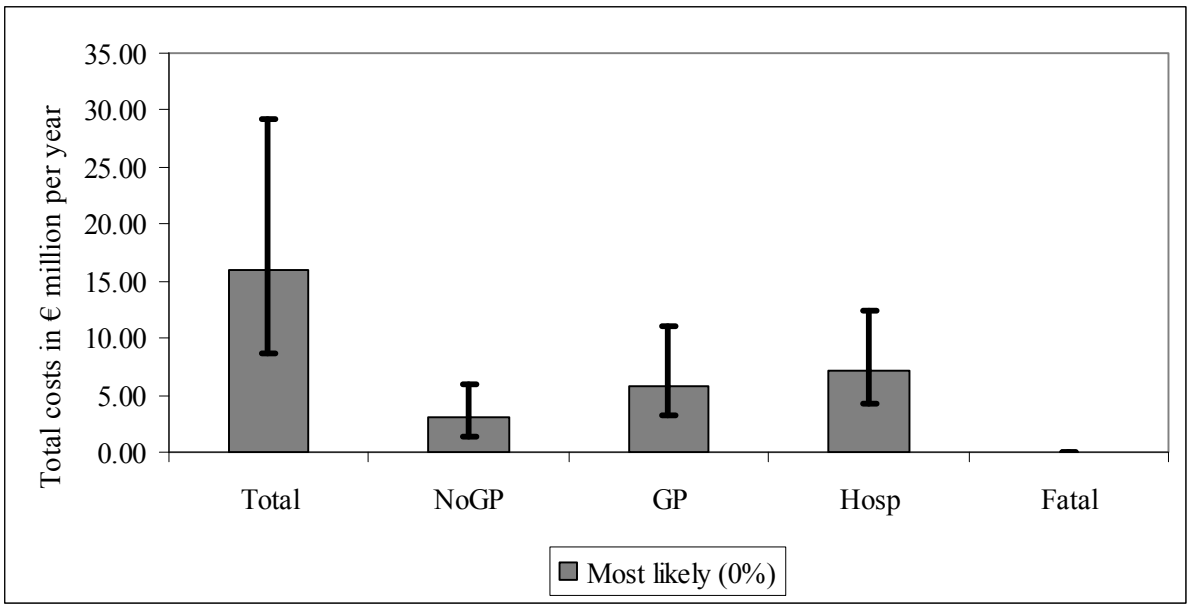

Figure 8. Total cost-of-illness of community acquired *S. aureus*-associated gastroenteritis, using most likely estimates. Error bars express an uncertainty interval that results from using low and high estimates. Discounting was not required as all costs occur within the first year.

Total costs associated with community acquired *S. aureus*-associated GE totalled to 15.9 million euros (8.7 million euros to 29.3 million euros), about 45% due to hospitalization.

6.4 Scenario analysis

In the current study, the number of cases with gastroenteritis due to *S. aureus* that consulted a GP was based on data from the study of Adak et al. who found a GP consultation rate of 0.40 for *S. aureus* in the UK [53]. This rate was then adapted for the Dutch situation, resulting in a GP consultation rate of 0.14. This latter adaptation contains some uncertainties, since general differences in consultation rates between the Netherlands and the UK were used for the adaptation. It is unclear whether the difference in consultation rates between UK and the Netherlands hold true for the relatively mild symptoms of gastroenteritis caused by *S. aureus*.

In Table 24 we have summarized the incidence and burden of disease if we apply the GP consultation rate of 0.40 rather than the adapted consultation rate. Using the UK GP consultation rate for *S. aureus* increases the number of DALYs lost significantly by 160% from 109 to 1,740 DALYs and the cost-of-illness with 75% from 9.1 to 15.9 million euros.

Table 24. Incidence, DALY and cost-of-illness of community acquired *S. aureus*-associated gastroenteritis for the different health states [a].

Pathogen	Incidence	DALY (0%)	Cost (0%)
Gastroenteritis	270,000	1,740	15.9
No GP	160,000	0	3.0
GP	110,000	1,643	5.8
Hospitalization	1400	57	7.1
Fatal	3	39	0

a) Summations might not necessarily tally because of rounding

6.5 Discussion

With respect to incidence, *S. aureus* with 270,000 cases of gastro-enteritis in the Dutch population per year outnumbers all other pathogens except for norovirus (470,000 cases). The course of the disease is generally mild and fatal cases are very rare. Annually, an estimated 3 cases per year die due to food poisoning. Despite the relatively high incidence of *S. aureus*-associated gastroenteritis, the associated burden of disease is about 688 DALYs per year, with an uncertainty range of 367 DALYs to 1,122 DALYs per year (undiscounted). The disease burden of patients visiting the GP attributed the majority (86%) to the burden of disease.

Total costs associated with *S. aureus*-associated gastroenteritis amounted to 15.9 million euros (uncertainty range 8.7 million euros to 29.3 million euros). DHC accounted for 57% of all costs associated with *S. aureus* gastroenteritis cases. INHC accounted for 42% of the total cost-of-illness of *S. aureus* food poisoning.

Similarly to *C. perfringens*, with each case of *S. aureus* food poisoning on average 0.003 DALYs are lost. The mean cost-of-illness of *S. aureus* food poisoning is 58 euros per case, which is slightly lower compared to the average 61 euros of a *C. perfringens* food poisoning case.

Data on *S. aureus* is scarce. Hence, assumptions were made based on sources such as literature. These assumptions concerned health care use, fatalities, and duration of symptoms; variables that are used for both burden of disease estimates and cost-of-illness calculations. This implies that the results presented in this section have a relatively high uncertainty which should be taken into consideration.

7 Bacillus cereus

Bacillus cereus (*B. cereus*) is a facultative anaerobic Gram-positive spore former that is ubiquitous in the environment. The highly resistant *B. cereus* spores may survive heating, drying, radiation, freezing, as well as pasteurization [74].

Consumption of food contaminated with between 10^5 to 10^7 *B. cereus* cells may cause food poisoning, although lower numbers have also been suggested [75].

B. cereus causes two distinct types of illness; the emetic type of illness on the one hand, or the diarrheal type of illness on the other hand [76]. The emetic type is caused by emetic toxin, a heath-stable peptide which is preformed in the food [77]. The incubation time of the emetic type of illness is 1 to 5 hours and the symptoms, characterized by nausea, vomiting and abdominal cramping usually lasting for 6 to 24 hours, mimic those of *Staphylococcus aureus* food intoxication [77].

The diarrheal type might be caused by several enterotoxins consisting of proteins, which are released in the small intestine after ingestion. The symptoms of the diarrheal type, characterized by abdominal pain and watery diarrhea, and occasionally nausea, are similar to those of *Clostridium perfringens* food poisoning. The symptoms start 8 to 16 hours after ingestion of the contaminated food, and abate within 12 to 24 hours.

There are several foods associated with *B. cereus* food poisoning, including beef, poultry, vanilla sauce, pasteurized cream, pudding, pasta and cooked rice dishes (emetic type), as well as fish, vegetables, soups, sauces, and dairy products (diarrheal type) [78].

7.1 Outcome tree, incidence and duration of illness

7.1.1 Outcome tree and incidence

We used data from the SENSOR-study [3] in order to estimate the incidence of *B. cereus* food poisoning. By adjusting the SENSOR-data collected in 1998 and 1999 to the population growth and age composition of the year 2006, we estimated that the annual incidence of *B. cereus* food poisoning in the Dutch population was 47,000, with an uncertainty ranging from 21,000 (low estimate corresponding to the 5th percentile of the distribution) to 87,000 (high estimate corresponding to the 95th percentile of the distribution).

The number of cases that would visit a GP due to *B. cereus* food poisoning is unknown for the Netherlands. Adak et al. estimated that in England/Wales 40% of patients with *B. cereus* food poisoning would visit the GP [53]. However, due to differences in consultation rates between England/Wales and the Netherlands, this percentage is most probably higher than the percentage of cases consulting the GP in the Netherlands [3]. We therefore supposed that in the Netherlands 14% of *B. cereus* food poisoning cases consulted the GP, amounting to an estimated 6,700 cases that consulted

the GP due to *B. cereus* food poisoning in 2006, with a minimum estimation of 3,100 and a maximum estimation of 13,000.

Of the cases with *B. cereus* food poisoning, 0.004 was hospitalized. This percentage was calculated using data from PHLs that participated in ISIS. Mead et al. found a similar hospitalization rate [54]. Hence, most likely 190 cases of *B. cereus* food poisoning were hospitalized, with a minimum of 90 cases, and a maximum of 360 cases.

Fatal cases of *B. cereus* food poisoning are extremely rare, and mortality was not taken into account [53, 54, 79].

The outcome tree of *B. cereus* is shown in Figure 9. Table 25 presents the estimated incidence of *B. cereus* food poisoning.

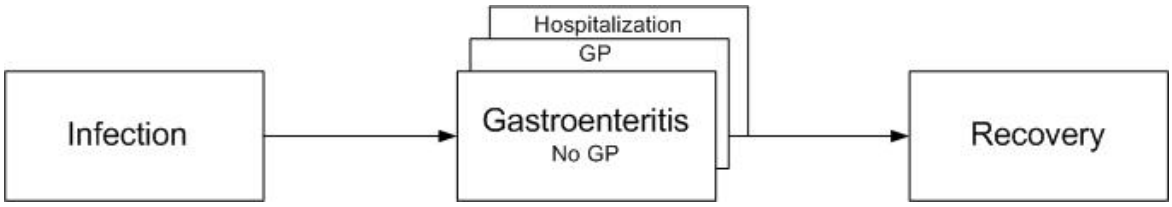

Figure 9. Outcome tree *B. cereus*-associated gastroenteritis.

Table 25. Incidence and duration of illness of *B. cereus*-associated gastroenteritis and sequelae for 2006.

	Incidence estimates (cases per year)		
	Most likely	Low	High
Gastroenteritis	47,000	21,000	87,000
No GP	40,000	18,000	74,000
GP	6,700	3,100	13,000
Hospitalization	190	90	360

7.1.2 Duration of illness and age-distribution

In general, both the emetic and diarrheal type *B. cereus* food poisoning symptoms do not persist longer than 24 hours [80]. This relatively short duration is endorsed by *B. cereus* outbreak studies reporting a median duration of symptoms lasting 4 through 19 hours [81, 82]. Studies reporting on duration of illness other than outbreak studies were not found. However, since the symptoms of the diarrheal type mimic those caused by *C. perfringens* food poisoning and the symptoms of the emetic type are similar to those caused by *S. aureus*, we assumed that the duration of *B. cereus* food poisoning is also similar, with an estimated duration of 2 days for cases not visiting the GP and an estimated duration of 4 days for cases that do visit the GP. For hospitalized patients, we assumed a mean duration of symptoms of 14 days.

The age distribution of *B. cereus*-associated gastroenteritis is summarized in Table 26. We assumed that the age distribution of gastroenteritis as found in SENSOR would be representative for *B. cereus* cases not visiting a GP (no GP) [3]. The age distribution of cases visiting a GP or hospitalized cases was based on ISIS data.

Table 26. Age distribution of *B. cereus*-associated gastroenteritis.

	Age classes				
	0-4 years	5-9 years	10-14 years	15-64 years	> 65 years
Gastroenteritis					
No GP[a]	33%	14%	8%	35%	10%
GP[b]	13%	-	3%	47%	37%
Hospitalization[b]	21%	2%	8%	40%	29%

a) no information available. We used laboratory confirmed cases reported by PHLs from ISIS as a proxy.
b) based on *B. cereus* cases reported by PHLs from ISIS

7.2 Disease burden

Incidence, duration and estimated results for YLD, YLL and DALY of *Bacillus cereus* food poisoning, both discounted (4%) and undiscounted (0%) are shown in Table 27. In Figure 10 the DALY estimates for the most likely and the uncertainty (low and high estimate) are shown for the total estimation as well as for each health state separately. Both the discounted and the undiscounted number of DALYs lost are shown.

Table 27. Incidence and disease burden of *B. cereus* food poisoning for 2006 (most likely estimates).

	Incidence	Disability weight	YLD	YLL	DALY (0%)	DALY (4%)
Gastroenteritis	42,000					
No GP	37,000	0	0	-	0	0
GP	6,000	0.015	101	-	101	101
Hospitalization	170	0.041	8	-	8	8
Total					109	109

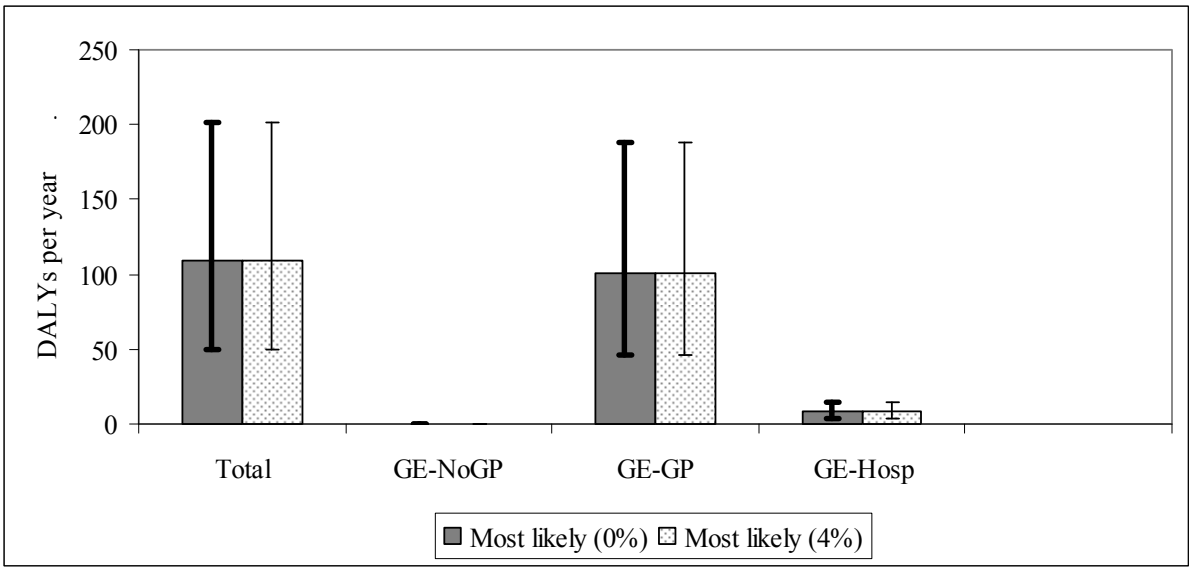

Figure 10. Disease burden of *B. cereus*-associated gastroenteritis for 2006, using most likely estimates, discounted (4%) and undiscounted (0%). Error bars express and uncertainty interval that results from using low and high estimates.

7.3 Cost-of-illness

Based on the incidence and duration of illness shown in Table 27, and following in general the assumptions described in section 2 and in the previous report, we estimated the direct health care costs for the different non-fatal health states. An average hospital stay of fourteen days was assumed for bacillus cereus cases. DHC results of *B. cereus* cases are summarized in Table 28 for the most likely estimate only.

Table 28. DHC of *B. cereus*-associated gastroenteritis in million euros for 2006 (most likely estimates).

	Drugs & medicine	GP consultations	Hospitalization	Other	∑ DHC
Gastroenteritis	0.3	0.4	0.9	-	1.6
No GP	<0.1	-	-	-	<0.1
GP	0.2	0.4	-	-	0.6
Hospitalization	<0.1	<0.1	0.9	-	1.0

Productivity losses due to 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 assumptions described in chapter 2. The estimated overall work absence for *B. cereus* patients not visiting a GP and *B. cereus* patients visiting a GP only, were estimated to be a 0.18 days and 0.55 days, respectively. In Table 29 we have summarized the estimated number of days paid

employment lost for adult patients and for third persons taking care of a sick person. We further present in Table 29 the most likely estimate of Indirect Non Health Care Costs (INHC).

Table 29. Number of days paid employment lost and INHC of community acquired *B. cereus*-associated gastroenteritis in million euros for 2006 (most likely estimates).

	No. of days paid employment lost		Productivity losses		∑ INHC
	Patient	Third person	Patient	Third person	
Gastroenteritis	-	-	1.2	0.3	1.5
No GP	0.2	-	0.7	0.3	0.9
GP	0.6	1	0.5	0.1	0.5
Hospitalization	5.0	3	0.1	-	0.1

In Table 30 we present the cost-of-illness of community acquired *B. cereus*-associated GE in detail for the different health states in million euros for 2006.

Table 30. Cost-of-illness of community acquired *B. cereus*-associated gastroenteritis for the different health states in million euros for 2004 (most likely estimates).

	DHC (0%)	DNHC (0%)	INHC (0%)	∑ Costs (0%)
Gastroenteritis	1.6	<0.1	1.5	3.2
No GP	<0.1	<0.1	0.9	1.0
GP	0.6	<0.1	0.5	1.1
Hospitalization	1.0	-	0.1	1.1

In Figure 11 we have summarized the most likely estimate and the most likely estimate with attendant uncertainty, respectively, for the total cost of community acquired *B. cereus*-associated GE cases. Given that all costs occur within one year, discounting is not an issue.

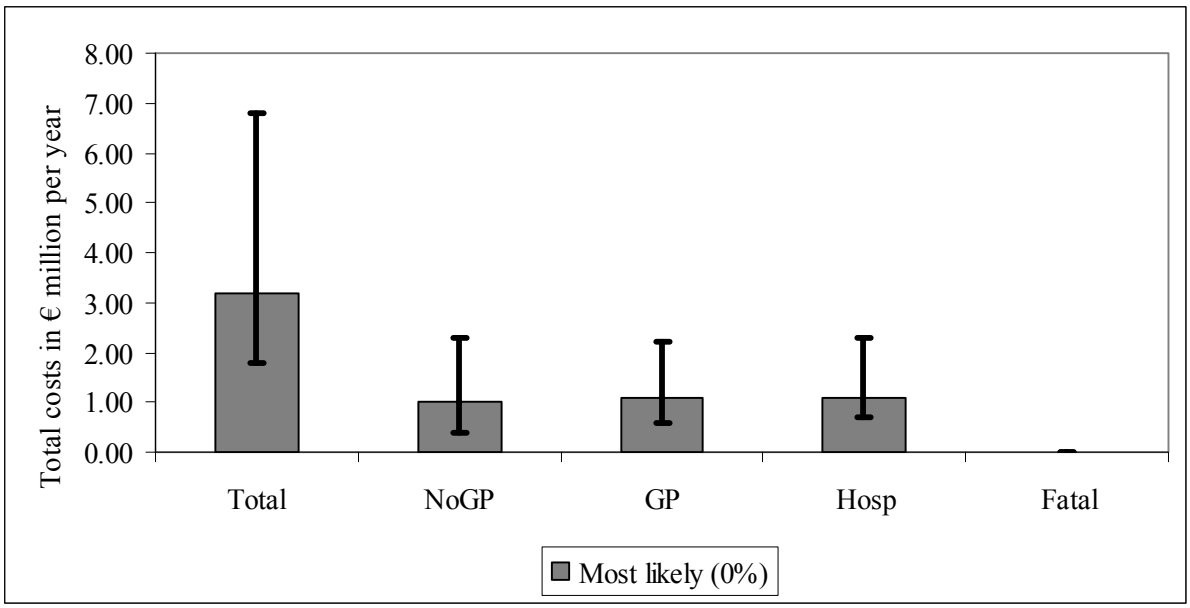

Figure 11. Total cost-of-illness of community acquired *B. cereus*-associated gastroenteritis, using most likely estimates. Error bars express an uncertainty interval that results from using low and high estimates. No fatal cases occur. Discounting was not required as all costs occur within the first year.

Total costs associated with community acquired *B. cereus*-associated gastroenteritis totalled to 3.2 million euros (1.8 million euros to 6.8 million euros), more than 50% due to DHC.

7.4 Scenario analysis

It should be noted that in the current study the number of cases with gastroenteritis due to *B. cereus* that consulted a GP was based on data from the study of Adak et al. who found a GP consultation rate of 0.40 for *B. cereus* in the UK [53]. This rate was then adapted for the Dutch situation, resulting in a GP consultation rate of 0.14. This latter adaptation contains some uncertainties, since general differences in consultation rates between the Netherlands and the UK were used for the adaptation. It is unclear whether the difference in consultation rates between UK and the Netherlands hold true for the relatively mild symptoms of gastroenteritis caused by *B. cereus*.

In Table 31 we have summarized the incidence and burden of disease if we apply the GP consultation rate of 0.40 rather than the adapted consultation rate. Using the UK GP consultation rate for *S. aureus* increases the number of DALYs lost significantly by 157% from 109 to 280 DALYs and the cost-of-illness with 59% from 3.2 to 5.1 million euros.

Table 31. Incidence, DALY and cost-of-illness of community acquired *B. cereus*-associated gastroenteritis for the different health states [a].

Pathogen	Incidence	DALY (0%)	Cost (0%)
Gastroenteritis	47,000	288	5.1
No GP	28,000	0	0.7
GP	19,000	280	3.1
Hospitalization	190	8	1.2

a) Summations might not necessarily tally because of rounding

7.5 Discussion

Annually about 47,000 cases of *B. cereus* food poisoning occur in the Dutch population. About 14% of *B. cereus* food poisoning request medical help and less than 1% is hospitalized. *B. cereus* food poisoning results in a loss of 109 DALYs per year, with an uncertainty range of 50 DALYs to 202 DALYs per year (undiscounted). Total costs associated with *B. cereus*-associated gastroenteritis amounted to 3.2 million euros (uncertainty range 1.8 million euros to 6.8 million euros). DHC and INHC, with 50% and 47% respectively, comprised almost all costs associated with *B. cereus* gastroenteritis cases.

On average, 0.002 DALYs are lost per *B. cereus* food poisoning case, slightly less than *C. perfringens* and *S. aureus* (both 0.03 DALYs per case). The cost-of-illness per case of *B. cereus* food poisoning is 68 euros. This is higher compared to the cost-of-illness of *C. perfringens* (61 euros per case) and *S. aureus* food poisoning (58 euros per case).

Again, the burden of disease and cost-of-illness estimates of *B. cereus* food poisoning contain a high level of uncertainty, since several variables of the validation criteria were based on assumptions from literature rather than actual registered data from the Netherlands. Especially information on duration of symptoms for the levels of health care use was scarce. This is problematic because duration of symptoms is a crucial variable for both burden of disease and cost-of-illness calculation.

Moreover, we assumed that there were no fatal cases of *B. cereus* food poisoning. Several studies pointed out that fatality is extremely rare [53, 54]. Nonetheless, there have been reports of outbreaks that did include fatal cases of *B. cereus* food poisoning [83-85]. As a result, the burden of disease and cost-of-illness of *B. cereus* food poisoning reported might be lower than the actual burden of *B. cereus* food poisoning.

8 Listeria monocytogenes

Listeriosis is an infection caused by the gram-positive bacterium *Listeria monocytogenes*. *Listeria monocytogenes* is widely spread in the environment and ingested with raw contaminated food, or transmitted from the mother to the fetus during pregnancy or birth [86, 87].

Infection with *Listeria monocytogenes* occurs sporadically. The incidence rate ranges from 2 to 15 cases per 1,000,000 individuals per year [88-90]. It manifests itself by a range of diseases, like meningitis, sepsis, gastroenteritis and pneumonia. While listeriosis in previously healthy individuals may cause a usually mild and self-limiting gastroenteritis, in unborn, newborn and individuals with increased susceptibility listeriosis is potentially life-threatening [91, 92].

Listeria monocytogenes is commonly found in soil and water, and it has been isolated from a wide range of domestic and wild animals [91]. Vegetables and fruit can become contaminated with Listeria from soil or manure used as fertilizer [93]. Meats and dairy products can become contaminated through animals that carry the bacteria without apparent illness. *Listeria monocytogenes* has been found in raw foods, like uncooked meats, vegetables, fruits and dairy products made from unpasteurized milk [89, 94]. However, contamination after pasteurization can also occur, because Listeria can readily adapt to and live in the environment of food processing, distribution, and retail facilities [91]. Unlike most foodborne pathogens, *Listeria monocytogenes* can grow at refrigeration temperatures in many foods. It can also tolerate and grow in relatively acid foods, foods with relatively low moisture content, and foods with high salt concentration [94]. These abilities make *Listeria monocytogenes* a particularly difficult micro-organism to control. On the other hand, Goulet et al. suggested that there is a causal relationship between preventive measures in the food industry, reduction in *Listeria monocytogenes* contaminated food and listeriosis incidence [95].

8.1 Perinatal listeriosis

8.1.1 Outcome tree and incidence

Perinatal listeriosis encompasses both pregnant women and their fetuses or newborns. Of the pregnant women with listeriosis, about two out of three will present with a prodromal influenza symptoms like fever, chills and headache. Three to seven days after the prodromal symptoms, the pregnant woman may abort the fetus or have premature labor [96]. To the mother listeriosis is rarely life-threatening; however, infection in the first trimester of pregnancy may result in spontaneous abortion, and in later stages in stillbirth or a critically ill newborn [89]. The newborns may present with an early-onset or a late-onset form of listeriosis. Early-onset listeriosis is defined as a case of listeriosis in a newborn that is less than seven days old. Early-onset listeriosis is acquired by the fetus prenatal. Mostly, newborns with early-onset listeriosis develop sepsis and meningitis [86, 97]. Late-onset listeriosis is defined as listeriosis in a newborn between eight and 28 days of life. In this case, the unborn is infected during

childbirth when passing through the birth canal. Newborns with late-onset listeriosis are usually born healthy and at full term, but they are at higher risk to develop meningitis during their first weeks of life [89].

In the current study, the disease burden for health outcomes of early- and late-onset listeriosis are combined into one category.

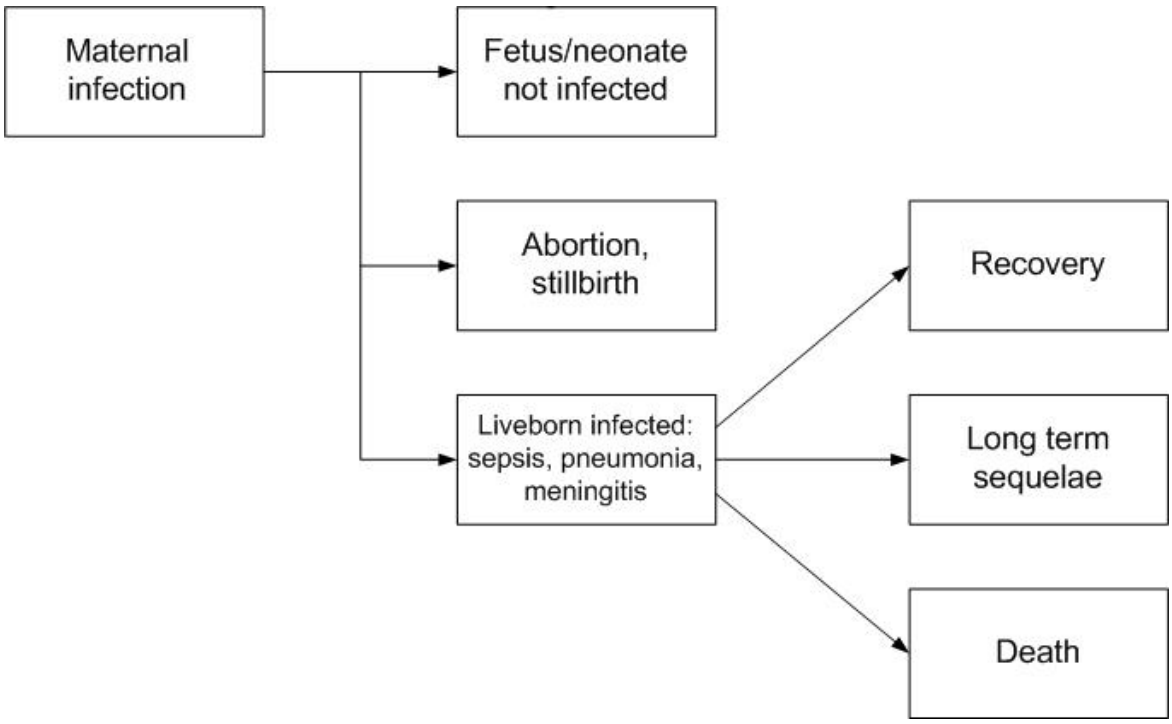

Figure 12. Outcome tree for perinatal listeriosis.

Enhanced surveillance in the Netherlands

Since January 2005, there is an enhanced surveillance of *Listeria monocytogenes* in the Netherlands [98]. Each positive case of *Listeria monocytogenes* found by a laboratory is reported to the public health services. Listeria isolates from patients with meningitis or septicaemia are submitted to the Netherlands Reference Laboratory for Bacterial Meningitis (RBM) and to the RIVM.

Incidence of health outcomes

In 2005, the enhanced surveillance reported six newborns with perinatal listeriosis. Four cases were recorded to be born prematurely. Of these four premature newborns, two were healthy and two died. A fifth newborn also died, and of the sixth newborn with perinatal listeriosis the health outcome was unknown [99].

In 2006, five newborns with a perinatal listeria infection were identified [100]. Two of these newborns died. The three surviving newborns all had meningitis. Besides meningitis, one newborn also had

cerebral hemorrhage; another also had encephalitis, sepsis and a cerebral infarction. Apart from the latter newborn, all newborns were born prematurely.

The uncertainty of the mean annual incidence rate of fatal cases and health outcomes in 2005 and 2006 are shown in Table 32.

Table 32. Mean annual incidence and duration of illness of perinatal listeriosis for 2005 and 2006.

	Incidence estimates			Duration
	Most likely	Low	High	
Meningitis	1.5	0.4	6.9	0.5
Sepsis	0.5	0	3.2	0.02
Death in perinatal period	2.5	1	4.5	79
Long term sequelae	0.5	0	0.6	79

8.1.2 Disease burden

In 2005 237 DALYs and in 2006 237 DALYs were lost due to perinatal listeriosis. Table 33 presents the mean annual incidence, duration and burden of disease per health outcome for perinatal Listeria infection. The mean annual burden of perinatal listeriosis was estimated at 203 DALYs lost. Most DALYs (98%) were lost due to death in the postnatal period. When the discount factor is taken into account the annual disease burden is reduced to 62 DALYs.

Table 33. Mean annual incidence and disease burden of perinatal listeriosis (most likely estimates).

	Incidence	Duration (years)	YLD	YLL	DALY (0%)	DALY (4%)[b]
Meningitis	2	0.5	0	0	0	0
Sepsis	1	0.02	0	0	0	0
Death in postnatal period	3	79	0	198	198	59
Long term sequelae	0.3	79	5	0	5	2
Total			5	198	203	62

Uncertainty analysis

To calculate the uncertainty in the estimate of burden of disease of perinatal listeriosis, we used the lowest and highest estimated incidence rates (see Table 32). This resulted in a minimum annual disease burden of 75, and a maximum disease burden of 363. When the discount factor of 4% was taken into

account, the disease burden ranged from 23 to 110. Figure 13 shows the uncertainty in disease burden of perinatal listeriosis.

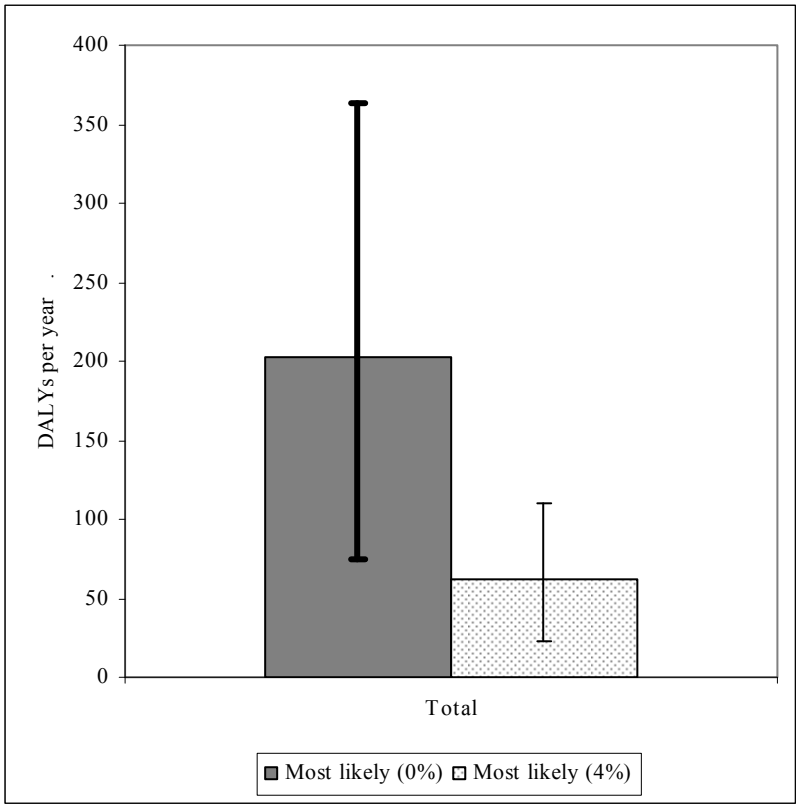

Figure 13. Annual disease burden of perinatal listeriosis for 2005 and 2006, using most likely estimates. Error bars express an uncertainty interval that results from using low and high estimates

8.2 Acquired listeriosis

8.2.1 Outcome tree and incidence

The Dutch enhanced surveillance identified in the year 2005 85 cases and in 2006 63 cases of acquired listeriosis [99, 100]. On average, the estimated annual incidence is 4.8 cases per 1,000,000 individuals. This is consistent with incidence rate, ranging from 1.7 to 7.4, found in previous studies [1].

Figure 14 shows the outcome tree for acquired listeriosis. According to results of the Dutch enhanced surveillance, meningitis (60%) due to *Listeria monocytogenes* infection occurred most frequently. Other reported manifestations were septicaemia (24%), pneumonia (23%), and gastroenteritis (22%) [99, 100]. One in five patients (21%) died due to the consequences of listeria infection, resulting in an average case fatality rate of 1.1 per 1,000,000 individuals per year.

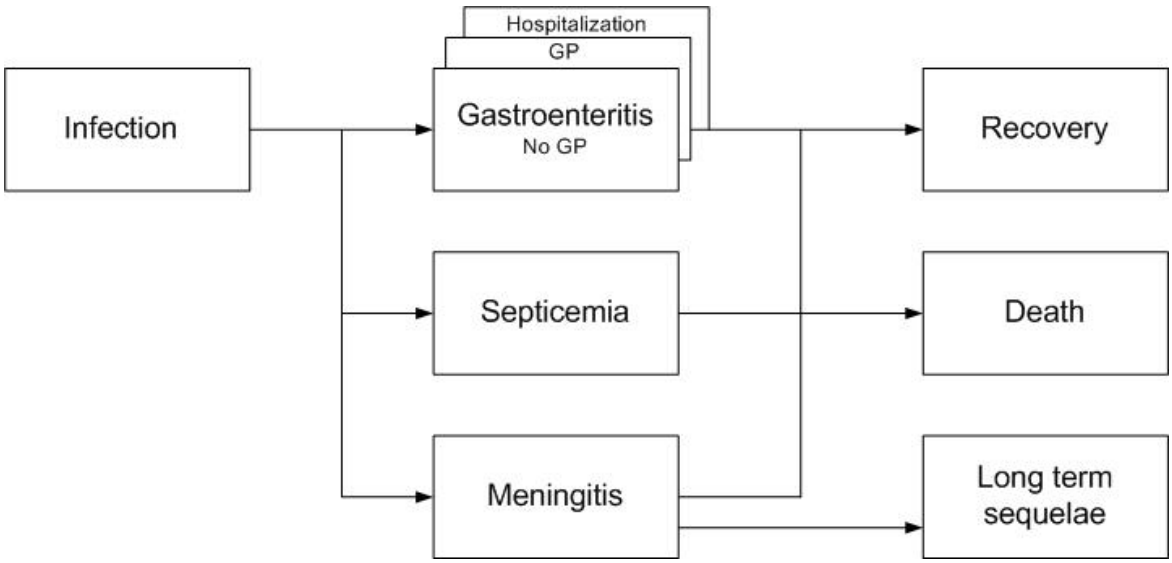

Figure 14. Outcome tree for acquired listeriosis.

Listeriosis mostly affects people that have an increased susceptibility [87]. This includes people with a pre-existing illness that reduces their immune system function, and people that have an impaired immune system resulting from age or immunosuppressive treatments. The Dutch enhanced surveillance reported that 77% of patients with listeriosis had pre-existing illnesses [99, 100].

To calculate the uncertainty in the incidence estimates of acquired listeria infections, we expected that the observed cases of listeriosis resulted from a Poisson distribution process. The Poisson distribution is a discrete distribution that is used express the probability of the number of events (in this case: cases of listeria infection) occurring in a specific time period. The uncertainty in the incidence estimates can then be modelled with a Gamma distribution. For listeriosis the most likely average estimate for the incidence rate was 144 cases per two years. This number corresponds to the median of this distribution. Low and high estimates correspond to the 5^{th} and 95^{th} percentile of the distribution: 124-164 per two years.

The Gamma distribution can also be used to express the uncertainty in the incidence of health outcomes. Additional information on health outcomes was available for 50 of the 63 patients with acquired listeriosis. Therefore, the uncertainty in the incidence of health outcomes can be expressed as a Gamma (n) * 114/110 distribution.

Of the patients who died as a result of listeriosis, median age was 73 years (Doorduyn, personal communication). At the age of 73, life expectancy is 12 years. However, each of the deceased patients had pre-existing illnesses, which reduced their life expectancy. Therefore, we assumed that the pre-existing illnesses would reduce life expectancy with 50% (i.e. 6 years). This reduced life expectancy was used as the most likely estimation. Furthermore, we assumed a minimum life expectancy of 3 years (50% of the most likely estimation) and a maximum life expectancy of the total 12 years.

Of the patients who did not die as a result of listeriosis, median age was 65 years. At 59, the expected life expectancy is 18 years. When we make assumptions about life expectancy similar to the deceased

patients, the most likely duration of long-term sequelae is 9 years, with a minimum and maximum of 4.5 and 18 years, respectively.

The low and high estimates of duration are given in Table 34.

Table 34. Average annual incidence and duration of illness of acquired listeriosis for 2005 and 2006.

	Incidence estimates			Duration
	Most likely	Low	High	
Meningitis	30	23	38	0.5
Gastroenteritis	13	9	18	0.02
Pneumonia	15	10	20	0.02
Sepsis	16	11	21	0.02
Death	16	11	20	3 – 6 – 12[b]
Long term sequelae [a]	5	3	6	4.5 – 9 – 18[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

It was estimated that in 2005 78 DALYs and in 2006 142 DALYs were lost due to acquired Listeriosis (Kemmeren et al., 2006). The average annual burden of disease of acquired listeria infection is presented in Table 35. The lion's share of DALYs (86%) was lost due to death from meningitis, gastroenteritis or sepsis. Long term sequelae and meningitis contributed 9% and 5%, respectively, to the burden of disease.

Table 35. Mean annual Incidence and disease burden of acquired listeriosis for 2005 and 2006 (most likely estimates).

	Incidence	Duration (years)	YLD	YLL	DALY (0%)	DALY (4%)[b]
Meningitis	30	0.5	5	0	5	5
Gastro-enteritis	13	0.02	0	0	0	0
Pneumonia	15	0.02	0	0	0	0
Sepsis	16	0.02	1	0	1	0
Death from meningitis, gastroenteritis or sepsis	16	6	0	93	93	83
Long term sequelae [a]	4	9	10	0	10	8
Total			15	93	108	96

a mainly neurological disorders as a result of meningitis (i.e. 14% of all meningitis cases)
b discounted disease burden

Uncertainty analysis

To calculate the uncertainty in the estimated burden of disease of acquired listeriosis, the lowest and highest parameter values (see Table 34) were used. The resulting uncertainty is shown in Figure 15.

The minimum estimation of DALYs lost is 40 DALYs, the maximum estimation of DALYs lost is 272. When the discount factor of 4% is taken into account, the burden of disease of acquired listeriosis ranges from 38 to 216 DALYs. Figure 15 shows the uncertainty in disease burden of acquired listeriosis.

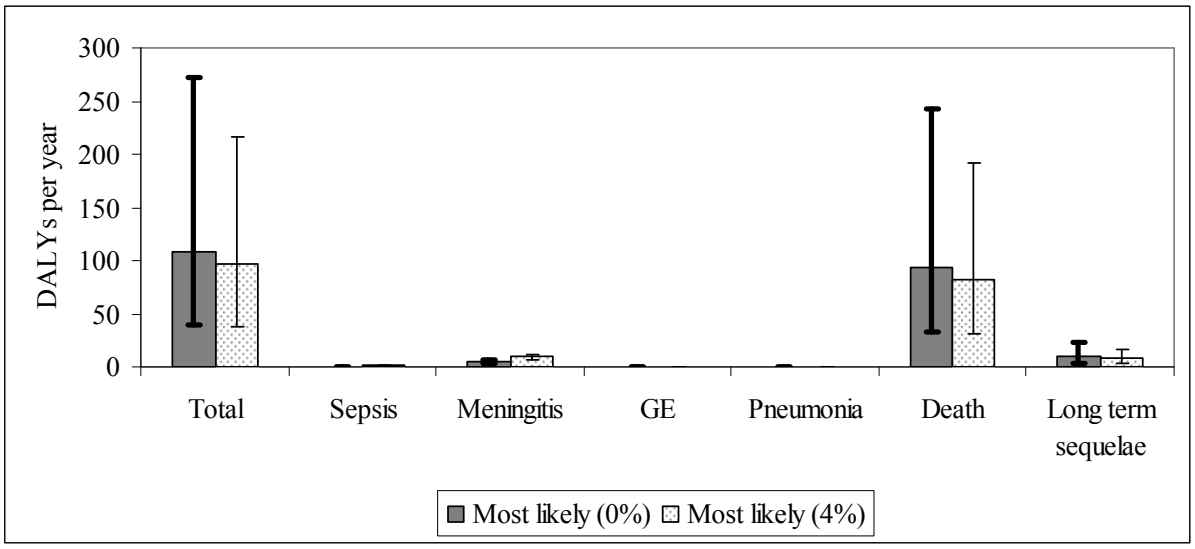

Figure 15. Annual disease burden of acquired listeriosis for 2005 and 2006, using most likely estimates. Error bars express an uncertainty interval that results from using low and high estimates.

8.3 Cost-of-illness

The costs of both acquired and perinatal listeriosis were combined to give an estimation of the total cost-of-illness due to *Listeria monocytogenes*. Only acquired listeriosis can manifest in gastroenteritis, hence only for these patients the general methods used in this and previous reports for other GE-pathogens can be applied to calculate all costs. For all other outcomes, shown in the outcome trees of perinatal and acquired listeriosis, a different approach should be followed. Unfortunately, literature on specific cost estimations for e.g. sepsis and/or meningitis caused by *Listeria monocytogenes* is scarce. Unit costs of disease outcomes other than GE were taken from costing studies regarding other infections if available, otherwise general cost estimates regarding that disease outcome were applied. All unit costs were indexed in 2004 euros.
Volumes per disease outcome were based on the incidence over 2005 and 2006. The averages of these incidence rates were used and only the reported cases were used as the most likely estimates. Multiplying all volumes by unit costs resulted in the total costs per disease outcome as shown in Table 36.

Table 36. Costs of *Listeria monocytogenes* for 2005 and 2006 (most likely estimates per year).

	Volume (n)	Unit costs (2004 €)	Costs (€)	Source (unit costs)
Acquired Listeriosis			*2,300,000*	
Sepsis	15.5	22,000	340,000	[101, 102]
Meningitis	30	8,000	240,000	[103, 104]
GE	13	6,200	80,000	
Pneumonia	14.5	4,100	60,000	[105]
Neurological disorders	4.2	320,000	1,400,000	[103]
Death	15.5	17,000	260,000	
Perinatal Listeriosis			*170,000*	
Sepsis	0.5	22,000	11,000	[101, 102]
Meningitis	1.5	8,000	12,000	[103, 104]
Neurological disorders	0.47	320,000	150,000	[103]
Death	2.5	-	-	
Total			€ 2,500,000	

The most likely estimate of the annual cost-of-illness for *Listeria monocytogenes* in this study results in 2.5 million euros. This estimate is based on above mentioned disease outcomes, but is influenced by underlying assumptions. It was assumed that all patients with listeriosis were hospitalized, which explains the relatively high cost (6,200 euros) per GE patient. Further the unit cost of GE comprises non-health care costs as productivity losses, but with a median age of 65 these costs are low. In case of a patient with acquired listeriosis who died the unit cost of *death* in Table 36 is an average of costs due to a friction period of 154 days per worker based on the total age distribution for all patients with acquired listeriosis. Death following from perinatal listeriosis always regarded an unborn or newborn, thus no productivity losses were accounted for and therefore this unit cost is zero.

Equal unit costs of the different disease outcomes (sepsis, meningitis and neurological disorders) were assumed for acquired and perinatal listeriosis which can be debated. Furthermore, some patients have multiple disease outcomes e.g. sepsis and meningitis following in separate cost estimates where an overlap (e.g. days hospitalized) of costs is possible, resulting in an overestimation of costs per patient. On the other hand, direct health care costs of a combination of meningitis and sepsis can be much higher than the sum of both [3], resulting in an underestimation of total costs. Lack of data hampers sensitivity analyses on these issues.
One way to give a range of the total cost-of-illness estimate for *Listeria monocytogenes* is to apply the low and high incidence rates (see Table 34, chapter 8.2.1). As shown in Table 37, multiplying these incidence rates to the unchanged unit costs result in 1.7 to 3.5 million euros per year for *Listeria monocytogenes* in the Netherlands.

Table 37. Costs of *Listeria monocytogenes* for 2005 and 2006 (min. and max. estimates per year).

	Minimum estimates		Maximum estimates	
	Volume (n)	Costs (€)	Volume (n)	Costs (€)
Acquired Listeriosis		*1,700,000*		*3,000,000*
Sepsis	10.8	230,000	21	460,000
Meningitis	22.85	180,000	37.9	300,000
GE	8.55	53,000	18.2	110,000
Pneumonia	9.6	40,000	19.7	80,000
Neurological disorders	3.2	1,000,000	5.25	1,700,000
Death	11	180,000	20.15	330,000
Perinatal Listeriosis		*6,400*		*480,000*
Sepsis	-	-	3.2	69,000
Meningitis	0.8	6,400	6.9	55,000
Neurological disorders	-	-	1.1	350,000
Death	1.9	-	8.9	-
Total		€ 1,700,000		€ 3,500,000

8.4 Discussion

The update for enhanced surveillance of *Listeria monocytogenes* infection registered in 2005 and 2006 11 cases of perinatal listeriosis and 148 cases of acquired listeriosis occurred in the Dutch population. Most newborns with listeriosis were born prematurely. Five newborns died as a result of listeriosis. Of the cases with acquired listeriosis, 41% had meningitis and one in five cases with acquired listeriosis died. In total the undiscounted and discounted mean annual disease burden of listeriosis was 311 DALYs and 158 DALYs respectively over the two year time period. Perinatal listeriosis contributed most to the disease burden: 203 DALYs (undiscounted) and 62 DALYs (discounted). The main share of DALYs was lost due to fatal cases of listeriosis. In total, perinatal and acquired listeriosis fatalities contributed 291 DALYs (undiscounted) and 143 DALYs (discounted). Figure 16 shows the mean annual disease burden of listeriosis over 2005 and 2006.

On average, the undiscounted number of DALYs lost per perinatal listeriosis case is 37. This number is higher compared to the mean 1.5 DALYs (undiscounted) lost per acquired listeriosis case and much higher than the mean number of DALYs lost due to the spore-forming bacteria *C. perfringens, S. aureus* (both 0.003 DALYs per case), and *B. cereus* (0.002 DALYs per case).

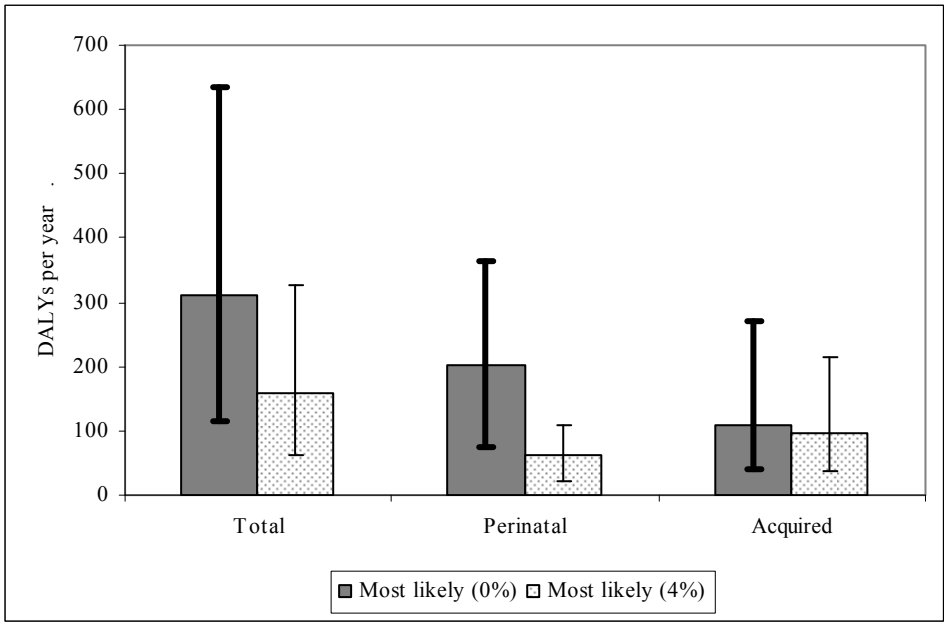

Figure 16. Annual disease burden of listeriosis for 2005 and 2006, using most likely estimates. Error bars express an uncertainty interval that results from using low and high estimates.

The cost-of-illness of listeriosis is 2.5 million euros per year, of which 2.3 million euros were attributed to acquired listeriosis. Neurological disorders due to listeriosis contributed the majority of costs (1.5 million euros, 60%). The difference between discounted and undiscounted in Figure 17 consists only of the cost difference of neurological disorders, approximately 900,000 euros undiscounted and 300,000 euro per case when discounted. Figure 17 shows the mean annual cost-of-illness of listeriosis over 2005 and 2006.

On average the cost-of-illness of perinatal listeriosis and acquired listeriosis is 32,000 euros and 31,000 per case, respectively. This is also much higher than the mean cost-of-illness of a case of *C. perfringens* (62 euros per case), *S. aureus* (59 euros per case) and *B. cereus* food poisoning (73 euros per case).

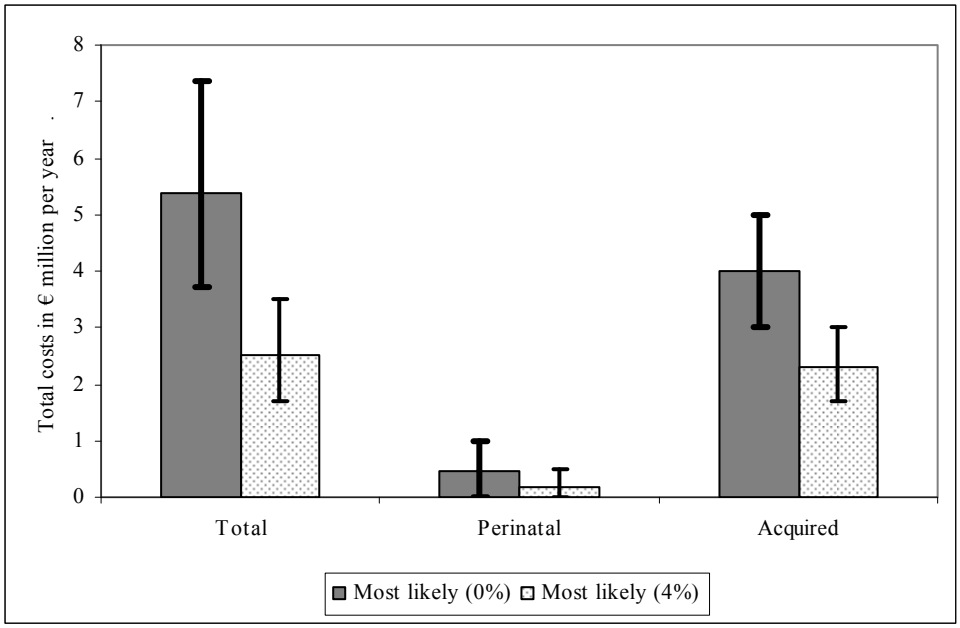

Figure 17. Annual disease cost-of-illness of listeriosis for 2005 and 2006, using most likely estimates. Error bars express an uncertainty interval that results from using low and high estimates.

The disease burden estimation of listeriosis we calculated (311 DALY undiscounted) is lower compared to the previous disease burden estimation of listeriosis in the report of Kemmeren et al. [1], who found an annual disease burden of 390 DALYs. This is mainly because Kemmeren et al. assumed a higher number of annual fatalities due to perinatal listeriosis, resulting in a burden of perinatal listeriosis of 320 DALYs, a disease burden 58% higher than the burden of perinatal listeriosis estimated in the current report. Because Kemmeren et al. based their disease burden estimates on information from the first half of 2005 of the enhanced *Listeria monocytogenes* surveillance as opposed to the two-year surveillance data used in the current study, we presume that the burden of disease of *Listeria monocytogenes* reported in the current report is a more accurate one than the estimate reported by Kemmeren et al.

9 Hepatitis A virus

Hepatitis A virus (HAV) is a small non-enveloped RNA virus that belongs to the *Picornaviridae* family. It can be transmitted by ingesting food or water that is contaminated with feces or by person-to-person contact. HAV is most frequently transmitted among close contacts, especially in households, day care centers and elementary schools [106, 107]. Sexual contact and international traveling are also common risk factors for HAV infection [108, 109].

The time between exposure to the virus and onset of the symptoms is two to six weeks [110]. During this relatively long incubation period the virus is shed extensively in the stool of the infected person who then is a potential source of infection for other persons, especially in cases of poor sanitation and/or crowding. Otherwise healthy adults remain infectious up to two weeks after onset of symptoms; in children the infectious period may last several months after onset [111, 112] .

HAV causes hepatitis A, an acute inflammation of the liver. The symptoms of hepatitis A may vary between cases [113]. Frequently reported symptoms are jaundice, dark urine, fatigue, loss of appetite, abdominal pain and light-colored stool lasting for several weeks [114]. Asymptomatic infection occurs regularly as well. About 30% of infected adults do not develop symptoms [115]. In children, an even larger share of approximately 70% has an asymptomatic infection. Children who do develop a symptomatic infection often experience a mild form of hepatitis A. Relapse or a prolonged course of illness of several months occurs in about 10 to 20% of the symptomatic patients [113, 116].

Besides symptom severity, the case-fatality rate is also affected by the age of the patient. Overall the case-fatality rate is 0.3-0.6%, yet in persons over 50 years it reaches 1.8% [12, 114, 117].

Transmission via food is associated with only a small number of cases [106, 118]. Data elicited from food safety experts suggested that 11% of hepatitis A cases were transmitted via food [118]. Uncooked foods, such as oysters, salads and fruit (juice), are often involved in HAV transmission, since heating food to 85 ºC inactivates the virus [116, 119]. Nevertheless, foods can also be contaminated after cooking by HAV infected food handlers in restaurants or food processing plants. Freezing, detergents and acids do not affect the virus [120].

9.1 Outcome tree, incidence and duration of illness

9.1.1 Outcome tree and incidence

The seroprevalence of HAV in the Dutch adult population ranges from 34% (overall Dutch population) [121] to 57% (residents Amsterdam) [121, 122]. Among Surinamese, Turkish and Moroccan immigrants of the first generation seroprevalence is significantly higher; among those living in Amsterdam a seroprevalence of 100% was reported [122]. Like many other countries, in the Netherlands the GP or other health care provider is obliged to report a case of HAV infection to the health authorities. Nevertheless, many cases have an asymptomatic course, and patients with a mild

course of hepatitis A might not consult a physician. If a patient does consult a physician, HAV infection might not be recognized because in some cases, especially in children or young adults, the symptoms resemble influenza symptoms. As a result, the reported number of HAV is most probably lower than the actual number of cases. Studies that have quantified underreporting of hepatitis A cases found high rates of underreporting ranging from 34 through 83% [123-127].

In 2006, 269 cases of HAV infection were reported by the Dutch PHL participating in ISIS. We assumed that the observed cases resulted from a Poisson process and expressed the uncertainty of the incidence as a Gamma distribution. Adjusting the registered number of hepatitis A cases for underreporting, which was assumed to be 73% [128] and patients not consulting the GP which was assumed to be 20%, we estimated that annually 1,200 cases of symptomatic HAV infection occur in the Dutch population, with an uncertainty ranging from 1,000 cases (low estimate corresponding to the 5^{th} percentile) to 1,500 cases (high estimate corresponding to the 95^{th} percentile). Of these patients, we estimated that most likely 960 cases sought medical advice, with minimum and maximum estimate of 820 and 1,100, respectively.

The Dutch National Disease Registry for Hospitalization reported that in 2006 a total of 39 patients were hospitalized due to HAV infection, 15% of notified cases. This is slightly lower than the 17-25% hospitalization reported in previous studies [109, 129-131], though it should be noted that the hospitalization rate of HAV cases increases with the age of the patient [130, 131]. Based on these studies, we assumed that most likely of the notified cases 20% was hospitalized. For the minimum and maximum estimate, we assumed hospitalization rates of 15% and 25%, respectively. Hence, we estimated that most likely, 39 HAV cases were hospitalized, with minimum of 26 cases and a maximum of 55 cases.

The case-fatality rate of HAV reported in literature varies from 0.1 through 1.8% [54, 119, 120, 131]. In the year 2006 Statistics Netherlands did not report any fatalities due to acute HAV in the Netherlands. In 2004 and 2005 each year one fatal case of hepatitis A was reported. In sporadic cases patients may develop fulminant hepatitis causing liver failure. If these patients eventually die after liver transplantation, they may not be registered under the ICD-code of acute hepatitis A. Moreover, patients suffering from hepatitis A who have an underlying comorbid disease have a higher risk mortality risk. Since mortality registrations allow solely one cause of death, the case might be attributed to the underlying disease rather than HAV. Taking this into account, we assumed a most likely estimate of one fatal case (case-fatality rate of 0.1% [54]) and a maximum estimate of 4 fatal cases (case-fatality rate of 0.3% [119]).

The incidence of hepatitis A is shown in Table 38. The outcome tree of HAV is presented in Figure 18.

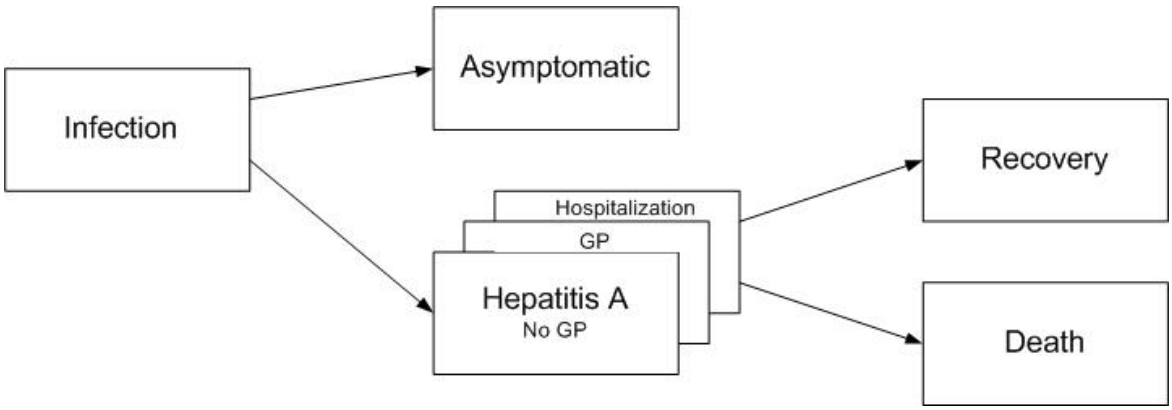

Figure 18. Outcome tree of hepatitis A virus.

Table 38. Incidence of illness of foodborne hepatitis A virus for 2006.

	Incidence estimates (cases per year)		
	Most likely	Low	High
Hepatitis A	1,200	1,000	1,500
No GP	250	200	280
GP	960	820	1,100
Hospitalization	39	26	55
Fatal	1	0	4

* Summations do not necessarily tally.

9.1.2 Duration of illness and age-distribution

The severity and duration of the illness is related to the age of patient. Young children often have mild flu-like symptoms without icteric symptoms lasting for about one or two weeks [132]; among adults about 80% is ill up to 8 weeks [114], although disease duration is rather variable, ranging from 7 to 30 days [12, 106, 133]. Based on the information from literature, we assumed that the duration of disease is 30 days. There was no data available for adults not consulting the GP (no GP). For this group we supposed a length of illness of 14 days. For hospitalized cases, the average length of hospitalization was 6 days [134, 135] and length of illness of was estimated to be 30 days.

The age-distribution of hepatitis A is summarized in Table 39. Both hospitalized and GP cases are based on hepatitis A cases reported by the Dutch PHL participating in ISIS. There was no information available on the age distribution of cases not consulting the GP, hence we used the age distribution of the reported hepatitis A cases consulting the GP as a proxy. Additionally, data on the age distribution of fatal cases was lacking. Hence, we adopted the age distribution reported in literature [131].

Table 39. Age distribution of hepatitis A virus infection.

	Age classes				
	0-4 years	5-9 years	10-14 years	15-64 years	> 65 years
Gastroenteritis					
No GP[a]	14%	24%	19%	40%	3%
GP[b]	14%	24%	19%	40%	3%
Hospitalization[b]	8%	8%	10%	64%	10%
Fatal[c]	-	-	11%	56%	33%

a) no information available. We used laboratory confirmed cases reported by PHLs from ISIS as a proxy.
b) based on hepatitis A cases reported by PHLs from ISIS.
c) based on fatal cases reported by the Hepatitis surveillance of the CDC [131].

9.2 Disease burden

The estimated number of YLD, YLL and DALYs lost due to foodborne hepatitis A is shown in Table 40. Both the discounted (4%) and the undiscounted number of DALYs lost are calculated. The incidence, duration and disability weights used for the estimations are also shown in Table 40. In Figure 19 the DALY estimates for the most likely estimate and the uncertainty (low and high estimate) are shown for the total estimation as well as for each health state separately, both discounted and undiscounted.

Table 40. Incidence, duration and disease burden of hepatitis A virus infection (most likely estimates).

	Incidence	Disability weight	YLD	YLL	DALY (0%)	DALY (4%)[b]
Hepatitis A	1,200					
No GP	250	0.011	3	-	3	3
GP	1,000	0.058	56	-	56	56
Hospitalization	39	0.353	4	-	4	4
Fatal	1	1.000		41	41	24
Total			62	41	103	85

* Summations do not necessarily tally

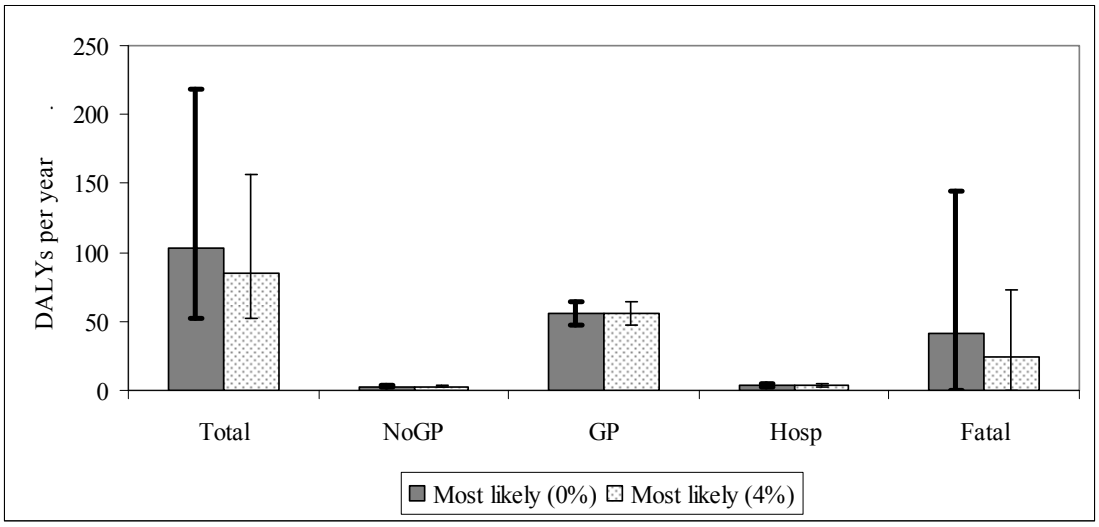

Figure 19. Disease burden of hepatitis A virus for 2006, using most likely estimates, discounted (4%) and undiscounted (0%). Error bars express an uncertainty interval that results from using low and high estimates.

9.3 Discussion

Annually about 1,200 cases of HAV infection occur in the Dutch population. About 80% of cases with Hepatitis A request medical help and 3% is hospitalized. HAV results in a loss of 103 DALYs per year, with an uncertainty range of 52 DALYs to 218 DALYs per year (undiscounted).

On average, with each case of HAV infection 0.08 DALYs are lost. This is higher compared to the average number of DALYs lost due to toxin-producing bacteria *C. perfringens, S. aureus* and *B. cereus* (0.002-0.003 DALYs lost per case), yet it is lower compared to the DALYs lost due to listeriosis (acquired: 1.5 DALYs per case; perinatal: 37 DALYs per case).

Regarding the high seroprevalence of HAV in the Dutch population, the annual number of HAV seems rather low [121, 122]. However, this might be due to the fact that many cases of HAV have an asymptomatic course. An asymptomatic infection may cause patients to test positive based on serology tests, while they did not actually experience any disease.

The fraction of HAV transmitted via food might is estimated to be about 11% [118].

10 Hepatitis E virus

The hepatitis E virus (HEV) consists of a small, non-enveloped particle with single-stranded RNA. On its discovery, HEV was classified under the *Caliciviridae* family, yet more recently the virus has been allocated to the *Hepeviridae* family on account of its genomic properties [123, 136].

The main mode of HEV transmission among humans is the feacal-oral route; especially consumption of contaminated water is a major source of infection [137, 138]. HEV can also be spread through consumption of contaminated meat [139, 140], through parenteral transmission (for instance blood transfusions) [141] or from mother to child (perinatal transmission) [138, 142].

After an incubation time of approximately two to ten weeks, hepatitis E manifests itself [137, 143]. The symptoms closely resemble Hepatitis A symptoms, and to ascertain the specific cause of the symptoms serological testing is required [144, 145]. Although symptoms vary between cases, in general two phases of illness can be distinguished [146]. During the first phase, the prodromal phase, the patient may experience nausea and fever. The second phase, the icteric phase, encompasses symptoms like jaundice and dark urine [147]. Other frequently reported symptoms are malaise, anorexia, abdominal pain and hepatomegaly (enlargement of the liver) [146, 147]. Hepatitis E lasts for one to four weeks, although in some cases it has a prolonged course lasting up to six months or may even be chronic [137, 148]. Apart from the clinical picture described above, hepatitis E may also cause mild, flu-like symptoms or have an asymptomatic course. This is more often the case in young children [144]. The case-fatality rate of HEV infection ranges from 0.5 to 4% in the general population [137, 149].

Among pregnant women, especially those in the second and third trimester, the risk of HEV infection is higher, and in case of infection they have a higher risk of adverse health outcomes and may be fatal in 15 to 25% of the cases [150, 151].

Like HAV, it is difficult to retrieve the mode of transmission because of the relatively long incubation period. An expert elicitation obtained an estimated 14% of HEV cases that is transmitted by food, of which the majority by pork [118].

10.1 Outcome tree, incidence and duration of illness

10.1.1 Outcome tree and incidence

The seroprevalence of HEV in the general Dutch population was estimated to be approximately 2%, which is significantly lower than the 34% seroprevalence of HAV [122, 152]. This estimated HEV seroprevalence rate is in line with the reported 2% seroprevalence of general population of Germany [153], yet data from Spain suggested a slightly higher seroprevelance of 7% in the Spanish general population [154].

HEV is a non-notifiable disease in the Netherlands. However, Borgen et al. (2008) have conducted a descriptive case series of laboratory confirmed non-travel related HEV in the Netherlands and found an incidence rate of 0.4 cases per 1.000.000 population per year [147]. This is in line with the 0.6 per 1.000.000 incidence rate of non-travel related HEV infection in England and Wales reported by Lewis et al. (2008) [155]. Including other transmission pathways and adjusting the number of HEV cases for the number of laboratories that did not supply samples for the study of Borgen et al., we estimated that annually 300 cases of hepatitis E infections occur, with an uncertainty ranging from 210 cases (low estimate corresponding to the 5th percentile of the distribution) to 430 cases (high estimate corresponding to the 95th percentile of the distribution) [118, 155]. Based on the frequency of clinical features, like jaundice, fever and malaise, we estimated that most likely 250 cases sought medical advice, with minimum and maximum estimate of 190 and 340, respectively [137, 156].

Borgen et al. reported a hospitalization rate of 58% [147]. Other studies on HEV infection cases reported equally high hospitalization rates [156-158]. Hence, we estimated a most likely number of hospitalized cases of 150 cases per year, with an uncertainty ranging from 92 to 216 hospitalizations.

Evidence from literature suggests that the case-fatality rate is relatively low, ranging from 0 through 4%, yet among pregnant women the case-fatality rate is much higher [137, 149, 155, 159]. Statistics Netherlands has no data on fatal Hepatitis E cases, since there is no distinct ICD-code for HEV infection. Nevertheless, Statistics Netherlands reported that in 2006 two cases died of acute viral hepatitis other than hepatitis A. We supposed that in 2006 most likely three cases died from hepatitis E, with a minimum of 1 and a maximum estimate of 6 fatal cases.

The incidence of hepatitis E is shown in Table 41. The outcome tree of HEV is presented in Figure 20.

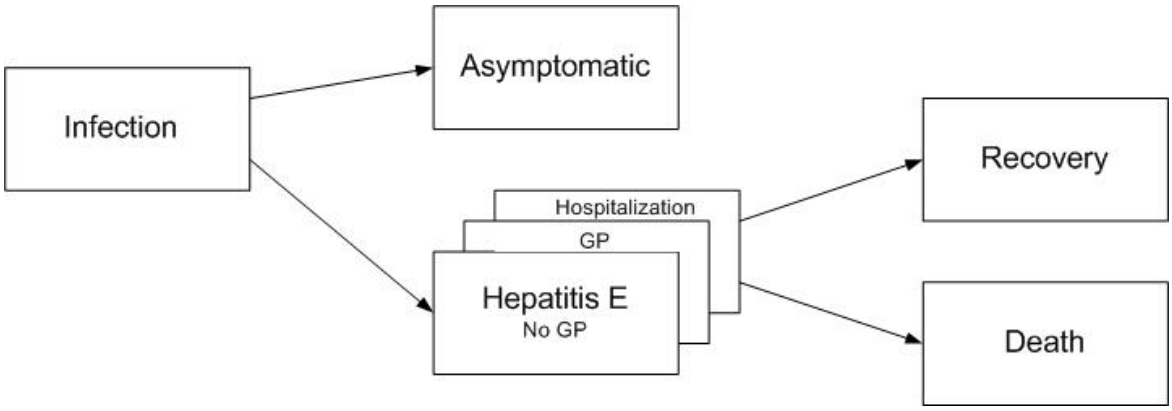

Figure 20. Outcome tree of hepatitis E virus.

Table 41. Incidence of illness of foodborne hepatitis E virus for 2006.

	Incidence estimates (cases per year)		
	Most likely	Low	High
Hepatitis E	300	210	430
No GP	50	16	90
GP	110	100	120
Hospitalization	150	92	220
Fatal	3	1	6

* Summations do not necessarily tally.

10.1.2 Duration of illness and age-distribution

To estimate the length of illness, we used data reported in the study of Borgen et al. [147]. They reported that length of illness for non-hospitalized cases was approximately 30 days, whereas for hospitalized patients length of illness was approximately two months (median length of stay 8 days) [147]. For patients not consulting the GP (no GP), there was no data available. Hence, we used APM disability weights that incorporated a duration of one month.

The age-distribution of hepatitis E is summarized in Table 42. Lewis et al. (2005) showed that the median age of non-travel related cases was higher compared to the median age of travel-related cases [155]. Because of this, we used the age-distribution of HEV cases in England/Wales as a proxy for cases not-consulting and GP cases [155]. For the age-distribution of hospitalized cases, information on HEV cases was not available. Therefore, we used the age-distribution of hospitalized non-travel related HEV cases reported by Borgen et al. [147]. Additionally, data on the age distribution of fatal cases was lacking. Hence, we adopted the age distribution reported in literature [158].

Table 42. The age-distribution of hepatitis E virus infection.

	Age classes				
	0-4 years	5-9 years	10-14 years	15-64 years	> 65 years
Gastroenteritis					
No GP[a]	-	-	1%	75%	23%
GP[a]	-	-	1%	75%	23%
Hospitalization[b]	-	-	-	64%	36%
Fatal[c]	-	-	-	50%	50%

a) no information available. We used laboratory confirmed cases reported by Lewis et al.
b) based on hepatitis E cases reported by Lewis et al.
b) based on non-travel related hepatitis E cases reported by Borgen et al. [147]
c) based on fatal cases reported by the Péron et al. [158]

10.2 Disease burden

The estimated number of YLD, YLL and DALYs lost due to foodborne hepatitis E is shown in Table 43. Both the discounted (4%) and the undiscounted number of DALYs lost are calculated. The incidence, duration and disability weights used for the estimations are also shown in Table 43. In Figure 21 the DALY estimates for the most likely estimate and the uncertainty (low and high estimate) are shown for the total estimation as well as for each health state separately, both discounted and undiscounted.

Table 43. Incidence, duration and disease burden of hepatitis E virus infection (most likely estimates).

	Incidence	Disability weight	YLD	YLL	DALY (0%)	DALY (4%)[b]
Hepatitis E	140					
No GP	27	0.011	1	-	1	1
GP	45	0.058	6	-	6	6
Hospitalization	63	0.353	13	-	13	13
Fatal	3	1.000	-	115	115	66
Total			19	115	135	94

* Summations do not necessarily tally.

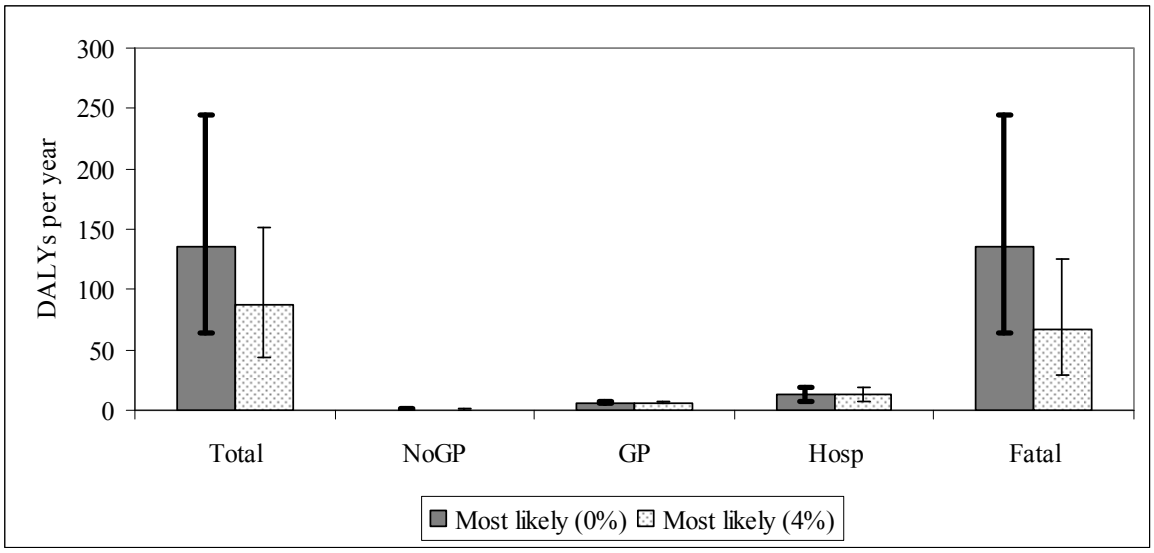

Figure 21. Disease burden of hepatitis E virus infection for 2006, using most likely estimates, discounted (4%) and undiscounted (0%). Error bars express an uncertainty interval that results from using low and high estimates.

10.3 Discussion

Annually an estimated 300 cases of HEV occur in the Dutch population. About 80% of HEV cases request medical help and approximately 50% is hospitalized. HEV results in a loss of 136 DALYs per year, with an uncertainty range of 64 DALYs to 244 DALYs per year (undiscounted).

On average, with each case of HEV infection 0.5 DALYs are lost. This is six times higher compared to the average number of DALYs lost due to HAV (0.08 DALYs lost per case), yet it is lower compared to the DALYs lost due to listeriosis (acquired: 1.5 DALYs per case; perinatal: 37 DALYs per case).

11 Integration of results

11.1 Disease burden

Table 44 presents a summary of disease burden of the six pathogens studied in this report, and the eight pathogens that were evaluated in the two preceding studies on the burden of foodborne disease in the Netherlands. The results show that the disease burden of *S. aureus* and *C. perfringens*-associated gastroenteritis are in the middle range, whereas the disease burden of *B. cereus*, hepatitis A and E virus are in the lower range.

Also, Table 44 presents the mean disease burden per case of illness of the pathogens studies in this report and those previously studies. The results show that the mean disease burden per case is highest for listeriosis. The mean disease burden per case of illness of *C. perfringens*, *S. aureus* and *C. perfringens* are in the lower range. Hepatitis A and E virus are in the middle range.

Figure 22 shows the disease burden of the six pathogens that were evaluated in this report in relation to the previous studies pathogens.

Figure 23 presents the break down of the disease burden of the pathogens studies.

The data presented in this chapter are also accessible online on the RIVM website (http://www.rivm.nl/vtv/object_class/kom_voedsel_micro.html).

Table 44. Overall disease burden and mean disease burden per case of illness of 14 pathogens studied so far, 2006.

Pathogen	DALY* (0%)	DALY* (4%)	DALY per case (0%)	DALY per case (4%)
Bacteria-infections				
Campylobacter spp.	1,833	1,421	0.023	0.018
STEC O157	117	-	0.063	-
Salmonella spp.	1,053	874	0.024	0.020
Listeria monocytogenes (perinatal)	237	62	47.4	12.4
Listeria monocytogenes (acquired)	108	96	2.25	1.52
Clostridium perfringens	509	497	0.003	0.003
Staphylococcus aureus	688	667	0.002	0.002
Bacillus cereus	109	109	0.002	0.002
Viruses				
Norovirus	1,083	1,064	0.002	0.002
Rotavirus	841	835	0.003	0.003
Hepatitis A virus	103	85	0.080	0.066
Hepatitis E virus	136	67	0.450	0.220
Protozoa				
Cryptosporidium parvum	77	73	0.001	0.001
Giardia lamblia	160	160	0.001	0.001
Toxoplasma gondii (congenital)	620	190	5.64	1.73

* including the sequel post-infectious irritable bowel disorder

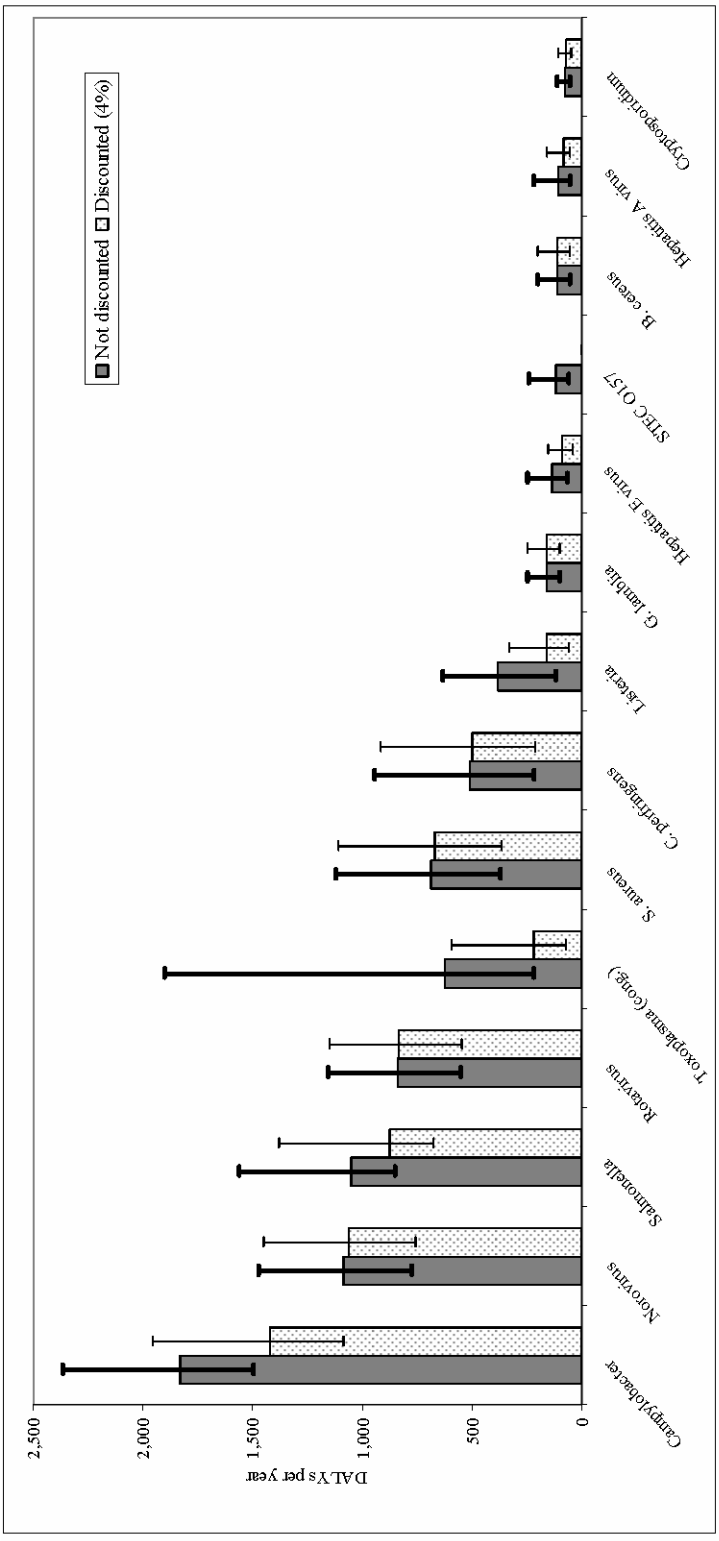

Figure 22. Disease burden of fourteen pathogens studied. Error bars express the uncertainty interval that results from using low and high estimates.

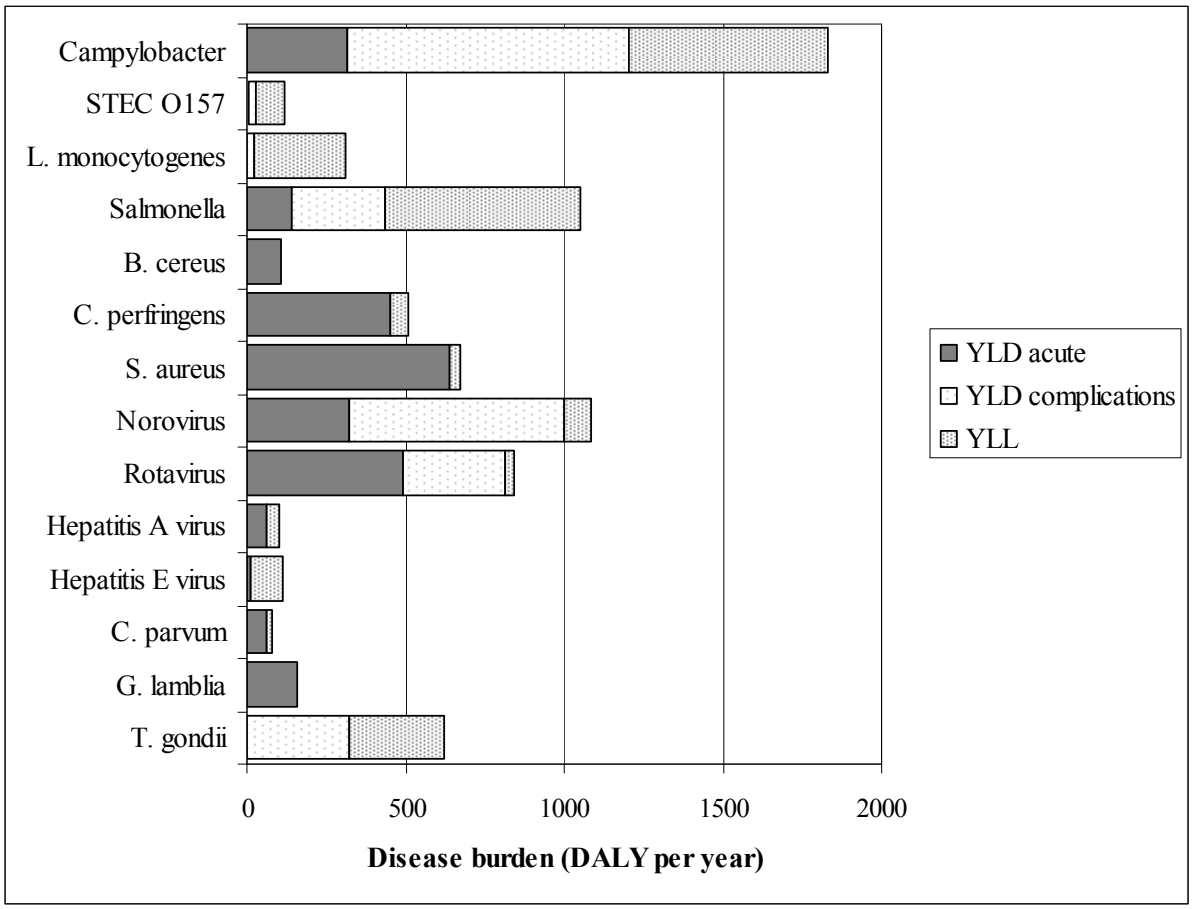

Figure 22. Breakdown of disease burden of fourteen pathogens studied.

11.2 Cost-of-illness

Table 45 presents a summary of the cost-of-illness of the six pathogens studied in this report and the eight pathogens studied previously. The results in this table show that the costs of *S. aureus*-associated gastroenteritis are high in comparison with *C. perfringens*-associated health effects and Salmonella. With a cost-of-illness of 2.5 million euros, the cost-of-illness of *Listeria monocytogenes* is lowest of the fourteen pathogens studied. Nonetheless, the mean cost per case of illness is highest for Listeria monocytogenes compared with the other thirteen pathogens. For *C. perfringens*, *S. aureus* and *B. cereus* the cost per case of illness is in the lower range.

Figure 24 shows the cost-of-illness of the pathogens that were evaluated in this report in relation to the previously studied pathogens.

Table 45. Overall cost estimates (in million euros) and mean cost per case of illness (in euros) of 14 studied pathogens studied so far, 2006.

Pathogen	Cost-of-illness (0%)	Cost per case (0%)
Bacteria-infections		
Campylobacter spp.	27.4	347
STEC O157	-	-
Salmonella spp.	10.8	249
Listeria monocytogenes	2.5	31,250
Clostridium perfringens	9.8	64
Staphylococcus aureus	17.6	64
Bacillus cereus	3.5	75
Viruses		
Norovirus	36.0	57
Rotavirus	35.8	119
Hepatitis A virus	-	-
Hepatitis E virus	-	-
Protozoa		
Cryptosporidium parvum	4.1	73
Giardia lamblia	15.6	141
Toxoplasma gondii (congenital)	-	-

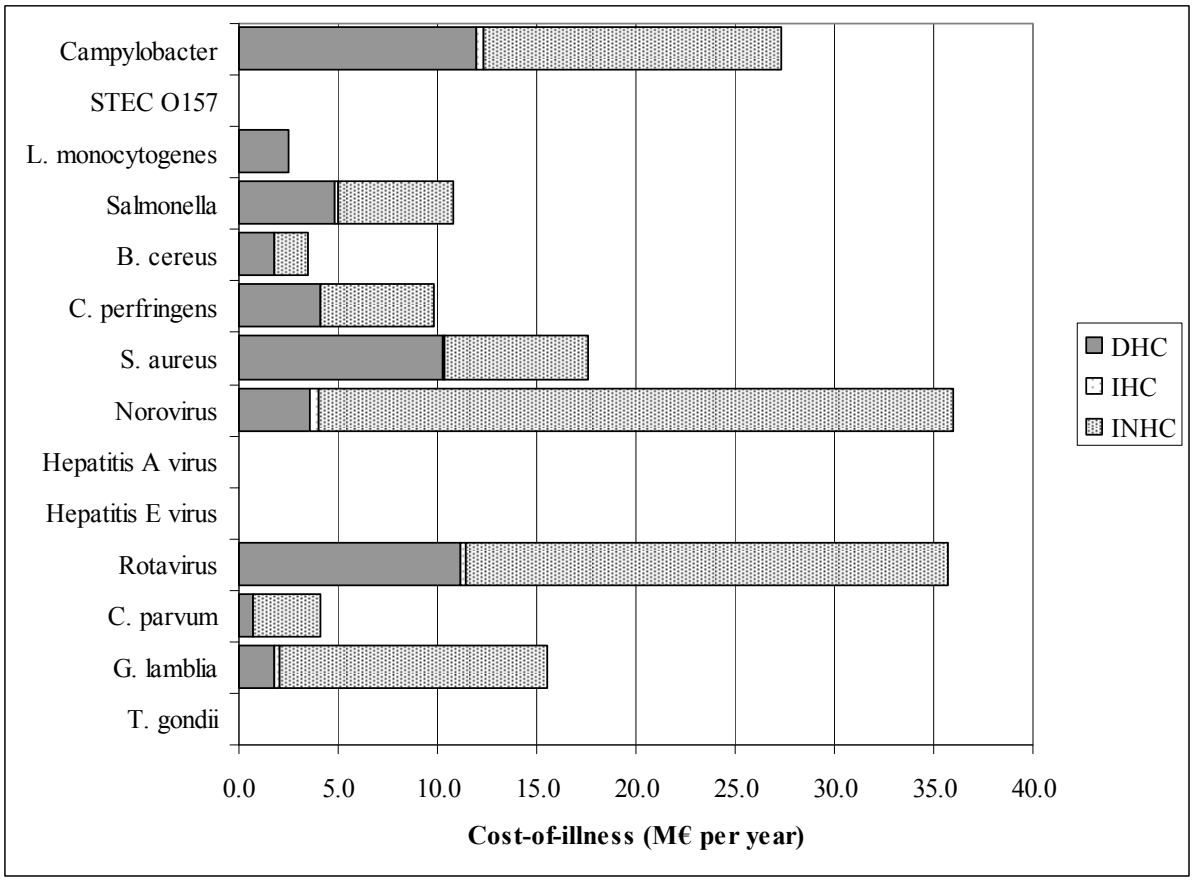

Figure 24. Breakdown of disease burden of fourteen pathogens studied.

11.3 Transmission pathways

The fourteen pathogens that were studied can be transmitted via food; other pathways of transmission are the environment, transmission from person to person through the fecal-oral route and direct contact with animals. Havelaar et al. performed an expert study to estimate the fraction of cases of enteric illness transmitted by the major pathways and the food groups involved within the foodborne pathway [160]. Table 46 and Figure 19 show the attribution of the incidence, fatalities, disease burden and cost-of-illness to the pathways of transmission. The attribution of disease burden and cost-of-illness to the pathways of transmission per pathogen are presented in Table 47 and 48, respectively, as well as in Figure 25 and 26.

Table 46. Attribution of the incidence, fatalities, disease burden and cost-of-illness to the transmission pathways.

Transmission pathway	Food	Environment	Human	Animal	Total
Incidence	690,000	250,000	670,000	100,000	1,700,000
Fatal	79	24	16	18	135
Disease burden (in DALY)	3750	1306	1608	720	7384
Cost-of-illness (in M€)	65.5	27.2	56.8	13.6	163.1

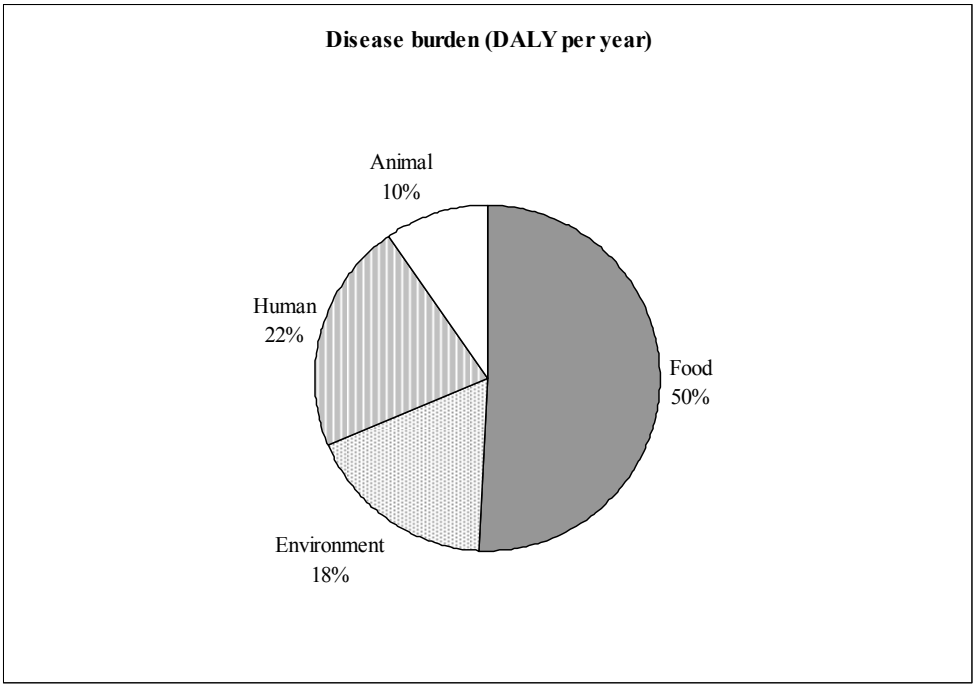

Figure 25. Attribution of the disease burden to the transmission pathways, 2006.

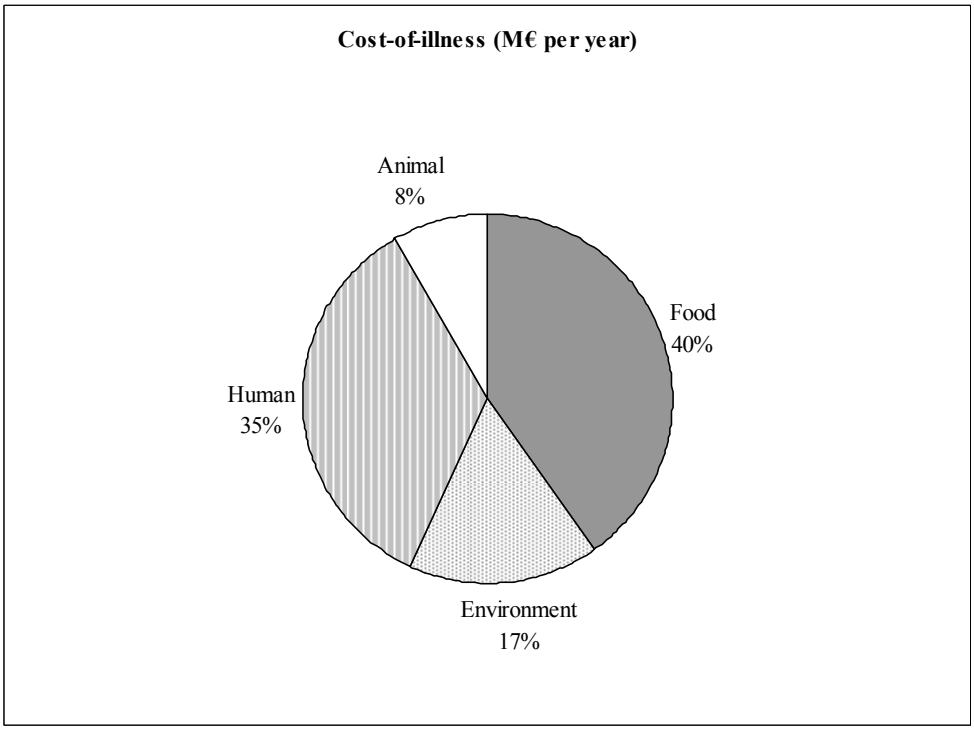

Figure 26. Attribution of the cost-of-illness to the transmission pathways, 2006.

Table 47. Attribution of the disease burden to the transmission pathways per pathogen.

Transmission pathway	Food	Environment	Human	Animal	Total
Campylobacter	874	429	132	398	1,833
STEC O157	54	23	14	27	118
L. monocytogenes	248	24	19	19	310
Salmonella	668	158	114	113	1,053
B. cereus	102	1	1	1	105
C. perfringens	477	12	11	11	511
S. aureus	610	25	22	15	672
Norovirus	198	169	658	58	1,083
Rotavirus	120	157	537	28	842
C. parvum	11	27	26	13	77
G. lamblia	25	46	68	21	160
T. gondii	363	235	6	16	620
Totaal	3,750	1,306	1,608	720	7,384

Table 48. Attribution of the cost-of-illness (in million euros) to the transmission pathways per pathogen.

Transmission pathway	Food	Environment	Human	Animal	Total
Campylobacter	13.1	6.4	2.0	5.9	27.4
STEC O157	0.0	0.0	0.0	0.0	0.0
L. monocytogenes	2.0	0.2	0.1	0.2	2.5
Salmonella	6.9	1.6	1.2	1.1	10.8
B. cereus	3.5	0.0	0.0	0.0	3.5
C. perfringens	9.2	0.2	0.2	0.2	9.8
S. aureus	16.0	0.6	0.6	0.4	17.6
Norovirus	6.6	5.6	21.9	1.9	36.0
Rotavirus	5.1	6.7	22.8	1.2	35.8
C. parvum	0.6	1.4	1.4	0.7	4.1
G. lamblia	2.5	4.5	6.6	2.0	15.6
T. gondii	0.0	0.0	0.0	0.0	0.0
Totaal	65.5	27.2	56.8	13.6	163.1

11.4 Food group attribution

Havelaar et al. also elicited expert opinions on the attribution of food groups involved within the pathway [160]. Table 49 and Figure 27 show the attribution of disease burden to the food groups within the foodborne pathways of transmission. To attribution of the cost-of-illness to the food groups are presented in Table 50 and 28.

Table 49. Attribution of disease burden to the food groups within the foodborne pathways of transmission.

	Beef and mutton	Pork	Poultry	Eggs	Dairy	Fish and shellfish	Fruit and vegetables	Beverages	Cereal products	Other food	Human and animal	Total
Campylobacter	35	44	472	26	79	61	44	18	18	44	26	867.0
STEC O157	24	3	2	1	4	2	4	2	2	2	9	55.0
L. monocytogenes	27	22	17	10	62	45	19.9	7.4	14.9	14.9	12.4	252.5
Salmonella	87	93	100	147	47	27	40	20	27	40	40	668.0
B. cereus	7	3	2	4	6	2	2	2	17	55	2	102.0
C. perfringens	229	38	33	14	19	28	33	10	14	38	19	475.0
S. aureus	49	49	49	18	91	37	12	12	43	183	73	616.0
Norovirus	6	6	6	4	4	32	14	6	10	10	101	199.0
Rotavirus	0	3.6	0	0	2.4	23	29	5	8.4	6	43.3	120.7
C. parvum	3	0.5	0.3	0.3	1	2.5	2.4	0.3	0	0.3	0.7	11.3
G. lamblia	5.1	1.3	0.8	0	2	3.3	8.3	0.8	0	0.8	3	25.4
T. gondii	83	181	18	0	18	15	22	0	0	7	22	366.0
Totaal	555.1	444.4	700.1	224.3	335.4	277.8	230.6	83.5	154.3	401.0	351.4	3,757.9

Table 50. Attribution of cost-of-illness (in million euros) to the food groups within the foodborne pathways of transmission.

	Beef and mutton	Pork	Poultry	Eggs	Dairy	Fish and shellfish	Fruit and vegetables	Beverages	Cereal products	Other food	Human and animal	Total
Campylobacter	0.5	0.6	7.0	0.4	1.2	0.9	0.7	0.3	0.3	0.4	0.7	13.0
STEC O157	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
L. monocytogenes	0.2	0.2	0.1	0.1	0.5	0.3	0.2	0.1	0.1	0.1	0.1	2.0
Salmonella	0.9	1.0	1.0	1.5	0.5	0.3	0.4	0.2	0.3	0.4	0.4	6.9
B. cereus	0.2	0.1	0.1	0.1	0.2	0.1	0.1	0.1	0.5	1.8	0.1	3.4
C. perfringens	4.4	0.7	0.6	0.3	0.4	0.6	0.6	0.2	0.3	0.7	0.4	9.2
S. aureus	1.3	1.3	1.3	0.5	2.4	1.0	0.3	0.3	1.1	4.8	1.9	16.2
Norovirus	0.2	0.2	0.2	0.1	0.1	1.0	0.5	0.2	0.3	0.3	3.4	6.5
Rotavirus	0.0	0.2	0.0	0.0	0.1	1.0	1.2	0.2	0.4	0.3	1.8	5.2
C. parvum	0.2	0.0	0.0	0.0	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.5
G. lamblia	0.5	0.1	0.1	0.0	0.2	0.3	0.8	0.1	0.0	0.1	0.3	2.5
T. gondii	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total	8.4	4.4	10.4	3.0	5.7	5.6	4.9	1.7	3.3	8.9	9.1	65.4

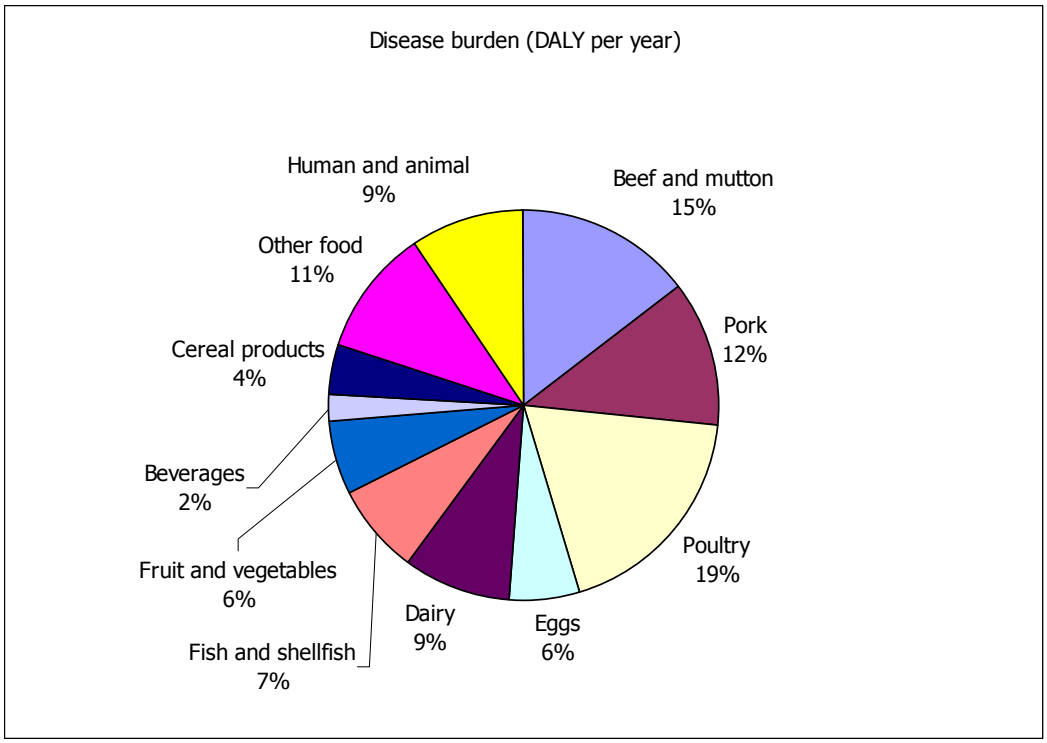

Figure 27. Attribution of the disease burden to the food groups within the foodborne pathways of transmission.

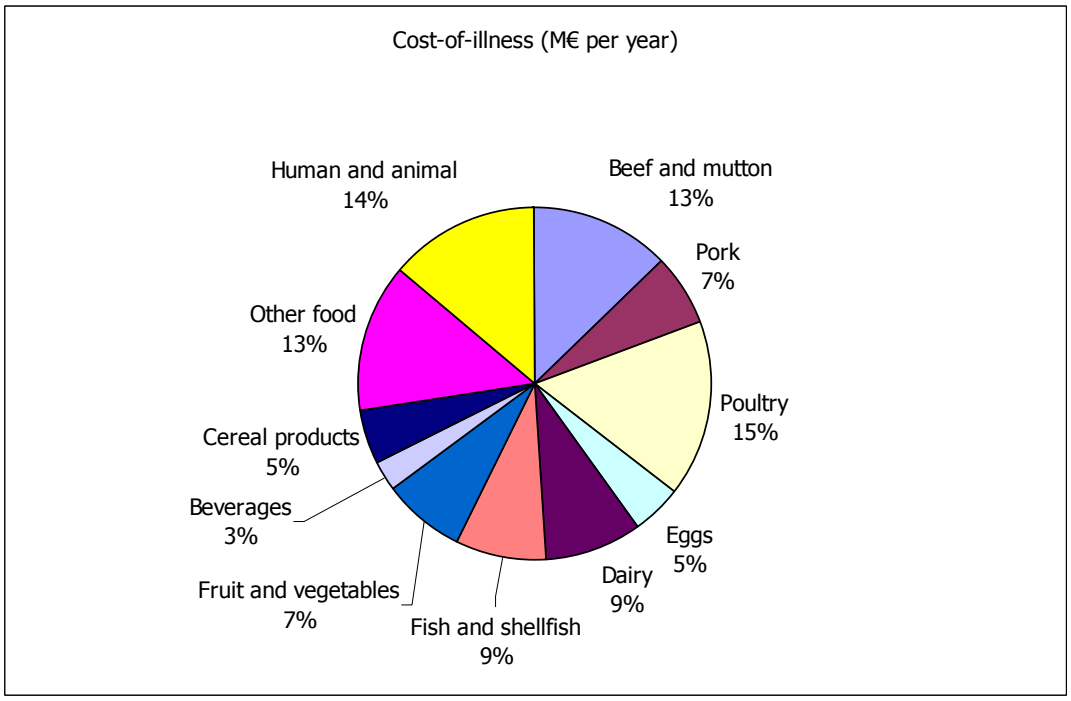

Figure 28. Attribution of cost-of-illness to the food groups within the foodborne pathways of transmission.

12 General discussion

The aim of this report was to describe the disease burden of post-infectious irritable bowel syndrome following an acute episode of gastroenteritis, and to assess the disease burden and cost-of-illness of five specific pathogens: *Clostridium perfringens, Staphylococcus aureus*, *Bacillus cereus,* Hepatitis A and E virus. Also, the disease burden of *Listeria monocytogenes* was updated and the associated cost-of-illness was described. This was accomplished as a continuation of the development of a model that facilitates 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. The current study follows two preceding studies on the burden of foodborne disease [1, 2] and the results of the study integrate complex information in a structured framework so that it is easily accessible to decision makers. We focused on two indicators, disease burden and cost-of-illness. The methods used to calculate both indicators are based on a broad range of practical and theoretical studies. Regarding the incidence of gastroenteritis and the methodology to assess the non-fatal burden of disease some important adjustments have been made compared to the previous two studies.

For *C. perfringens, S. aureus, B. cereus* and Hepatitis A and E virus, pathogen specific information for the Netherlands was not always available. Therefore, several assumptions had to be made which increases uncertainty. We tried to quantify those uncertainties by performing uncertainty and scenario analyses.

The GE incidence in the entire population was based on data from SENSOR, a prospective population-based cohort study with a nested case-control study [3]. The findings of the case-control study showed that toxins of *C. perfringens*, *S. aureus* and *B. cereus* were frequently present in the stool samples of controls. As was done for infectious agents, the GE incidence estimates of *C. perfringens*, *S. aureus* and *B. cereus* were not adjusted for this, which might have resulted in an overestimation of the incidence of GE due to *C. perfringens*, *S. aureus* and *B. cereus* in the population of the Netherlands. The extent of overestimation is currently not quantifiable, but may differ between toxins and infectious agents. For infectious agents, such as *Campylobacter spp*., acquired immunity may protect infected persons from developing illness, leading to high rates of asymptomatic carriership [161].

Little information is known on GP-visits and hospitalizations due to *Clostridium perfringens, Staphylococcus aureus, Bacillus cereus* and Hepatitis A and E virus. Research is recommended in this field. The Dutch Ministry of Health, Welfare and Sports has asked RIVM to initiate a study to find out the incidence of hospitalizations due to gastroenteritis-associated pathogens. With those results better estimations regarding disease burden and costs of *Clostridium perfringens, Staphylococcus aureus* and *Bacillus cereus*-associated gastroenteritis can be made.

In the analyses we used 4% discount rates for both costs and health effects like the Dutch guidelines for public health economic evaluation [162]. Since 2005, however, the Dutch guidelines for public health economic evaluation has changed and recommend to use a discount rate of 1.5% for health effects and 4% for costs [163]. We decided in the current report to follow the earlier recommendations, which was

4% for both costs and effects, and we show the undiscounted estimates. This allowed us to analyze the impact of discounting on the results. If we had followed the new recommendation, the estimated discounted disease burden would have been somewhere in between both presented figures, whereas the cost estimates would remain unchanged. But by following the earlier recommendations we do have the advantage that our results can be compared with earlier work done before 2005 in the Netherlands, as well as with the work done in other countries where it is common practice to use the same discount rate for both monetary and health effects.

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Appendix – Detailed methodological choices

Disease burden and cost-of-illness calculations involve the need to make several choices on the exact methodology that have an impact on the final results. These choices must be appropriate for the decision context of the study, and should reflect the values that exist in the societies under study. The choices for this particular project are discussed below.

Incidence or prevalence approach

In the incidence-based approach to disease burden and cost-of-illness calculations, all health outcomes (including those in future years) are assigned to the initial event, that is the acute (symptomatic) infection. The incidence approach reflects both the future burden of disease and the future costs of illnesses, based on current events. This approach contrasts with the prevalence approach, in which the health status of a population and the related cost-of-illness at a specific point of time are assessed, possibly followed by attribution of the prevalent diseases to etiological agents or conditions. The prevalence approach reflects the current burden of disease and the current cost-of-illness, based on previous events.

In this study, we chose the incidence approach for several reasons. Firstly, most communicable diseases have such a rapid course that prevalence is not very informative. Secondly, because the incidence approach is based on current events it is more sensitive to current epidemiological trends than the prevalence approach. Thirdly, the incidence approach is more informative on health gains and related savings of avoided cost-of-illness expenses that can be obtained now and in the future by current control programs that aim to prevent new cases (= incidence). Lastly, with the incidence approach calculation of time lived with disability is more consistent with the calculation of time lost due to mortality: the burden is ascribed to the age of onset (instead of to the age at which the disability is lived) or the age at which death occurs [164]. This applies also to the cost-of-illness estimation. Using the incidence approach costs-of-illnesses made due to chronic and long-lasting diseases in the remaining life time are ascribed to the age of onset, similar to the estimations of productivity losses due to premature mortality that are ascribed to the age at which death occurs.

Outcome or agent-based approach

The outcome-based approach assigns the disease burden and the associated costs-of-illness to clinically defined categories of diseases (ICD-codes), irrespective of their cause. This approach is mainly used to assess the overall public health situation and the associated costs in a country or region. In contrast, the agent-based approach focuses on all relevant health outcomes and the associated costs that can be attributed to one particular agent. These outcomes can cover different disease categories (ICD-codes). The latter approach gives a more complete insight into the public health impact and related costs of a particular cause, and the expected impact of preventive measures on both public health costs and associated costs. Therefore, the agent-based approach is chosen in this project.

Outcome trees

To provide a basis for disease burden and cost-of-illness calculations, the construction of an outcome tree is a useful first step (see Figure A.1-1). An outcome tree represents a qualitative representation of the disease progression over time by ordering relevant health states following infection and illustrating their conditional dependency. For infectious diseases, the first blocks in the outcome tree typically represent the incidence of infection and acute illness in a particular period. Subsequent blocks represent the incidence of possible outcomes, including recovery, and/or (not) request of specific resources. For late outcomes, this incidence is accumulated over the lifetime of affected individuals so that the link between the blocks reflects the lifetime probability of developing an outcome/requesting a specific resource, given the previous outcome/resource request. Once the outcome tree is designed, valuations of each block can be made. In this project, valuations related to health related quality of life and to resource requests.

Constructing outcome trees implies making choices on which outcomes and/or resource requests to include and which to exclude. This is based on preliminary estimations of a) the relative impact of all possible outcomes on the total disease burden and b) the relative impact of all possible resource requests on the total cost-of-illness. Outcomes and/or resource requests may not be included if they contribute little to the final result (because they are extremely rare and/or because their severity is low and/or because the associated costs are only minor). Construction of outcome trees is usually also guided in part by data availability. It is an iterative process that involves reviewing the tree while the study progresses.

For some outcomes, the causal link with the agent of concern may not be fully established. For example, a statistical association has been reported but this has not (yet) been repeated in other independent studies and/or the causal mechanism has not (yet) been elucidated. In that case, a professional but subjective choice must be made whether or not to include this outcome in the baseline model. The impact of this choice can be evaluated by scenario analysis both on the disease burden and the cost-of-illness estimate.

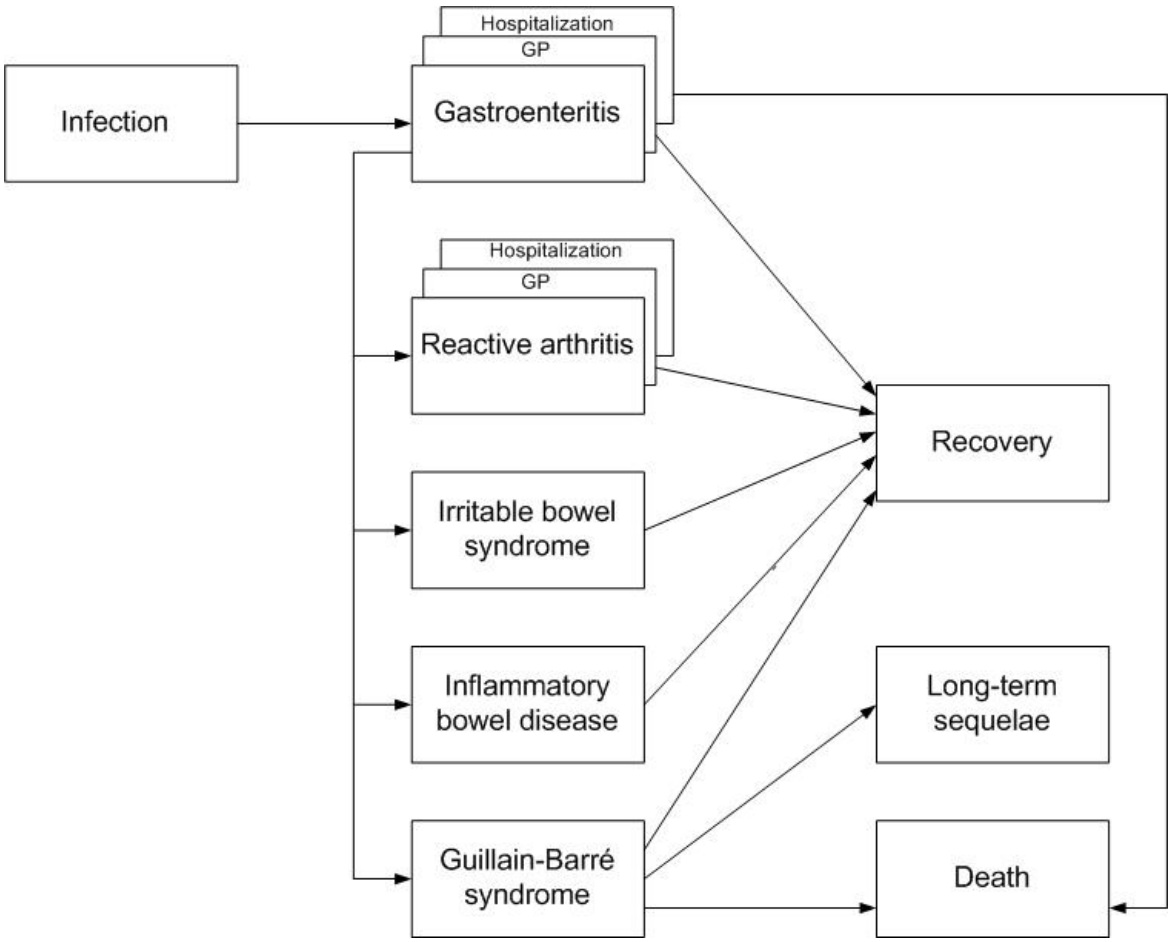

Figure A.1-1 Outcome tree Campylobacter-associated GE and sequelae.

Perspective of economic evaluation

A critical step in economic evaluation is to define the perspective taken. This perspective determines which potential 'costs' and eventual 'benefits' are included in the evaluation. Possible perspectives are the patient perspective, the societal perspective and the third player perspective (health insurances and/or ministry of health). Most published cost-of-illness studies use either the third payer perspective or the societal perspective. In this project we used the societal perspective to estimate disease burden and cost-of-illness, which is the most complete evaluation possible.

Discounting

In most programs financial costs and revenues occur on different points over time. In order to be able to value and compare different projects, the net present values (NPV) of each single program is estimated taking into account all investments and revenues made over time. This is achieved by calculating the *net* cash flow in each period, and then discounting this stream back to the present. According to Drummond et al. [165] the applied rate is often the real rate of return on long-term government bonds. This concept is not only applied to financial costs and revenues, but, although not undisputed, is also commonly applied in economic analysis of medical or other public health interventions for the non-monetary health effects. When the principle of discounting is applied in disease burden estimates, it means that future life years are assigned less value than those lived today.

This is based on the economic concept that immediate profits are generally preferred over benefits later in time [166]. In general, health today is valued higher than health in the future because there is uncertainty about future possibilities to 'better' treat diseases and about possible future co-morbidity.

Discounting of health benefits is disputed because its application results in a lower efficiency of prevention programs, whereas not discounting, or the use of a low discount rate - lower than the discount rate used for the costs - favour preventive measures due to benefit in the far future. We use in the current report a discount rate of 4% for both costs and effects [162], and also show the undiscounted estimates. This allows a comparison of our results with other work using discounted or undiscounted health effects, but also to analyze the impact of discounting on the results.

Data needs

For all relevant outcomes as represented in the outcome tree, data must be available on mortality, incidence, duration and severity in order to estimate the disease burden. For the cost-of-illness estimate data must be available for all relevant outcomes on resources used, the quantity required of each used resource and the cost price per used resource unit, where the chosen perspective of economic evaluation decides which resources to include in the analysis and which not. However, as the resources used are not only depending on outcomes but often also on the age, additional information on the age of the patients affected is required.

Furthermore, the impact of infectious diseases on a society and their related costs can be measured at different levels, often represented by the 'iceberg' metaphor or surveillance pyramid (see Figure A.1-2). The impact of illness and/or the related costs at different levels of the pyramid may differ greatly, as well as the availability of data. Therefore it is useful to separate these different levels in burden of disease studies and in cost-of-illness studies. The degree of underreporting varies greatly between diseases as well as between countries or even within one country in different periods.

To calculate disease burden and costs, data on mortality, incidence, duration, severity and resources used, including the quantity required and their associated costs is used. All these data need to be broken down into different age and sex categories where possible. In the current project we used the following age categories: 0-4, 5-9, 10-14, 15-64, 65+.

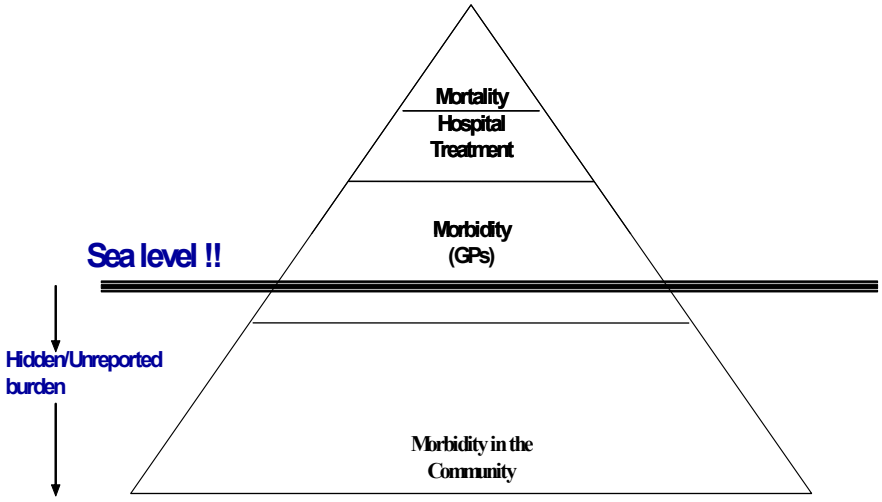

Figure A.1-2. The surveillance pyramid of communicable diseases [167].

Incidence of non-fatal health outcomes

Depending on the complexity of the outcome tree, the incidence must be assessed for a varying number of non-fatal outcomes. Ideally, this task would involve the establishment of the incidence of one outcome at the root of the tree (e.g. acute gastro-enteritis) and the (conditional) probability of progressing to the next stage or to recovery. In practice, such data are rarely available for a complete outcome tree and supplementary data are necessary. Such probabilities may be available from cohort or outbreak studies. It is also possible to directly use surveillance data or special studies for the incidence of the specific outcomes. As many outcomes can be triggered by more than one agent, information on the attributable fraction must also be available. Note that these two approaches are only equivalent in a stable situation, if this cannot be assumed some kind of back-calculation should be applied.

Ideally, data are available for all relevant levels of the surveillance pyramid: non-consulting cases, cases consulting a GP and hospitalized cases. In this order, data availability may be expected to increase, but will seldom be complete. In this project, incidental studies such as for example SENSOR and NIVEL, but also case-control studies and surveillance data readily available from the Basic Surveillance Network or Dedicated Surveillance Networks will be used, relying wherever possible on Dutch studies that will be complemented, where necessary, by published international literature studies. Data include all community-acquired infections in the Netherlands in the chosen time period, including travel-related cases but excluding illness contracted in closed settings such as hospitals and nursing homes.

Duration of non-fatal health outcomes

In this project duration of non-fatal health outcomes will be derived from various publications (both Dutch and non-Dutch studies), the Global Burden of Disease study and review articles.

Number of fatal cases
Mortality from infectious diseases is typically underreported in most routine surveillance systems. However, YLLs often are an important component of the total disease burden and lost productivity due to premature death and can be an important component of the total cost-of-illness, especially if the human capital approach is applied. Therefore, this problem of underreporting requires further attention. We obtained additional data from case-fatality ratios in outbreak studies, from registry-based cohort studies etc. We then applied these data to incidence estimates for different blocks of the outcome tree. Extrapolation to different levels of the surveillance pyramid might be problematic.

Life expectancy of fatal cases.
In the absence of co-morbidity, the life expectancy of fatal cases can directly be derived from standard life tables if the age distribution of fatalities is known. This information may typically not be available in routine surveillance data and as a result additional datasets must be sought. These may include broad categories (e.g. the age distribution of deaths from gastroenteritis as a proxy for any specific pathogen-associated GE) or special studies (e.g. intensified surveillance). In the presence of co-morbidity, the use of standard life tables may overestimate the YLL and cohort-specific data must be obtained.

For this project we used the Dutch life expectancy. Another possibility would have been to use the global life table as developed for the GBD project, which is based on Japanese survival tables (the Japanese have the highest realized life expectancy in the world). The main difference is that in the Netherlands, the life expectancy of men is shorter than in Japan, which would result in slightly higher disease burden estimates.

Information on the age at death and the life expectancy of fatal cases is also important when estimating the productivity losses and the indirect health care costs that would have been made in the remaining life-years if the illness would not have been fatal.

Disability weights for non-fatal outcomes
Disability weights reflect the health impact of a condition and they are based on the preferences of a panel of judges. Ideally, the disability weights used in DALY calculations reflect the preferences of the society under study. In the elicitations of disability weights, there are several aspects to consider, including:

The magnitude of the scale. In this project the disability weights range between 0, reflecting the best possible health state, and 1, reflecting the worst possible health state. This in contrast to some studies, which allow disability weights greater than 1, reflecting conditions that are considered worse than dying.

Whose values? Ideally, disability weights based on preferences of the general public are used in burden of disease studies aimed to inform policy making at the national or international level. Disability weights based on elicitation panels consisting of lay persons are increasingly becoming available. Previous work has depended on panels of medical professionals. Preferences of patients who actually suffer from the disease are biased because of coping behaviour. The international transferability of disability weights is also of concern. A study in Western Europe [168] concluded that there was ‘a reasonably high level of agreement on disability weights in Western European countries with the VAS and TTO methods, but a lower level of agreement with the PTO method’. However, a recent study [169] concluded that ‘meaningful differences exist in directly elicited TTO valuations of EQ-5D health

states between the US and UK general populations'. Hence, disability weights are ideally based on specific elicitations for the population under study, but this may be very difficult to realize for the EU.

Preference measurement methods. Several preference measurement methods are available for panel elicitation, including the standard gamble (SG), time trade-off (TTO), person trade-off (PTO) and visual analogue scale (VAS). All methods give different results (VAS > TTO > PTO > SG), but they are highly correlated. The SG and VAS are not considered informative because they are only sensitive to severe disease (SG) or very sensitive to mild diseases (VAS) leading to compression at either end of the scale. Additionally, the VAS is not choice-based because it does not allow a trade-off. The TTO and PTO methods are generally used.

Annual or period profiles. For chronic diseases, most descriptions are based on the impact of a disease in the course of a year. However, many infectious diseases have a rapid course, and consequently the disability weight can be assessed by focusing on the phase of acute disease only (period profile) or by focusing on a year in which an episode of acute illness is experienced (annual profile). Both methods have been used and using the annual profile may overvalue disability weights [170]. In practice, large differences may be found between these two methods for diseases that have a high incidence but low severity (e.g. norovirus-associated gastro-enteritis). For such diseases, using annual profiles may lead to very high estimates of disease burden. Following earlier work on foodborne infections, in this project period profiles were used.

Age-weighting

In the original GBD project, age-weighting was applied to reflect the fact that individuals have different roles and changing levels of dependency and productivity with age. Therefore it may be appropriate to consider valuing the time lived at a particular age unequally [171-173]. Age-weighting is highly debated. Although the principle of age-weighting makes sense, the exact quantitative implementation is controversial [174]. In this project, age-weighting will not be applied. The disease burden estimate of the current study reflects solely the impact of illness and premature death on public health, independent of any other factors. However, the fact that individuals have different roles and changing levels of dependency and productivity with age is nevertheless not neglected in this study, but is taken into account in the cost-of-illness estimate, which we consider more relevant. Furthermore, the cost-of-illness estimates allow, in comparison to disease burden, not only a distinction of changing levels of dependency and productivity with age, but they allow also to distinguish, if required, age-dependent resource requests of any kind.

Cost categories

There are several ways to split up the costs related to illness, and depending on the economic evaluations' perspective taken, all categories, or only some of the categories will be considered. Taking the payers perspective, there are four possible categories: 1) direct health care costs paid by health insurances and public health authorities; 2) indirect health care costs paid by health insurances and public health authorities; 3) costs paid by patients themselves; and 4) (indirect) costs paid by stakeholders in the society other than the health insurances/ public health authorities or the patients.

The first category includes the valuation for medical services such as general practice (GP) consultations, specialists' consultations, hospitalization, drugs, rehabilitation and other medical services used by the patients themselves as a consequence of the illness acquired. In most European countries, the largest part of these costs would be covered by health insurances, if the patient is insured. However, in some countries, co-payments of patients for some medical services may be required.

Indirectly related health care costs would comprise the future savings in health care costs in the YLLs.

Travel costs of patients, informal care, adjusting houses for disabled patients, additional diapers in case of gastroenteritis of infants, and other co-payments paid by patients are some examples of costs that are directly related to the illness, but that occur outside the health care sector, and are mostly paid by the patients themselves and/or by social security plans.

In the fourth category all types of costs occurring in other sectors than the health care sector would be considered. Most of these costs are indirectly related to the illness. Productivity losses due to work absence of patients and/or third persons taking care of sick people are the major costs in this category. Production losses could be the consequences of: a) temporary absence from work; b) permanent or long-term disability; and c) premature mortality. Apart from productivity losses, both from paid and unpaid work, there are other costs such as the costs for special education or re-education after having been disabled due to illness. Costs for monitoring and follow-up of (foodborne) outbreaks are also included in this category.

In this project we considered the categories 1), 3) and 4) but not 2) (indirect health care costs). This last category is hardly ever considered in cost studies. Reasons for exclusion are primarily ethical considerations, and also lack of data.

Differences in cost-of-illness valuations

Apart from the evaluation of productivity losses, there exist only few differences in the valuation of health care costs, patient costs or any other costs occurring. The main differences for these types of cost categorization are caused by differences in the different health care systems (e.g. consulting a specialist directly, or only after being referred by GP; needing a medical referral after one, three or ten days, etc.).

In the case of productivity loss, there are currently two methods in use, the human capital approach and the friction cost approach. The human capital approach, which is based on neoclassical labour theory, estimates the value of *potential* lost production (or the potential lost income) as a consequence of disease. In the case of permanent disability or premature death at a specific age the total productivity value (or income) from that age until the age of retirement is counted as productivity loss. But according to Koopmanschap et al. [175], the real production losses for society are smaller. The aim of the friction cost approach is to adjust the human capital estimates of productivity costs for the compensations that are likely to occur as a result of a labour market [176]. The friction cost method considers only production losses for the period needed to replace a sick, invalid or dead worker, the 'friction period' [177]. The friction cost method takes explicitly into account the economic processes by which a sick, invalid or dead person can and will be replaced after a period of adaptation [178]. The length of the friction period depends on the situation of 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. The friction cost method places a zero value on

persons outside the labour market, such as children aged 15 or younger and retirees of 65 years and older.

In the current project we chose the friction cost method, following the Dutch guidelines for farmaco economic evaluation [162, 179].

Productivity loss
Apart from the age at death, additional information on work relation and salary of the individuals is required. However, this information is often not available. Therefore, in the current project we used estimated productivity losses for an average Dutch (working) person in the working life of a specific age as given in Oostenbrink et al. [162] for the year 2005, increasing these costs by using the Dutch consumer price index.

Resources used, the quantity demanded and the cost per resource unit used
Ideally, data with respect to resources used, their quantity demanded, and the costs per resource unit should be available for all relevant levels of the surveillance pyramid. In this project information on resources used and the quantity demanded were collected from incidental studies such as SENSOR and NIVEL and case-control studies, as well as from surveillance data. If there were no Dutch data available, information was gathered from published literature, and if these data were not available either, experts were consulted and scenario analysis was conducted. In this project, we used solely Dutch prices for the cost price per resource unit, following wherever possible the recommended prices given in the Dutch guidelines [162].

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