National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Disease burden and cost-of-illness of food-related pathogens in the Netherlands

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M.J.J. Mangen et al.

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RIVM Report 330331007/2013

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This investigation has been performed by order and for the account of the Ministry of VWS, the department of Nutrition, Health protection and Prevention, within the framework of Project 5.2.1

Abstract

Cost-of-illness of food-related pathogens in the Netherlands, 2011

The Ministry of VWS has requested RIVM to present the cost-of-illness caused by fourteen food-related pathogens; this is done annually since 2011. These pathogens can be transmitted by food, the environment, animals and humans. In 2011, the costs of these 14 pathogens are estimated at 416 million euro. Most diseases are caused by norovirus, Campylobacter bacteria and rotavirus, they also cause the highest costs. The costs per patient are highest for the bacterium *Listeria monocytogenes,* the protozoan parasite *Toxoplasma gondii* and hepatitis E-virus, because these cause relatively severe diseases.

Subdivision of costs of foodborne illness
More than 40% of all costs-of-illness can be attributed to food (168 million euro per year). The other costs can be attributed to exposure from humans (28%), the environment (15%) and animals (7%), while 9% were travel-related.

The costs of foodborne infection have been specified more in detail. Products of animal origin account for 86 million per year (or 51% of the costs attributed to food) per year. Fish, fruit and vegetables, beverages, grains and other foods account for 8%, 6%, 2% 5% and 14% of the costs attributed to food, respectively. Human and animal contamination of foods accounts for 14% of the costs attributed to food.

Subdivision of cost types
The researchers have subdivided the costs of the 14 pathogens in three categories. First, there are costs for doctor's fees, hospitalisations and medicines, the so-called direct healthcare costs. They account for less than 25% of all costs. Costs paid by patients, such as travel costs to and from the doctor, are called direct non-healthcare costs. These are low. Productivity losses due to work absence of patients and special education as a consequence of neurological disease are called indirect non-healthcare costs. These are substantial and amount up to 75% of the total costs.

Keywords: food-related pathogens, costs, cost-of-illness, direct healthcare costs, indirect non-healthcare costs

Rapport in het kort

Maatschappelijke kosten van via voedsel overdraagbare pathogenen in Nederland in 2011

Op verzoek van het ministerie van VWS onderzoekt het RIVM de maatschappelijke kosten van 14 ziekteverwekkers; vanaf 2011 wordt dit jaarlijks in kaart gebracht. De infecties die de ziekteverwekkers veroorzaken, kunnen worden overgedragen via voedsel, de mens, het milieu of dieren (zoönosen). De geschatte kosten van de 14 ziekteverwekkers bedroegen in 2011 416 miljoen euro. De meeste mensen worden ziek van een besmetting met het norovirus, de *Campylobacter*-bacterie en het rotavirus waardoor deze de hoogste kosten met zich meebrengen. Als naar de kosten per patiënt wordt gekeken, zijn deze het hoogst bij een besmetting door de bacterie *Listeria monocytogenes*, *de* parasiet *Toxoplasma gondii*, en het hepatitis E-virus omdat deze relatief ernstige ziekteverschijnselen veroorzaken.

Onderverdeling kosten van voedselinfecties
Meer dan 40 procent van de totale kosten die de onderzochte ziekteverwekkers met zich meebrengen wordt via voedsel veroorzaakt (168 miljoen euro in 2011). De overige kosten worden toegeschreven aan de overdracht van mens op mens (28 procent), blootstelling via het milieu (15 procent) of via contacten tussen dieren en mensen (7 procent). De resterende 9 procent van de kosten is gerelateerd aan reizen naar het buitenland.

De kosten van voedselinfecties zijn nader gespecificeerd. Ruim de helft (51 procent oftewel 86 miljoen euro) van de kosten van voedselinfecties worden veroorzaakt door producten van dierlijke oorsprong, zoals vlees, eieren en zuivelproducten. Vis, fruit en groenten, dranken, graanproducten en andere niet-gespecificeerde voedselgroepen veroorzaken respectievelijk 8, 6, 2, 5 en 14 procent van de ziektekosten toegeschreven aan voedsel.

Onderverdeling soorten kosten
De onderzoekers hebben de maatschappelijke kosten van de 14 ziekteverwekkers onderverdeeld in drie categorieën. Ten eerste zijn er de kosten voor consulten aan artsen, ziekenhuisopnamen en medicijnen, de ‘directe medische kosten’. Deze bedragen minder dan 25 procent van alle kosten. Daarnaast bestaan ze uit kosten die door de patiënt zelf worden betaald, zoals reiskosten van en naar de arts (directe niet-medische kosten). Deze zijn laag. Als derde post zijn er de kosten die voortvloeien uit productiviteitsverliezen vanwege werkverzuim van de patiënten en speciaal onderwijs na neurologische aandoeningen (indirecte niet-medische kosten). Deze post is het meest substantieel en bedraagt bijna 75 procent van de totale kosten

Trefwoorden: voedselgerelateerde ziekte, kosten, ziektekosten, direct medische kosten, indirect niet-medische kosten

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Summary

Cost-of-illness of food-related pathogens in the Netherlands, 2011

Since 2008, RIVM regularly publishes estimates of the incidence, burden and costs of 14 food-related pathogens on its web pages. Using incident case data from 2011, the total costs-of-illness of fourteen food-related pathogens and associated sequelae were estimated at € 468 million, if undiscounted, and at € 416 million if discounted by 4%. Direct healthcare costs accounted for 24% of the total costs, direct non-healthcare costs for 2% and indirect non-healthcare costs for 74% of the total costs. At the population level norovirus, with € 106 million, had the highest total cost-of-illness, followed by *Campylobacter* spp.(€ 76 million) and rotavirus (€ 73 million). However, when considering only direct healthcare costs, then Campylobacter infections would cause the highest costs at the population level with € 27 million, followed by *Toxoplasma gondii* (€ 20 million) and rotavirus (€ 12.5 million). Cost-of-illness per infected case varied between € 150 for *Clostridium perfringens* to € 275,000 for perinatal listeriosis.

More than 40% of all costs-of-illness can be attributed to food, in total € 168 million per year. Beef, lamb, pork and poultry meat alone account for 39% of these costs. Foods of animal origin (meat products together with eggs and dairy products) account for € 86 million (or 51% of the costs attributed to food).

Staphylococcus aureus intoxications accounted for the highest share of costs attributed to food (€ 47.1 million), followed by *Campylobacter* spp. (€ 32.0 million) and norovirus (€ 17.7 million).

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The authors acknowledge the valuable input of earlier cost-of-illness work by Luqman Tariq, Bart van der Zande and Sylvia Vijgen, as well as the valuable input from all the people involved when setting-up the different outcome trees and incidence estimates. These are in particular Juanita Haagsma, Jeanet Kemmeren, Linda Verhoef and Yvonne van Duynhoven.

1 Introduction

The Dutch Ministry of Health, Welfare and Sports wishes to focus its food safety policy on the most relevant pathogens as a basis for effective and efficient decision making on control, prevention and surveillance of food-related disease. Therefore, the RIVM has been asked to perform a study to establish the priority of pathogenic micro-organisms in food. Disability Adjusted Life Year (DALY) and cost-of-illness (COI) were the two criteria chosen to evaluate the priority of pathogenic micro-organisms.

DALYs are used to measure the burden of illness due to morbidity and mortality related to the pathogens under study by integrating incidence data with indices of severity and duration (for details see Havelaar, Haagsma et al. (2012)). Cost-of-illness studies measure the costs related to the resources used within the healthcare sector (also referred to as direct healthcare costs (DHC)), the resources used by patients and their family (also referred to as direct non-healthcare costs (DNHC)), and productivity losses due to work absence of patients and caregivers and other non-health care costs indirectly related to illness (also referred to as indirect non-healthcare costs (INHC)).

In this report we present in Chapter 2 the models of disease process for the fourteen pathogens and associated sequelae. In Chapter 3 we show the incidence estimates for the year 2011 for the fourteen pathogenic micro-organisms that form the basis for the COI estimates. In Chapter 4 we present and discuss the estimated associated cost-of-illness for these fourteen pathogenic micro-organisms for the year 2011, describing the applied method and the underlying assumptions.

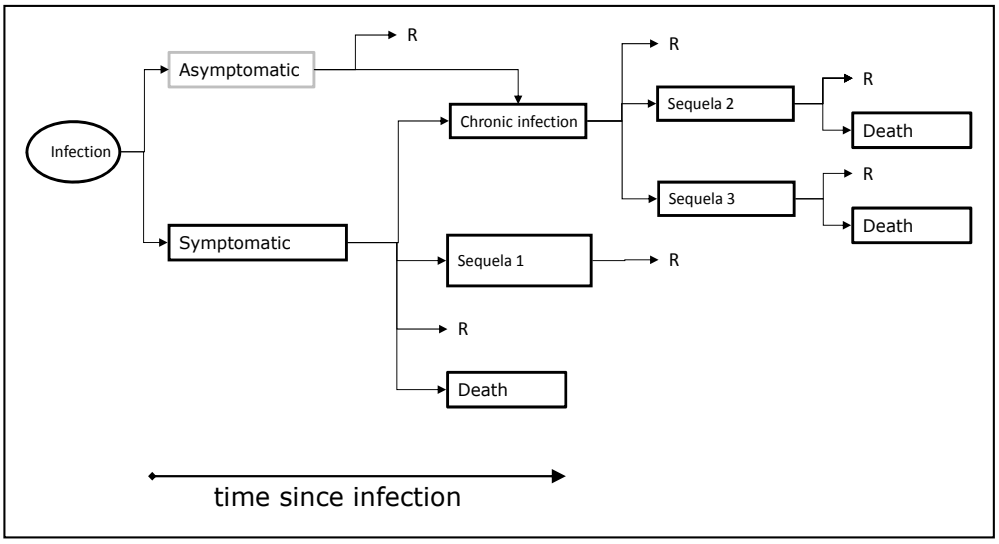
DALY estimates for the year 2011 are presented in a separate report by Bouwknegt et al. (2013).

2 Food-related pathogens

2.1 General

In order to assess the burden of disease and the cost of illness for the various pathogens under study, the disease outcomes following infection needs to be defined. Therefore, for each pathogen, a separate model of the disease process was designed, resulting in fourteen outcome trees. Each block in an outcome tree (see Figure 1) represents a health outcome with or without further separation of health states (see Box 1). Transition probabilities between all blocks were established. In this study the incidence and pathogen-based approach was used to estimate both the disease burden and the cost-of-illness (ECDC, 2010).

Figure 1: Generalized outcome tree (Source: ECDC, 2010)



Box 1 – Health outcome and health states

For example, the health outcome gastro-enteritis (GE) might be further split into three health states (ECDC, 2011), namely mild GE symptoms (i.e. patients not requiring medical services); moderate GE symptoms (i.e. patients consulting a general practitioner) and severe GE symptoms (i.e. hospitalized patients), all health states of the health outcome GE.

2.2 The pathogens under study

We estimated the costs, similar to Havelaar et al. (2012), for seven pathogens causing infectious gastroenteritis (GE), including three bacteria (thermophilic *Campylobacter* spp., Shiga-toxin producing *Escherichia coli* O157 (STEC O157), nontyphoidal *Salmonella* spp.), two viruses (norovirus and rotavirus) and two protozoa (*Cryptosporidium* spp., *Giardia* spp.); three GE toxinproducing bacteria (*Bacillus cereus*, *Clostridium perfringens* and *Staphylococcus aureus*), and four pathogens causing systemic infections (*Listeria monocytogenes*, hepatitis A virus, hepatitis E virus, *Toxoplasma gondii*). 'These pathogens are chosen because of data availability and because preliminary analysis indicates they

cause the highest burden of foodborne disease in the Netherlands' (Havelaar et al., 2012).

Acute gastroenteritis (GE) is in most cases self-limiting within a few days to weeks. For few patients the disease is fatal. Among the pathogens under study, apart from GE, no other illness was assumed to be related to norovirus, rotavirus, *Cryptosporidium* spp., *Giardia* spp., *Bacillus cereus* toxin, *Clostridium perfringens* toxin or *Staphylococcus aureus* toxin infections in humans. *Campylobacter* spp., Shiga toxin-producing *Echerichia coli* O157 (STEC O157) and *Salmonella* spp. infections however, do result in sequelae. Irritable bowel syndrome (IBS) is the most significant sequela occurring after salmonellosis and campylobacteriosis (Haagsma et al., 2010). Reactive Arthritis (ReA), an acute aseptic arthritis triggered by an infection elsewhere in the body, is a sequela occurring after salmonellosis and campylobacteriosis. Guillain-Barré syndrome (GBS), a neurological disease frequently preceded by an acute infectious illness and affecting at least the motoric, sensory and autonomic nerves supplying the limbs, is a sequela occurring after campylobacteriosis (Mishu et al., 1993; Jacobs et al., 1998; Poropatich et al., 2010). Crohn's disease and ulcerative colitis, collectively classified as inflammatory bowel disease (IBD), is a chronic intestinal disorder of unknown aetiology and is a sequela occurring after campylobacteriosis and salmonellosis (Helms et al., 2006). Post-diarrheal haemolytic uremic syndrome (HUS) and end stage renal disease (ESRD) are sequelae associated with STEC (Havelaar et al., 2004). In the current study we considered only STEC O157, but other subtypes can become more important in the future. The frequency of other post-infectious complications following GE is low and they were therefore disregarded in the current study.

Symptoms of a hepatitis A virus (HAV) and hepatitis E virus (HEV) infections in young children are often mild flu-like symptoms without icteric symptoms, whereas in adults frequently reported symptoms are jaundice, dark urine, fatigue, loss of appetite, abdominal pain and light-coloured stool lasting for several weeks (Koff, 1992). Post-complications like fulminant hepatitis, which might in very rare cases result in liver transplantation, are rare and therefore not considered (Havelaar et al., 2012) when estimating the disease burden, and are also not considered in current cost estimations.

Listeriosis is potentially life-threatening for risk groups like neonates, elderly (especially with co-morbidity) and patients with impaired cell-mediated immunity. Manifestations of acquired listeriosis are meningitis, septicemia, pneumonia, and gastroenteritis. Infections in previously healthy individuals are usually mild and self-limiting, but for some the disease is fatal. Further, a proportion of non-fatal cases with meningitis will develop neurological sequelae. Infection of pregnant women may lead to abortion or premature labour. Infection in newborns (so-called perinatal listeriosis) may lead to severe systemic infection, mainly meningitis with or without sepsis, which may result in death or long-term neurological sequelae (Havelaar et al., 2012).

An infection with *Toxoplasma gondii*, if 'acquired' (i.e. not perinatal), is in most cases asymptomatic and self-limiting (Rorman et al., 2006). Chorioretinitis is the most frequent reported symptom in immune-competent patients infected by *Toxoplasma gondii* and therefore considered in the current cost estimations (Burnett et al., 1998; Gilbert et al., 2008; Commodaro et al., 2009). Not considered were more severe forms of illness such as encephalitis, as they do occur only rare and mostly in immune-compromised patients (Rorman et al.,

2006). Also not considered were the less severe or aspecific symptoms such as chronic fatigue, malaise and lymphadenopathy.

Vertical transmission of *Toxoplasma gondii* from a newly infected pregnant woman to her foetus may lead to congenital toxoplasmosis (Rorman et al., 2006). Congenital toxoplasmosis can result either in asymptomatic infections, with or without developing symptoms later in life: mostly chorioretinitis (referred hereafter as post-1-year chorioretinitis) or mild to severe clinical symptoms at birth i.e. chorioretinitis, intracranial calcifications, central nervous system (CNS) abnormalities and hydrocephalus, some of them being fatal (so-called neonatal deaths) (Rorman et al., 2006; Havelaar et al., 2007; Kortbeek et al., 2009; Havelaar et al., 2012). Foetal infection may also result in natural abortion and stillbirth (Rorman et al., 2006) resulting in medical consultations of the affected women.

For each of the fourteen food-related pathogens, disease outcomes in relation to the different pathogen-specific gastroenteritis and pathogen-specific systemic infections respectively, had to be defined. A detailed description of the method and the underlying assumptions for outcome trees and transition probabilities are given in Havelaar et al. (2012).

The disease outcomes considered represent the state-of-the-art in 2011. However, new scientific knowledge becoming available in the future might result in the reconsideration of the different outcome trees of the pathogens under study, and the inclusion of additional disease outcomes linked to these pathogens.

3 Incidences estimates for 2011

The incident cases for 2011 in the Netherlands as estimated by Bouwknegt et al. (2013) are presented in the following Tables. The underlying methodology is described in Havelaar et al. (2012). These incident cases formed the input for the COI estimations presented in the following chapter. Incident cases of gastroenteritis by pathogen, and of non-gastrointestinal pathogens in the Netherlands are presented in Table 1 and Table 2 respectively, whereas Table 3 presents the incidence of sequelae by pathogen in the Netherlands.

Table 1. Incidence of gastroenteritis by pathogen in the Netherlands, 2011 (Source: Bouwknegt et al., 2013)

Pathogen	**General population (x 1,000)**	**GP visit (x 1,000)**	**Hospitalised (x 1,000)**	**Fatal cases**
All causes	4,810[†]	221	22.5	NA[#]
	3,995-5,705[‡]	73-511		
Bacteria – infectious				
Campylobacter spp.	108	26	1.1	34
	33-271	13-47	0.4-2.2	21-51
STEC O157	2.1	0.3	0.02	1
	0.22-8.8	0.01-0.9	-	0-3
Salmonella spp.	37	5.6	1.1	35
	6.5-107	3.0-9.3	0.5-2.2	30-39
Bacteria – toxin producing				
Bacillus cereus	51	7.0	0.2	0
	19-111	1.7-18	0.07-0.5	
Clostridium	171	31	0.3	5
perfringens	63-357	7.4-81	0.1-0.6	0-19
Staphylococcus aureus	292	41	1.5	7
	135-531	12-95	0.6-2.9	0-30
Viruses				
Norovirus	694	17	2.0	65
	481-988	9.6-27	1.1-3.3	29-121
Rotavirus	301	19	5.9	45
	157-528	12-28	4.4-7.8	15-97
Protozoa				
Cryptosporidium spp.	28	1.7	0.6	2
	10-67	0.8-3.1	0.2-1.2	0-8
Giardia spp.	64	5.7	0.4	2
	36-118	2.9-10	0.04-1.4	0-7

Note: [†]mean; [‡] 2.5-97.5 percentile; [#] not available.

Table 2. Incidence of non-gastroenteritis pathogens in the Netherlands, 2011 (Source: Bouwknegt et al., 2013)

Pathogen	Incidence	Fatal cases
Listeria monocytogenes		
Perinatal	9*	1*
Acquired	79*	4*
Hepatitis A virus	612†	2
	391-989‡	1-3
Hepatitis E virus	53	1
	31-81	0-1
Toxoplasma gondii		
Perinatal	364	13
	189-637	7-22
Acquired^	426	0
	203-727	

Note: * No uncertainty because cases were acquired through active surveillance; †mean; ‡ 2.5-97.5 percentile; ^ Chorioretinitis only.

Table 3. Incidence of sequelae by pathogen in the Netherlands, 2011 (Source: Bouwknegt et al., 2013)

Pathogen and sequelae	Incidence	Fatal cases
Campylobacter spp.		
Guillain-Barré Syndrome	79[†] (0-149) [‡]	2[†] (0-5) [‡]
Reactive arthritis	1,935 (829-3,919)	0
Irritable Bowel Syndrome	9,350 (2,668-24,150)	0
Inflammatory Bowel Disease	23 (16-31)	0
STEC O157		
Haemolytic Uremic Syndrome	22 (15-30)	2 (1-5)
End-Stage Renal Disease	3 (1-5)	1 (1-1)
Salmonella spp.		
Reactive arthritis	458 (163-954)	0
Irritable Bowel Syndrome	3,125 (468-9,440)	0
Inflammatory Bowel Disease	8 (6-11)	0
Listeria monocytogenes (perinatal)		
Meningitis	8[*]	NA
Neurological sequelae of meningitis	4 (2-5)	0
Listeria monocytogenes (acquired)		
Meningitis	22 (18-26)	NA
Neurological sequelae of meningitis	3 (2-5)	0
Toxoplasma gondii (perinatal)		
Chorioretinitis 1st year of life	49 (25-87)	NA
Chorioretinitis later years of life	59 (31-103)	NA
Intracranial calcifications	38 (19-69)	NA
Hydrocephalus	7 (3-14)	NA
Central Nervous System Abnormalities	10 (2-29)	NA
Toxoplasma gondii (acquired)		
Chorioretinitis	426 (203-727)	0

Note: [†]mean; [‡] 2.5-97.5 percentile; [*] No uncertainty because cases were acquired through active surveillance; NA Not applicable.

4 Cost-of-illness

4.1 General approach

Cost-of-illness studies measure the costs related to the resources used within the healthcare sector (also referred to as direct healthcare costs (DHC)), the resources used by patients and their family (also referred to as direct non-healthcare costs (DNHC)), and productivity losses due to work absence of patients and caregivers and other non-health care costs indirectly related to illness (also referred to as indirect non-healthcare costs (INHC)) (Hakkaart - van Roijen et al., 2010). Apart from those three categories, no other costs were considered in the current study.

In the current study we estimated the COI for the year 2011, using both the third payer (i.e. DHC) and the societal perspective (i.e. DHC, DNHC and INHC). Unit cost prices, where necessary, were updated to 2011 using the consumer price index of Statistics Netherlands (Statistics Netherlands, 2012).

In accordance with the Dutch guidelines for health economic evaluations (Hakkaart - van Roijen et al., 2010), this study did not consider indirect healthcare costs. Indirect healthcare costs would comprise the future savings in healthcare costs in the life years lost due to premature death.

Costs in future years were discounted with a rate of 4%[1], according to Dutch guidelines (Hakkaart - van Roijen et al., 2010).

4.1.1 Direct healthcare costs (DHC)

The DHC category included valuation for medical services such as general practice (GP) consultations, specialists consultations, hospitalization, drugs, rehabilitation and other medical services. DHC costs were estimated for each pathogen separately, the total direct healthcare costs were estimated by accumulating the costs for the different medical services for all illnesses including sequelae resulting from an infection and for all disease severity states related to this pathogen.

For each health outcome/health state (l) of that specific disease and for each specific medical service, the direct healthcare costs related to a specific pathogen were estimated by multiplying the number of cases requiring healthcare service (m) by the required healthcare service units per case (p) and by the costs per healthcare service unit (mc). All three factors may be age-dependent with a from 0 until a_{max}.

The formula for direct healthcare costs for a specific pathogen for health outcomes/health states l and for healthcare service i are in basic notation:

[1] Discounting is multiplying a cost-estimate by a discount rate to calculate its present value (the 'discounted value'). It is the opposite of 'putting money in a bank account' where interest rates are used in determining how an investment will grow on a monthly or yearly basis. For example, € 1,000 on a savings account at an annual interest rate of 10 percent will increase in five years total to € 1,610.51. Conversely, the present value of € 1,610.51 realized after five years of investment is € 1,000 when discounted at an annual rate of 10 percent.

$$DHC = \sum_{a=0}^{a=max} \left[\sum_{l} \left(\sum_{i} [m_i^a * p_i^a * mc_i^a)] \right)_l \right]$$

4.1.2 Direct non-healthcare costs (DHC)

Direct non-healthcare care costs are costs paid by the patients themselves. They are therefore also sometimes referred to as ´patient costs´. Travel costs of patients, costs for additional diapers, informal care and out-of-pocket costs for over-the-counter medication and other co-payments by patients are some examples of direct non-healthcare (DNHC) costs. DNHC costs were estimated for each pathogen separately. For each health outcome/health state (l) of a specific pathogen and for each specific non-healthcare service (j), DNHC costs related to a specific pathogen were estimated by multiplying the number of cases requiring non-healthcare service (r) by the required non-healthcare service units per case (q) and by the costs per non-healthcare service unit (rc). All three factors may be age-dependent a.

The formula for DNHC costs for a specific pathogen for health outcomes, respectively health states l and for non-healthcare service j are in basic notation:

$$DNHC = \sum_{a=0}^{a=max} \left[\sum_{l} \left(\sum_{j} [r_j^a * q_j^a * rc_j^a)] \right)_l \right]$$

4.1.3 Indirect non-healthcare costs (INHC)

Indirect non-healthcare costs (INHC) are mainly production losses for the society due to disease, but costs for special education as a consequence of disease (e.g. disabled children as a consequence to a perinatal listeriosis infection) are another example of INHC costs and, where applicable, therefore considered in the current study.

Production losses were considered if patients were absent from work due to illness or if caregivers were absent from work in order to take care of a sick patient. Based on the Dutch economic guidelines (Hakkaart - van Roijen et al., 2010), production losses due to absenteeism were considered for both paid and unpaid work. Unpaid work would be for example grandparents taking care of their grandchildren, but also other charity work. Production losses could be the consequences of:

- temporary absence from work;
- permanent or long-term disability; and
- premature mortality.

If information was available, we considered for paid work all three categories using the friction cost method. In this method, production losses are only considered for the period needed to replace a sick, invalid or dead worker, the so-called 'friction period' (Koopmanschap and Van Ineveld, 1992; Koopmanschap et al., 1995). This method takes into account the economic processes that ensure a sick, invalid or dead person can and will be replaced after a period of adaptation (Koopmanschap and Van Ineveld, 1992). The duration of the friction period depends on the situation of the labour market. A high unemployment rate generally allows fast replacement, whereas in the case of a low unemployment rate, on average more time is needed to find someone in the labour market that could fill the position. We assumed for 2011 a friction

period of 23 weeks, similar to the one reported for 2009 by Hakkaart - van Roijen et al., 2010.

For each health outcome/health state (l) of that specific disease and for each specific indirect non-healthcare service (k), INHC costs were estimated by multiplying the number of cases requiring indirect non-healthcare service (s) by the required indirect non-healthcare service units per case (u) and by the costs per indirect non-healthcare service unit (v). All three factors may be age-dependent (a).

The formula for INHC costs are in basic notation:

$$INHC = \sum_{a=0}^{a=max} \left[\sum_{l} \left(\sum_{k} [s_k^a * u_k^a * v_k^a)] \right)_l \right]$$

4.1.4 General

In order to calculate the COI for the different health outcomes, data on the number of cases per age-group, the resources used, the volumes for use of resources and the actual economic cost price of each of these resource units were necessary. We needed the information per age group, because of differences in resources use (e.g. sickness leave) and type of costs (e.g. hospital costs; production loss) by age. Dutch prices were used where available and are summarized in Table 4. Disease-specific costs are listed in the following sections. Some general assumptions were made for travelling and sickness leave of patients and caregiver, and are summarized in section 4.1.4.1. These assumptions were used if there were no disease-specific details available. Disease-specific details on assumptions made for the different cost categories are given in the following chapters.

For IBD, IBS, HUS and ESRD, the associated costs were derived from Dutch studies (Goettsch et al., 2004; Tariq et al., 2011; Van der Valk et al., 2012) and where necessary indexed to the year 2011.

Table 4. Unit costs in 2011 €

	Unit cost (€)	Source
Direct healthcare costs		
Delivery fee for pharmacy (per medication)	5.70	Hakkart-van Roijen et al. (2010)
Additional fee for first time delivery	3.11	Hakkart-van Roijen et al. (2010)
General practitioner		
visit (per consultation)	29.02	Hakkart-van Roijen et al. (2010)
house visit (per consultation)	44.57	Hakkart-van Roijen et al. (2010)
phone call (per consultation)	14.51	Hakkart-van Roijen et al. (2010)
Outpatient clinic visit (weighted mean; per consultation)	74.62	Hakkart-van Roijen et al. (2010)
Emergency department visit (per consultation)	156.50	Hakkart-van Roijen et al. (2010)

Table 4. Unit costs in 2011 € (suite)

	Unit cost (€)	Source
Direct healthcare costs (suite)		
Hospital admission adults (weighted mean, per day)	473.65	Hakkart-van Roijen et al. (2010)
Hospital admission children (weighted mean, per day)	615.75[a]	Hakkart-van Roijen et al. (2010)
Intensive care unit (per day)	2,262.55	Hakkart-van Roijen et al. (2010)
Revalidation – inpatient (per day)	352.39	Hakkart-van Roijen et al. (2010)
Revalidation (per hour)	114.01	Hakkart-van Roijen et al. (2010)
Physiotherapy (per visit / per 0.5 hour)	37.31	Hakkart-van Roijen et al. (2010)
Mentally and physically disabled institutional care (per day)	246.67	Hakkart-van Roijen et al. (2010)
Elderly nursing home (per day)	246.67	Hakkart-van Roijen et al. (2010)
Transport by ambulance to hospital – urgent (per trip)	522.37	Hakkart-van Roijen et al. (2010)
Transport by ambulance to e.g. revalidation centre / nursing home (per trip)	251.85	Hakkart-van Roijen et al. (2010)
Direct non-healthcare costs		
Car/public transport (per km)	0.21	Hakkart-van Roijen et al. (2010)
Parking fees (per visit)	3.11	Hakkart-van Roijen et al. (2010)
Indirect non-healthcare costs		
Additional cost for special education		
for primary school & kindergarten (per student/year)	17,400	Ministerie van Onderwijs Cultuur en Wetenschap (2011a,b)
for secondary school (per student/year)	22,158	Ministerie van Onderwijs Cultuur en Wetenschap (2011a,b)
Productivity loss (PL) due to work absence from unpaid work		
for work absence from unpaid work (per hour)	12.96	Hakkart-van Roijen et al. (2010)
Productivity loss due to work absence from paid work		
for average working person (per hour)	31.11	Hakkart-van Roijen et al. (2010)
for average working woman (per hour)	26.88	Hakkart-van Roijen et al. (2010)
for average working parenting caregiver (per hour)	27.20[b]	Hakkart-van Roijen et al. (2010)

Table 4. Unit costs in 2011 € (suite)

	Unit cost (€)	Source
Productivity loss due to work absence from paid work		
for working person between 15-19 years (per hour)	9.61	Hakkart-van Roijen et al. (2010)
for working person between 20-24 years (per hour)	18.15	Hakkart-van Roijen et al. (2010)
for working person between 25-29 years (per hour)	24.80	Hakkart-van Roijen et al. (2010)
for working person between 30-34 years (per hour)	29.85	Hakkart-van Roijen et al. (2010)
for working person between 35-39 years (per hour)	33.43	Hakkart-van Roijen et al. (2010)
for working person between 40-44 years (per hour)	35.16	Hakkart-van Roijen et al. (2010)
for working person between 45-49 years (per hour)	36.14	Hakkart-van Roijen et al. (2010)
for working person between 50-54 years (per hour)	36.91	Hakkart-van Roijen et al. (2010)
for working person between 55-59 years (per hour)	37.70	Hakkart-van Roijen et al. (2010)
for working person between 60-64 years (per hour)	37.74	Hakkart-van Roijen et al. (2010)
Productivity loss for a fatal case		
between 15-19 years (per death)	1,211[c]	Hakkart-van Roijen et al. (2010)
between 20-24 years (per death)	6,461[c]	Hakkart-van Roijen et al. (2010)
between 25-29 years (per death)	13,381[c]	Hakkart-van Roijen et al. (2010)
between 30-34 years (per death)	17,019[c]	Hakkart-van Roijen et al. (2010)
between 35-39 years (per death)	18,315[c]	Hakkart-van Roijen et al. (2010)
between 40-44 years (per death)	19,018[c]	Hakkart-van Roijen et al. (2010)
between 45-49 years (per death)	19,715[c]	Hakkart-van Roijen et al. (2010)
between 50-54 years (per death)	18,659[c]	Hakkart-van Roijen et al. (2010)
between 55-59 years (per death)	16,697[c]	Hakkart-van Roijen et al. (2010)
between 60-64 years (per death)	8,458[c]	Hakkart-van Roijen et al. (2010)

Notes:

a) Children receive more intensive care than adults. We therefore assumed the costs for children are about 1.3 times higher than for adults, based on Hoogendoorn et al. (2004).

b) Apart from single father households, we assumed in all other households the mother is the primary caregiver. According to Statistics Netherlands (2012) there were in 2011 about 2.9% single father households, 12.9% single mother households and 84.4% two-parent households (Mol, 2008; Statistics Netherlands, 2012).

c) Productivity losses for fatal cases were estimated assuming a friction period of 23 weeks (Hakkart-van Roijen et al., 2010). Furthermore, productivity losses were based on average working hours as reported by Statistics Netherlands (2012) in the corresponding age-group, but corrected by 18% for bank holidays, vacation, schooling etc. (Hakkaart - van Roijen et al., 2010) and corrected for the proportion of the non-working population in the specific age-group. Productivity losses were corrected for the proportion not working in the corresponding age-group (Statistics Netherlands, 2012).

4.1.4.1 General assumptions

4.1.4.1.1 Travel costs

Information on travelling to and from healthcare providers is scarce, and assumptions had to be made. We assumed, similar to Mangen et al. (2005), that no additional travelling was required in order to buy over-the-counter medicines. Medicines on prescription were assumed to be bought in a pharmacy on the way back from the GP (no additional travel costs). Travel costs were only considered when visiting a doctor, a healer, a physiotherapist or equivalent, when having an outpatient consultation and when being hospitalized. Based on Friesema et al., 2012 we assumed 77% and 97% of the persons younger than 15 years and 15 years and older respectively, would use either a car or public transport when visiting a GP, a healer or a physiotherapist. In the case of hospitalization 97% of persons younger than 15 years were assumed to be transported to the hospital by using either a car or public transport (Friesema et al., 2012). For patients older than 15 years we assumed 100% would be transported to the hospital by using either a car or public transport. When travelling by car or public transport, we assumed half of the patients would have taken a car and the other half would have used public transport. For the costs calculations we used average distances as reported in Hakkaart - van Roijen et al. (2010) and the unit cost prices as listed in Table 4.

4.1.4.1.2 Productivity losses due to absenteeism from paid work

Productivity losses from paid work of patients were, if not otherwise stated, valued using standard tariffs, according to the corresponding age-classes (see Table 4). We further assumed a productivity loss of € 27.20 per hour for caregivers of children and of € 31.11 per hour for caregivers of adults, who would be absent from paid work in order to take care of a sick child/adult patient. For unpaid work we assumed for all age-classes a productivity loss of € 12.96, for both patients and caregivers.

Sickness leave of patients

Information on duration of sickness leave of patients from paid work was not always available and assumptions had to be made. In the absence of disease-specific information, we assumed that per week of illness (being either duration of symptoms or duration of hospitalization), an average person between 15 and 64 years would be on average absent for 23,5 hours per week[2]. Additionally, we assumed an outpatient visit, a consultation with a GP or with a therapist or

[2] In 2011 74.9% of the Dutch population between 15 and 64 years had a paid job, and those with paid jobs worked on average 31.4 hours per week (Statistics Netherlands, 2012). For any average person between 15 and 64 years this corresponds to 23.5 hours/week.

healer would cause an average person between 15 and 64 years to be absent for on average 4.7, 2.4 and 1.2 hours per session respectively[3].

Sickness leave of caregivers
There was also not always information available on duration of sickness leave from paid work of caregivers for a sick person; assumptions had to be made. For the absence of caregivers from a paid job, we assumed per week of illness/hospitalization, caregivers of children from 0 to 4 years would be on average absent for 16.4 hours per week[4]. But according to the findings from the Pienter 2 study (Mollema et al., 2009), parents of children 5 years and older stay away from work for shorter periods than parents with younger children having similar symptoms (see Table 7 in section 4.2.1.3). This holds at least for mild to moderate health outcomes. We therefore assumed for health outcomes with mild and moderate symptoms that the average sickness leaves of caregivers for children 5 years and older would be equal to 50% of the sickness leave of caregivers for children 0 to 4 years with similar symptoms. For hospitalized children no age-distinction was made. We assumed a work absence of caregivers of 16.4 hours per week of hospitalization. Additionally, we assumed an outpatient visit, a consultation with a GP or with a therapist or healer would result in a 3.28, 1.64 and 0.82 hour work absence of caregivers per session, respectively[5].

For patients 65 years and older, we assumed zero work loss of caregivers in the case of mild to moderate symptoms, similar to the findings for GE patients (see section 4.2.1.3). But for severely affected and hospitalized patients we assumed, based on Friesema et al. (2012), a caregiver on average would be absent from paid work for 0.4 hours per hospitalization stay.

4.1.5 Uncertainty

Data necessary for the quantitative estimates of incident cases and the costs are often limited and/or absent, which leads to some degree of uncertainty.
Total uncertainty was therefore broken down into variability and uncertainty. Variability is defined as 'the inherent heterogeneity of a system', e.g. variations in the duration of the hospital stay of different patients. Uncertainty is usually defined as 'a lack of perfect knowledge about a factor in the model that represents the system' (Vose, 2001). Both uncertainty and variability can be expressed in a statistical distribution function, but require a different strategy to account for in the analysis.

[3] Assuming an outpatient visit, a consultation with a GP or with a therapist or healer would result in a 8, 4 and 2 hour work absence per session respectively, as they generally take place between Monday to Friday during regular working hours. But these hours are reduced to correct for the proportion of persons not working, about 25% (Statistics Netherlands, 2012), and the fact that since an average working week in the Netherlands is 31.4 hours (less than a 40-hour week) (Statistics Netherlands, 2012), then some of these consultations might have taken place outside working hours.
[4] Assuming that, except for single-father households, it would be always the mother who is the primary caregiver and would stay at home to take care of a sick child. In 2011 76% of the primary-caregiver would have paid work and those with a paid job worked on average 21.7 hours (Statistics Netherlands, 2012). For an average caregiver this corresponds to 16.4 hours/week.
[5] Assuming an outpatient visit, a consultation of a GP and of a therapist or healer would result in a 8, 4 and 2 hour work absence of caregivers per session respectively, as they generally take place between Monday to Friday during regular working hours. But correcting these hours for the proportion of caregivers not working, about 24% (Statistics Netherlands, 2012) and the fact that an average working week of a caregiver in the Netherlands is with 21.7 hours less than a 40-hour week (Statistics Netherlands, 2012), is why some of these consultations might have taken place outside working hours.

Variability cannot be reduced and is also less important from a decision making point of view and was therefore not modelled in the present study. Variable factors were represented by arithmetic means.

However, with the availability of more information on a system, the uncertainty might be reduced. For example the incidence of illness is not known but is estimated from observational data on a sample of the population. The larger the sample, the smaller the uncertainty in the incidence estimate. In the current analysis three kinds of uncertainty were distinguished:
• statistical uncertainty, due to small sample sizes;
• systematic uncertainty, due to the use of data which are not fully representative for the Dutch situation;
• uncertainty due to lack of data and the use of data from expert opinions.

Statistical uncertainty was analysed by representing uncertain parameters with an appropriate frequency distribution, followed by Monte Carlo simulation to estimate predictive intervals, as was done in the current study in particular for incident cases. Results presented are the mean, and the 95% credible intervals resulting from the stochastic simulations. Uncertainty is evaluated by Monte Carlo simulation (Analytica Professional 4.4.1, Lumina Decision Systems, Los Gatos, CA, USA; 10,000 iterations).

Scenario analysis is used to represent uncertainty due to lack of data and systematic uncertainty.

4.2 Health outcome specific assumptions

4.2.1 Gastroenteritis (GE)

4.2.1.1 Direct healthcare costs

Consultation with a GP in the Netherlands might occur either by phone, by a GP practice visit or by a house call from the GP to the patient. GP telephone consultations with the doctors' assistant were not included as consultations in the estimates of incident GE cases visiting a GP (De Wit et al., 2001b). We therefore assume per GE case visiting a GP additionally 0.97 telephone consultations would occur (De Wit et al., 2001b). A GP consultation itself is in 90% of cases a GP practice visit and in 10% of cases it would be a house call from the GP to the patient (De Wit et al., 2001b).

For hospitalized GE patients, the number of GP consultations during regular hours, GP consultations in weekends/evening hours, outpatient clinic visits and emergency department visits is slightly higher than for GE patients not requiring hospitalization and was assumed to be 1.3, 0.7, 0.4 and 0.1 for persons < 18 years, and 1.7, 0.3, 1.4 and 0.3 for persons ≥ 18 years respectively (Friesema et al., 2012).

For some patients consulting their GP, a faecal sample is submitted for laboratory testing in order to determine the etiologic agent. Doorduyn et al. (2011) reported that in 18% of all GE cases visiting a GP a faecal sample is taken. Based on Haagsma et al. (2012) we assumed a faecal sample is taken in 25% of bacteria or toxin–producing pathogens triggered GE cases visiting a GP and in 10% of virus or protozoa triggered GE cases visiting a GP. In case of hospitalization we assumed that in 100% of the cases a faecal sample would be submitted for laboratory testing (Friesema et al., 2012). Assuming that in general testing for 6 pathogens would be conducted (Van den Brandhof et al., 2004) the costs for testing would be € 73.18 (see Table 5).

About 27% of patients visiting a GP are assumed to get a prescription for antibiotics (Doorduyn et al., 2011), resulting in estimated costs of € 3.30 per episode visiting a GP (CVZ, 2012a), see Table 5.

The duration of hospitalization depends on the aetiology of the GE pathogen as well as on the age of the patient. But pathogen-specific hospitalization duration and/or age-dependent hospitalization duration are seldom reported. In the GEops study, a Dutch prospectively followed cohort of hospitalized GE cases, age-dependent hospitalization duration was reported. After correction for readmission, the age-dependent hospitalization duration was 2.82 days, 9.88 days and 12.28 days for GE patients younger than 18 years, GE patients between 18-64 years and elderly GE patients ($\geq$ 65 years) respectively (Friesema et al., 2012). This is in line with Ruzante et al. (2011) who reported that for hospitalized campylobacteriosis, salmonellosis, and norovirus cases the duration of hospitalization in days increased with age.

For bacterial GE we based our assumptions on hospitalization duration for campylobacteriosis, salmonellosis and STEC O157 on the GEops study, taking into consideration the age of the hospitalized patient (see Table 6).

Table 5. GE-specific DHC and DNHC costs in 2011

		Unit cost (€)	Source
DHC	Costs of antibiotics, including pharmaceutical fees (per episode)	3.30	Hakkaart - van Roijen et al. (2010); CVZ (2012a)
	Laboratory-confirmation for GE pathogens (per faecal sample)	73.18	Van den Brandhof et al. (2004)
DNHC	OCM - mild case; children (per episode)	1.36	CVZ (2012a)
	OCM - mild case; adults (per episode)	2.54	CVZ (2012a)
	OCM – moderate to severe case; children (per episode)	4.41	CVZ (2012a)
	OCM – moderate to severe case; adults (per episode)	8.19	CVZ (2012a)

Illness from the toxin-producing pathogens, especially *Clostridium perfringens* toxin results in longer hospitalizations, whereas for *Bacillus cereus* and *Staphylococcus aureus* the reported hospitalization stay is far lower than for any other hospitalized GE case. We therefore assume, based on Adak et al. (2002; 2005), an average duration of 2.59 days and 1.20 days for hospitalization due to *Bacillus cereus* and *Staphylococcus aureus* respectively (see Table 6). For *Clostridium perfringens* toxin the hospitalization duration was based on the GEops findings (see Table 6), which is more in line with the reported 14.8 days by Adak et al. (2002; 2005), although that might be a slight underestimation of the true duration of a hospitalization stay for *Clostridium perfringens* toxin cases.

The assumed hospitalization duration for rotavirus and norovirus was also based on the GEops study (see Table 6). In the GEops study most GE cases in children were associated with rotavirus. But also a larger proportion of the adult GE cases (> 20%) found in the GEops study were due to rotavirus. However, it has

to be noted that the 2.9 days of hospitalization (or 2.6 days if no readmission is included) for children is far lower than the 4 days found by De Wit et al. (2001a) or other European studies which report 3.8 days to 4.2 days for hospitalized rotavirus cases in children (Lynch et al., 2001; Gil et al., 2004). For norovirus Ruzante et al. (2011) found a mean stay of 17 days (median age was 72 years), whereas Adak et al. (2002; 2005) found an average duration of 3.9 days. The 17 days are higher than the mean stay for hospitalized adult GE cases in the GEops study (10.8 days). Therefore the hospital stay for norovirus patients might be underestimated, in particular for elderly patients when using the GEops study. But given the fact other studies do report far lower days in hospital than Ruzante et al. (2011), we prefer to base our estimates on the GEops study.

The observed hospitalization duration from the GEops study is also used for giardiasis cases and cryptosporidiosis cases (see Table 6). In the previous estimates, Vijgen et al. (2007) assumed 8 days for cryptosporidiosis cases based on Corso et al. (2003), who reported 5 days for cryptosporidiosis without underlying condition; 7 days for cryptosporidiosis with underlying condition others than AIDS and 16 days for cryptosporidiosis with AIDS, and overall 8 days. Collier et al. (2012) found 5.9 days. In contrast for giardiasis, Vijgen et al. (2007) assumed 4 days based on Lengerich et al. (1994), who reported a median duration of 4 days (0-32 days). Adak et al. (2002; 2005) found 3.7 days and Collier et al. (2012) 4.1 days. This is lower than found for an average GE case in the GEops study. Nevertheless did we assume the GEops study here also, as there is no reason why it should be different than for other GE-pathogens.

According to the GEops study we assumed about 1%, 19% and 71% of GE patients younger than 18 years, GE patients between 18-64 years and elderly GE patients ($\geq$ 65 years) respectively, would be transported to hospital by ambulance (Friesema et al., 2012).

In the GEops study approximately 5.9% of the elderly GE patients ($\geq$ 65 years) was transferred from hospital into a nursing home for some 60 days before returning home (Friesema et al., 2012). This is in line with Ruzante et al. (2011) who reported that about 5% of all salmonellosis and campylobacteriosis cases, 1% of all EHEC cases and 8% of all norovirus cases were sent home with support service; less than 6.5% of salmonellosis and campylobacteriosis cases, 11% of EHEC cases and 18% of norovirus cases were transferred to another institution (i.e. long-term care facility, another facility providing in-patient hospital care or another type of institution). We therefore assumed in the current study approximately 5.9% (modelled as Beta (1,16)-distribution) of non-fatal and elderly ($\geq$ 65 years) hospitalized GE patients would be admitted to a nursing home for an average of 60 days (Friesema et al., 2012).

We assume fatal cases would incur the same DHC costs as non-fatal GE cases, with one exception: the costs for being admitted to a nursing home. We assumed fatal cases would have died before being admitted to a nursing home.

Table 6. Assumed hospitalization duration for the different GE-pathogens

	Hospitalization duration (in days)			Source
	0-15 years	15-64 years	≥65 years	
Bacteria – infectious				
Campylobacter spp.	2.82	9.88	12.28	Friesema et al. (2012)
STEC O157	2.82	9.88	12.28	Friesema et al. (2012)
Salmonella spp.	2.82	9.88	12.28	Friesema et al. (2012)
Bacteria – toxin producing				
Bacillus cereus	2.59	2.59	2.59	Adak et al. (2002; 2005)
Clostridium perfringens	2.82	9.88	12.28	Friesema et al. (2012)
Staphylococcus aureus	1.20	1.20	1.20	Adak et al. (2002; 2005)
Viruses				
Norovirus	2.82	9.88	12.28	Friesema et al. (2012)
Rotavirus	2.82	9.88	12.28	Friesema et al. (2012)
Protozoa				
Cryptosporidium spp.	2.82	9.88	12.28	Friesema et al. (2012)
Giardia spp.	2.82	9.88	12.28	Friesema et al. (2012)

4.2.1.2 Direct non-healthcare costs

Over-the counter medication (OCM) such as anti-diarrheal drugs, ORS and painkillers are often used by patients with GE, independent of hospitalization, consulting with a GP or requiring no medical service. OCM costs are paid by the patients and therefore considered as category DNHC. We assumed, based on the SENSOR study (De Wit et al., 2001b; Van den Brandhof et al., 2004), that of mild GE cases (i.e. patients not requiring medical services) 31% would use anti-diarrheal drugs, 5% would use ORS and 5% would use painkillers. For moderate cases (i.e. patients requiring only doctor visits) and severe cases (i.e. hospitalized patients) we assumed the corresponding values would be 59%, 33% and 5% respectively. Using Dutch unit prices(CVZ, 2012a) OCM costs per episode in 2011 were estimated at € 1.36 for children and € 2.54 for adults for mild GE cases, and at € 4.41 for children and € 8.19 for adults for moderate to severe GE cases, see Table 5. We do know small children painkillers are rarely used. On the other hand, ORS and anti-diarrhoea application might be more common for small children than found in the SENSOR study. Therefore, the presented average drug costs are only an approximation of the potential daily drug costs.

Travel costs were only considered when visiting a GP and when being hospitalized (see section 4.1.4.1.1). Based on Friesema et al. (2012) we assumed 77% and 97% of the persons younger than 18 years and older than 18

years respectively would use either a car or public transport when visiting a GP. In the case of hospitalization 97% of persons younger than 18 years would be transported to the hospital by car or public transport; this applies for 72% of the persons older than 18 years (Friesema et al. 2012). When travelling by car or public transport we assumed, by lack of information, half of the patients would have taken a car and the other half would have used public transport. For the costs calculations we used average distances as reported in Hakkaart - Van Roijen et al. (2010); the unit prices are listed in Table 4.

If babies and small children do have GE, the daily use of diapers is increasing. We estimated, following the assumptions made by Kemmeren et al. (2006) that the costs for additional diapers for children younger than 5 years would be € 3.57, € 7.13 and € 7.61 for mild, moderate and severe GE cases respectively. No information was available on informal care, for example time costs of a neighbour taking care of a sick child. Therefore the costs for informal care were not considered in this study.

We assume fatal cases would incur the same DNHC costs as non-fatal cases until their death.

4.2.1.3 Indirect non-healthcare costs

Information about the duration of work loss (both paid and unpaid) for hospitalized cases and/or their caregivers was based on the GEops study (see Table 7). Whereas for non-hospitalized GE cases, we analysed data collected during the Pienter 2 study (Mollema et al. 2009; Van der Klis et al., 2009). Cases who reported having GE symptoms in the previous month (at least 3 bowel movements in 24 hours and/or at least 3 episodes of vomiting in 24 hours) were asked: if they had visited a GP for their symptoms; if they themselves and/or a caregiver were absent from work, both paid and unpaid work and for how many hours. Results are summarized in Table 7, distinguishing between GE cases visiting a GP or not. It seemed the obtained answers were strongly biased and in particular GE patients with long duration of symptoms had filled in the questionnaire. We therefore opt for the median when estimating costs.

Table 7. Assumed sick leave from paid and unpaid work for mild, moderate and severe GE cases

	No GP visit[a]	GP visit [a]	Hospitalized[b]
Sick leave of patients & caregivers from paid work (in hours/episode)			
GE cases: 0 – 4 years	2.50	7.47	26.4 [b]
GE cases: 5 – 14 years	0.63	0.50	26.4 [b]
GE cases: 15 – 64 years	10.04	19.72	26.4 [b]
GE cases: ≥ 65 years	0	0	0.4
Sick leave of patients & caregivers from unpaid work (in hours/episode)			
GE cases: 0 – 4 years	0.19	1.73	2.4 [b]
GE cases: 5 – 14 years	0.27	0.27 [c]	2.4 [b]
GE cases: 15 – 64 years	0.47	0.47 [c]	1.6 [b]
GE cases: ≥ 65 years	0	0	0.4

a) The median is reported. Results are based on questions collected during the Pienter 2 study (Mollema et al., 2009; Van der Klis et al., 2009).
b) Averages as reported in the GEops study by Friesema et al. (2012). In the GEops study data were collected for persons younger than 18 years (in the current study we applied these results to the 0-14 years old) and for persons between 18-64 years (in the current study we applied these results to the 15-64 years old).
c) There were not enough data available to allow an assumption for GE cases visiting a GP. We therefore assume sick leave from unpaid work for 5-14 years and for 15-64 years would be the same independent of a GP visit.

In concordance with the Dutch guidelines the estimate of work loss in case of death is based on the friction cost methods (see details in section 4.1.3). Productivity losses due to sickness leave from paid work are only estimated for patients in the working life years, which is, in the Netherlands, every person between 15 and 64 years as defined by Statistics Netherlands.

Productivity losses from paid work of patients were valued using a standard tariff, according to the corresponding age-classes (see Table 4). We further assumed a productivity loss of € 27.20 for caregivers of children and of € 31.11 for caregivers of adults who would be absent from paid work in order to take care of a sick child/adult patient. For unpaid work we assumed for all age-classes a productivity loss of € 12.96, for both patients and caregivers.

4.2.1.4 Scenario analysis

There is evidence from Dutch and international studies (Ruzante et al., 2011; Friesema et al., 2012) that in particular elderly GE patients are at risk of being transferred from hospital into a nursing home before returning home. However, information on the duration of stay was scarce. In our baseline we assumed an average stay in a nursing home of 60 days, only this assumption was based on one single case (Friesema et al., 2012). We therefore conducted scenario analyses by multiplying the duration of the nursing stay by 50% (Scenario analysis: GE: shorter stay in nursing home) and 150% (Scenario analysis: GE: longer stay in nursing home) respectively.

4.2.2 Hepatitis A and E virus

4.2.2.1 Direct healthcare costs

No medication costs were considered for HAV and HEV due to the non-availability of data.

Consultation with a GP, who is the gatekeeper to any further medical services in the Netherlands, might occur either by phone, by a GP practice visit or by a

house call from the GP to the patient. For HAV cases we assumed there would be 2.3 and 3.7 GP visits (Beutels et al., 2008; Suijkerbuijk et al., 2012) for non-hospitalized HAV cases and for hospitalized HAV cases respectively. The same assumptions were made for HEV cases.

Based on Suijkerbuijk et al. (2012) we assumed laboratory testing occurs for 21.6% of the patients consulting a GP and not being hospitalized, whereas we assumed 100% of all hospitalized HAV cases (Suijkerbuijk et al., 2012) were tested. The same assumptions were made for HEV cases. The cost for laboratory-confirmation was assumed to be € 35.34 per case tested (Suijkerbuijk et al., 2012), see Table 8.

The hospitalization duration of HAV patients is age-dependent. Based on Dutch hospitalization data the average duration for HAV patients was assumed to be 4.55 days, 5.27 days and 11.83 days for patients <18 years, patients from 18-64 years and patients ≥ 65 years respectively (Suijkerbuijk et al., 2012). Turner et al. (2010) report a median duration of 9 days for HEV patients. Borgen et al. (2008), a Dutch study, reported a median duration of 8 days. This is longer than what is observed for HAV. We therefore based our assumptions on Borgen et al. (2008) and in the absence of a mean assumed hospitalized HEV cases are admitted for 8 days.

In the case of being hospitalized for hepatitis an abdominal echo is standard procedure (Suijkerbuijk et al., 2012).
There was no information available on the use of ambulance transport to the hospital when admitted with HAV or HEV. By omitting these costs we have underestimated these costs, but only slightly as most patients are children or young adults, a population, at least for GE, known to rarely use ambulance transportation when admitted to hospital (Friesema et al., 2012).

We assumed fatal cases would incur the same DHC costs as non-fatal cases.

Table 8. Hepatitis-specific DHC costs in 2011

	Unit cost (€)	Source
Laboratory-confirmation (per case tested)	35.34	Suijkerbuijk et al. (2012)
Echo abdominal (per case)	89.34	Suijkerbuijk et al. (2012)

4.2.2.2 Direct non-healthcare costs

Travel costs to the GP and to the hospital were the only DNHC considered, applying the assumptions described in section 4.1.4.1.1.

We assume fatal cases would incur the same DNHC costs as non-fatal severe cases until their death.

4.2.2.3 Indirect non-healthcare costs

The duration of sickness leave of patients for absence from paid work was based on the duration of illness, assuming a patient would be absent for 23,5 hours per week of illness (see section 4.1.4.1.2). The duration of sickness leave for caregivers of children from 0 to 4 years was based on the duration of illness, assuming caregivers would be absent for 16.4 hours per week of illness (see section 4.1.4.1.2). For children between 5 and 14 years with mild to moderate HAV/HEV symptoms we assumed the average sickness leaves of their caregivers

would be equal to 50% of the sickness leave of caregivers of children 0 to 4 years with similar symptoms.

The duration of illness for HAV was assumed to be 14 days for mild (i.e. no GP visit), 14 days for moderate (i.e. GP visit only) and 30 days for severe (i.e. hospitalized) HAV cases (Haagsma et al., 2009). The duration of illness for HEV was assumed to be respectively 14 days, 25.5 days and 42.8 days for mild, moderate and severe HEV cases (Borgen et al., 2008; Haagsma et al., 2009). In concordance with the Dutch guidelines the estimate of work loss in case of death is based on the friction cost methods.

For patients 65 years and older we assumed, similar to GE, that only in case of hospitalization a caregiver would be absent from paid work for a total of 0.4 hours per episode (Friesema et al., 2012).

Productivity losses from paid work of patients were valued using standard tariffs, according to the corresponding age-classes (see Table 4). Productivity losses from paid work for caregivers were valued, assuming a productivity loss of € 27.20 for caregivers of sick children and of € 31.11 for caregivers of sick adults.

4.2.3 Inflammatory bowel disease (IBD)

4.2.3.1 Direct healthcare costs

IBD patients are either in remission, inflammation or require an operation, depending on which phase of the disease they are experiencing. IBD is not fatal but cannot be cured. Consequently, IBD costs occur throughout the whole life starting at disease onset and persisting until death.

In the current study we use average annual costs of IBD patients as a proxy for estimating life-long IBD costs. Annual IBD costs were based on a newly available Dutch study by Van der Valk et al. (2012), assuming 70% of Campylobacter- and Salmonella-associated IBD cases would be ulcerative colitis (UC) cases and the remaining 30% would be Crohn's Disease (CD) cases (Mangen et al. (2004; 2005). Van der Valk et al. (2012) collected information on DHC, DNHC and INHC from 1,315 Crohn's disease (CD) patients and from 937 ulcerative colitis (UC) patients from seven university hospitals and seven general hospitals for the year 2011 using a web-based questionnaire. They reported no significant difference in costs of patients from university hospitals and of patients from general hospitals (Van der Valk et al., 2012). As cost items were derived from a three-month follow-up questionnaire we multiplied the costs by four to get an annual cost estimate. Costs are summarized in Table 9.

Further we assumed that in the first year additional diagnostics would be required for getting the diagnosis of IBD, in total € 854.03 (Mangen et al., 2004; 2005) resulting in first year diagnostic costs of € 986.33.

Table 9. IBD-specific DHC costs in 2011

	CD €/case/year	UC €/case/year	IBD €/case/year
Annual diagnostic costs (Van der Valk et al., 2012)	162.40	119.40	132.30
Additional diagnostic costs in 1st year to get diagnosis (Mangen et al., 2004; 2005)	854.03	854.03	854.03
Medication costs (Van der Valk et al., 2012)	4,581.32	2,379.56	3,040.09
Gastroenterologist and other medical specialist consultations, including GP visits (Van der Valk et al., 2012)	456.48	273.52	328.41
Costs for hospitalization incl. surgery (Van der Valk et al., 2012)	1,300.60	587.20	801.22

4.2.3.2 Direct non-healthcare costs

Travel costs and other out-of-pocket costs were, according to Van der Valk et al.(2012), € 300/year for CD cases and € 228/year for UC patients or € 249.60 for an average IBD case per year.

4.2.3.3 Indirect non-healthcare costs

Based on the information provided by Van der Valk et al. (2012) we estimated IBD patients between 15 - 64 years would be on average 34.09 hours per year absent from paid work. Caregivers of IBD patients would be absent for 2.042 hours per year from paid work. Further we assumed IBD patients themselves or their caregivers would be absent from unpaid work for on average of 0.885 hours per year (Van der Valk et al., 2012).
Productivity losses from paid work of patients were valued using a standard tariff according to the corresponding age-classes (see Table 4). Further we assumed a productivity loss of € 27.20 for caregivers of children and of € 31.11 for caregivers of adults, who would be absent from paid work in order to take care of an IBD patient. For unpaid work we assumed for all age-classes a productivity loss of € 12.96, for both patients and caregivers.

4.2.4 Irritable bowel syndrome (IBS)

IBS stands for a group of functional bowel disorders. Abdominal discomfort or pain associated with a change of bowel habits and features of disordered defecation characterize this health outcome. Besides these symptoms IBS patients suffer, more than healthy individuals, from symptoms like nausea, headache, backache, anxiety, sleep disturbances and tiredness (Donker et al., 1999). However, the aetiology of IBS is still largely unclear and pathogenic mechanisms are only partly understood.

4.2.4.1 Direct healthcare costs

About 20% to 75% of IBS patients, depending on the studies and the countries concerned, seek professional care (Le Pen et al., 2004).

For example, Le Pen et al.(2004) reported 61% of IBS patients identified via a survey conducted in the French general population in 2000, had used at least one type of medicine for their disorder during the previous 4 weeks. This was **75% if IBS patients had visited a doctor in the previous 3 months and**

46% for IBS patients not consulting a doctor. The authors speculated the latter group could be considered in part as self-medicating but did not provide data. In another French study, about 64.2% of IBS patients fulfilling Rome II criteria, and selected from a nationally representative sample of 20,000 French subjects, had on average 2.8 times consulted a doctor (GP or specialist) in the previous 12 months for IBS (Dapoigny et al., 2004). 17.3% had a colonoscopy; 23.4% had laboratory tests done; 13.8% had an abdominal ultrasound done; for 8% stool examinations were done; 6.4% had a small bowel study and/or plain film of the abdomen done; 8% had a gastroscopy; 6.4% had an upper gastrointestinal series done; 3.2% had abdominal magnetic resonance imaging and/or computerized tomography scan done; 7.4% had thyroid tested and 1.7% had other examinations done (Dapoigny et al., 2004). About 8% had been admitted in the previous 12 months to hospital for IBS (Dapoigny et al., 2004) with an average duration of stay of 6.6 days.

In a Finnish population-based study (Hillila et al., 2010) IBS cases selected using Manning criteria had on average 0.8 gastro-intestinal (GI) related visits, this was 1.5 for IBS cases selected using Rome II criteria and 0.2 for the control group. IBS patients had on average 3.0 and 3.2 non-GI visits, whereas controls had on average 2.3 non-GI visits (Hillila et al., 2010). The proportion on continuous medication was 53% in the Rome II and 45% in the Manning group, while this was 32% for the controls.

In a British case-control study (Akehurst et al., 2002), where IBS patients were selected via GP records, an average IBS patient (Rome I criteria) had, when compared with non-IBS patients, in the 12-month study period 1.35 additional GP consultations, 2.58 additional prescriptions, 0.04 additional A&E attendances, 0.33 additional outpatient attendances and 0.08 additional inpatient attendances, resulting in additional costs of £ 123 (1999 values).

In an European community survey (Hungin et al., 2003), where screening interviews were used to identify individuals with medically diagnosed IBS, as well as individuals not formally diagnosed but fulfilling IBS diagnostic criteria (Manning, Rome I or II), the authors reported about 60%, 86%, 85%, 82%, 47%, 68%, 79%, 83% and 71% of the identified IBS cases were undiagnosed cases for UK, France, Germany, Spain, Italy, the Netherlands, Belgium, Switzerland and Europe respectively. Of those 71% undiagnosed IBS cases, 37% reported they had seen no one for their symptoms (Hungin et al., 2003), or about 26% of IBS cases in the community would not search for medical help for their IBS symptoms. The expectation is that in the Netherlands about 90% of these diagnosed IBS cases would be followed by their GP whereas 10% would be referred to a medical specialist (NHG, 2011).

There was also one Dutch case-control study available for the year 1998 on treatment patterns and health care costs where mebeverine users were used as proxy for IBS patients (Goettsch et al., 2004). If medication is required, the antispasmodic agent mebeverine is the drug recommended for IBS patients (CVZ, 2012b). Mebeverine was also in 1998 the only drug exclusively registered for the treatment of IBS in the Netherlands (Goettsch et al., 2004). Goettsch et al.(2004) estimated an incidence of use of mebeverine of 8.4 per 1,000 in 1998, while according to these authors the annual incidence of IBS in the Netherlands is 10-20 per 1000, which corresponds to 42% to 84% seeking medical care. This is in line with other European studies (Dapoigny et al., 2004; Le Pen et al., 2004).

Mebeverine-treated patients, in total 3,431, were matched with controls, i.e. non-mebeverine users, by age, gender and pharmacy (Goettsch et al., 2004) and excess costs due to co-medication and hospital admission in mebeverine users were estimated. Their findings are summarized in Table 10, but updated to 2011, using consumer price indices.

Table 10. IBS-specific DHC costs in 2011

	Unit cost (€)	Source
Cost for IBS medication (mebeverine & laxatives) per IBS patients seeking medical care[a] per year	70.55	Goettsch et al. (2004)
Cost for co-medication for treatment of IBS or IBS-related symptomatology (excluding mebeverine & laxatives) per IBS patients seeking medical care[a] per year	103.21	Goettsch et al. (2004)
Costs for hospitalization for intestinal-illness and IBS-related complaints per IBS patients seeking medical care[a] per year.	156.78	Goettsch et al. (2004)

a) Goettsch et al. (2004) reported these costs as costs 'per mebeverine-user per year'. In the current study we assumed each IBS patients seeking medical care would make these costs.

4.2.4.1.1 Assumptions made for DHC in the baseline

Based on Hungin et al. (2003) and Goettsch et al. (2004) we assumed most likely that 74%, with minimum 42% and maximum 84% (pert-distribution), of all IBS patients would seek medical care. For each IBS case seeking medical care we considered the excess costs due to co-medication as listed in Table 10. Additionally, we estimated the delivery fee for pharmacy, using standard tariffs (see Table 4) and assuming 62.9% of all mebeverine users require only one prescription per year, whereas 18.0%, 18.1% and 1.0% required 2, 3-10 (recoded as 4) or more than 10 prescriptions (recoded as 11) per year (Goettsch et al., 2004).

We further assumed IBS patients would visit their GP for each individual prescription, which is equal to 1.82 GP visits per year, which is slightly more than the 1.35 found by Akehurst et al.(2002) but less than the 2 found by Hillila et al. (2010).

About 2.7% of all mebeverine IBS-users were hospitalized in 1989 for gastrointestinal and IBS related complaints (Goettsch et al., 2004). This is less than found in other European studies (Akehurst et al., 2002; Dapoigny et al., 2004). Having no other information at hand, we use in our baseline the hospitalization costs as found by Goettsch et al. (2004) and assume hospitalization costs per IBS patients seeking medical care would be equal to € 153.19 (see Table 10). Goettsch et al.(2004) is so far (September 2012) the only available Dutch cost study of IBS-associated DHCs.

4.2.4.1.2 Scenario analysis

In a recent overview (NHG 2011) the authors concluded the cost categories considered by Goettsch were rather restricted; other DHC cost-of-illness studies conducted in neighbouring countries such as Germany (Muller-Lissner and Pirk, 2002) and France (Le Pen et al., 2004) reported annual direct healthcare costs per IBD patient which were more than twice as high as reported by Goettsch et

al. (2004). We therefore conducted a scenario analysis by doubling the baseline direct healthcare costs related to IBS (Scenario analysis: IBS: Doubling DHC).

4.2.4.2 Direct non-healthcare costs

Based on claims and questionnaires, Nyrop et al. (2007) estimated that out-of-pocket expenditure (i.e. antacids; laxatives; antidiarrheals; stool softeners; gas relief medications; pain medications; antispasmodics; other medications; fiber; bran; special diet; exercise program; ginger root or tea, fennel seed, senna tea, psychotherapy, megavitamins, homeopathic methods, special diet, hypnotherapy, massage therapy, biofeedback, acupuncture, yoga, aromatherapy) do account for 5.7% of the total healthcare expenditure of IBS patients (Nyrop et al., 2007). In the case of IBS cases seeking medical care, this would be in the current study € 23.99 annually. However, not only IBS cases seeking medical care would have out-of-pocket expenditure. We therefore assumed all IBS cases would have these costs.

Other DNHC costs considered were travel costs to the GP and to the hospital, applying the assumptions described in section 4.1.4.1.1.

4.2.4.3 Indirect non-healthcare costs

Dean et al.(2005) conducted a 2-phase survey within the workforce of a large US bank to assess the presence of IBS among employees and to measure their work productivity. According to these authors the incremental work productivity loss associated with IBS was equal to an additional 39 days of reduced productivity at work (=presenteeims) and an additional 3.4 days of absence per year (=absenteeisms) for each employee with IBS. Productivity at work was reduced by more than 21% because of gastrointestinal symptoms related to IBS (Dean et al., 2005).

In a French study (Le Pen et al., 2004), 12.1% of IBS individuals in employment were absent from work at least once during the 6-month study period, or 6.7% of the total study sample. This is similar to the findings of Dapoigny et al.(2004), who reported 6.7% of IBS patients or 11% of working subjects, had taken time off from work due to IBS in the 12-month study period. The average number of absences from work amongst these individuals was 1.7 days, with a mean duration of absence of 9.6 days (Le Pen et al., 2004). Calculated for a year this corresponds to 3.92 days per year per IBS individuals in employment, or 2.19 days per year per IBS in the study population.

In a British case-control study (Akehurst et al., 2002), the IBS group had 0.2 days more days off work than the control group within the 3-month study period, or extrapolated to a one-year study 0.8 days per year.

Hillila et al. (2010), who conducted a population based study in Finland, reported the average number of missed work days (absenteeisms) because of gastrointestinal symptoms per year to be 0.9 (IBS selected using Manning criteria), 1.8 (IBS selected using Rome II criteria) and 0.3 days in the control group. In addition, 32% of the Rome II group subjects and 21% of the Manning group reported impaired productivity at work (presenteeims) weekly or more frequently (Hillila et al., 2010).

In 2005, Ten Berg et al. (2006) administered a questionnaire to IBS patients identified at community pharmacies using mebeverine as a proxy for IBS (a similar approach as applied by Goettsch et al. (2004) when estimating the excess costs for health care, see section 4.2.4.1). They asked IBS patients to

estimate the number of days they were unable to perform their daily activities. On average 1.8 days (95% CI, 1.1–2.5) per month, or if calculated per year, on average 21.6 days mebeverine-using IBS patients had troubles with their daily activity. This is slightly lower than the 43.4 days (39 days of reduced productivity at work and 3.4 days of absence per year) reported by Dean et al.(2005) within the workforce of a large US bank.

4.2.4.3.1 Assumptions made for INHC in the baseline

Having so far only considered productivity losses related to absenteeisms, we considered also, for IBS only, productivity losses due to absenteeisms. Lacking a Dutch study, we based our assumptions on Le Pen et al. (2004), who reported a work absence of 3.92 days per year per IBS patients in work. But as only 76% of persons between 15-64 years have paid employment in the Netherlands (Statistics Netherlands, 2012), we assumed for persons between 15-64 years the work absence from paid work would be equal to 18.43 hours per year taking into consideration the average Dutch working hours. This is slightly more than found in other European studies (e.g. Akehurst et al. (2002); Hillila et al. (2010)). For caregivers of IBS patients younger than 5 years who would take their children to a GP and/or outpatient visits, we estimated they would be absent from paid work for 2.21 hours/year. This would be 1.11 hours/year for caregivers of IBS children from 5 years to 14 years. We assumed no productivity losses for caregivers of IBS patients 15 years and older.

Productivity losses from paid work of patients were, if not otherwise stated, valued using standard tariffs, according to the corresponding age-classes (see Table 4). We further assumed a productivity loss of € 27.20 for caregivers of children, who would be absent from paid work in order to take care of a sick child/adult patient.

4.2.5 Reactive arthritis (ReA)

4.2.5.1 Direct healthcare costs

Reactive Arthritis (ReA) is a non-fatal health outcome and mostly self-limiting within a few weeks to months. Mild ReA cases were assumed not to need medication and would also not ask for other medical services (Mangen et al., 2005). We assumed about 57.4% of the moderate ReA cases (Townes et al., 2008) and 100% of the severe ReA cases would require medication to cure ReA. The medication costs, based on Söderlin et al (2003), were estimated at € 145 per case requiring medication. Further it was assumed moderate ReA cases would visit a GP, whereas severe ReA cases would have 3.3 GP visits and 4.4 outpatient visits (Söderlin et al., 2003) and would be admitted to hospital for 9.1 days (Mangen et al., 2004; 2005).

4.2.5.2 Direct non-healthcare costs

Travel costs to the GP and to the hospital for outpatient and inpatient visits were the only DNHC costs considered, as applying the assumptions described in section 4.1.4.1.1.

4.2.5.3 Indirect non-healthcare costs

There was no information about sickness leave of potential caregivers. We therefore estimated productivity losses for caregivers of children with ReA and younger than 15 years. Depending on ReA severity, we assumed caregivers would be absent from work for GP visits, outpatient visits and during the hospitalization stay of their child, in total 9.1 days, as applying the assumptions described in section 4.1.4.1.2. For patients 65 and older we assumed in the case of hospitalization a caregiver would be absent for 0.4 hours per episode (see section 4.1.4.1.2).

For patients between 15 and 64 years, depending on severity of ReA symptoms, productivity losses for work absence were considered. It was assumed mild ReA cases would cause no sickness leave. For moderate ReA cases between 15 and 64 years we assumed, based on the findings of Townes et al. (2008), 35% would be absent from work for 15.21 hours. According to Söderlin et al. (2003), hospitalization of severe ReA cases would result in a sick leave of 53 days. This corresponds to a sick leave of 178.02 hours (see assumptions in section 4.1.4.1.2). In addition, we assumed sick leave for both moderate and severe ReA patients for GP consultations and outpatient visits, applying the assumptions described in section 4.1.4.1.2.

Productivity losses from paid work of patients were valued using standard tariff, according to the corresponding age-classes (see Table 4). We further assumed a productivity loss of € 27.20 for caregivers of children, and of € 31.11 for caregivers of adults, who would be absent from paid work in order to take care of a sick child/person.

4.2.6 Guillain-Barré Syndrome (GBS)

Not all GBS patients are equally severe. Some develop mild symptoms (F-score[6] up to 2), whereas others are more severely affected (F-score of 3 and higher). The age of the GBS patient plays a role when developing symptoms and recovering from the diseases, in particular patients younger than 50 years have a better outcome than those older than 50 years (Van Koningsveld et al., 2000). We therefore distinguish mild and severe GBS cases, taking the age into consideration (see Table 11) when estimating costs.

Table 11 Campylobacter-associated GBS patients split up in age-groups according to severity (Source: Havelaar et al. (2000a,b))

	Younger than 50 years	Older than 50 years
Mild GBS cases	70%	30%
Severe GBS cases	47%	53%

4.2.6.1 Direct healthcare costs

In accordance with the Dutch system, where the GP is the gatekeeper to all further medical services, we assumed all GBS patients visit their GP first. The GP would refer the patient to an outpatients' clinic or in severe cases directly to hospitalization. In order to confirm the diagnosis, a spinal puncture and an electromyogram examination would be performed by the neurologist (Mangen et al. 2004; 2005), see Table 12. In the Netherlands all GBS patients are admitted to hospital. The duration of the hospitalization and the applied treatment however depends on the severity grade and the age of the patient.

[6] F-scores are used to express the severity of GBS symptoms ranging from 0 (=no symptoms) up to 6 (=death).

Van der Maas et al. (2011) reported an average hospital stay of 19.3 days for all GBS cases, similar to Ruzante et al. (2011), who found 19.8 days. About 8.3% would have a readmission (van der Maas et al., 2011). Based on van der Maas et al. (2011) and Mangen et al. (2004; 2005), we estimated the hospital stay, including correction for readmission, would be 9.12 days, 12.84 days, 19.22 days and 26.66 days for young and mildly affected GBS patients, elderly and mildly affected GBS patients, young and severely affected GBS patients and elderly and severely affected GBS patients respectively. About 25% of all GBS cases, mostly severe GBS cases, were assumed to require mechanical ventilation (Van der Maas et al., 2011), therefore staying in an ICU for 48.5% of the total hospital stay (Mangen et al., 2004; 2005).

According to Van der Maas et al. (2011) about 88% of all GBS cases in the Netherlands would receive an intravenous immunoglobulin (IVIG) treatment. Assuming severe GBS cases (83% of all GBS cases) would always receive an IVIG treatment, only 29.2% of the mild GBS cases were assumed to receive an IVIG treatment. 8.7% of all GBS cases were assumed to have a relapse requiring a second or third IVIG treatment (Van der Maas et al., 2011). In order to stimulate the mobility of GBS patients is assumed every day half an hour of physiotherapy is applied during hospitalization stay (Mangen et al., 2005). For severe GBS cases we assumed during the last week of hospitalization there would be even two physiotherapy consultations per day (Mangen et al., 2004; 2005).

Table 12. GBS-specific DHC costs in 2011

	Unit cost (€)	Source
EMG examination	47.98	Mangen, Havelaar et al. (2004; 2005)
Spinal puncture	60.48	Mangen, Havelaar et al. (2004; 2005)
IVIG treatment	6,247.57	Mangen, Havelaar et al. (2004; 2005)

We assume an ordered ambulance is requested in 75% of the cases when transferring GBS patients to an inpatient revalidation center, and 100% of the cases when transferring GBS patients to a nursing home (Mangen et al., 2004; 2005).

After hospital discharge it was expected 67.5% of mildly affected GBS patients would need physiotherapy for approximately twelve weeks with two consultations per week (Mangen et al., 2004; 2005). Approximately 5% of mildly affected GBS patients would need nine additional physiotherapy consultations to further improve their mobility (Mangen et al., 2004; 2005). Furthermore was assumed two additional consultations with the neurologist were scheduled after leaving the hospital as a follow-up (Mangen et al., 2004; 2005).

For severely affected GBS patients some patients do recover quickly and can return home after hospital discharge, whereas other GBS patients will need additional rehabilitation when leaving hospital. Based on data from Bernsen et al. (1997; 2001; 2002) and on Mangen et al. (2004; 2005) we estimated that severely affected GBS patients younger than 50 years about 18.5% and 12.5% would be admitted to inpatient rehabilitation and outpatient rehabilitation respectively (Mangen et al., 2004; 2005). In comparison for severely affected

GBS patients aged 50 to 74 years, 34.8% and 12.5% would be admitted to inpatient rehabilitation and outpatient rehabilitation (Mangen et al., 2004; 2005). Of severely affected GBS patients older than 75 years we assumed 17.8% and 12.5% would be admitted to an inpatient rehabilitation and outpatient rehabilitation respectively. We assumed 17% of severely affected GBS patients older than 75 years with an F-score of 3 and higher would be transferred from hospital to a nursing home (Mangen et al., 2004; 2005). The average rehabilitation duration was assumed to be 115 days and 225 days for young and elderly GBS patients respectively (Mangen et al., 2004; 2005), independent of inpatient or outpatient rehabilitation. Based on Meythaler (1997) and on Meythaler et al. (1997) we assumed 3.5 hours rehabilitation exercises per day. Outpatient rehabilitation was assumed to occur 3 times per week (Mangen et al., 2004; 2005). Furthermore, we assumed 3 additional consultations with the neurologist after leaving the hospital as a follow-up (Mangen et al., 2004; 2005).

Additional physiotherapy for severely affected GBS is needed once leaving the hospitalization/rehabilitation centre. In this report we made the same assumptions as Mangen et al. (2004; 2005). Patients with a good outcome (F-score 0 to 1), see Table 13, would get physiotherapy during half a year, on average 1.5 sessions per week. Patients with an F-score of 2 would get physiotherapy for one additional year, on average 1.5 sessions per week. Patients with a bad outcome (F-score 3 to 4) would get physiotherapy for two years once per week.

Table 13 Outcome of severe GBS cases (Source: Mangen et al. (2004; 2005))

	Young GBS patients	Elderly GBS patients
F-score 0 to 1	78%	62%
F-score 2	18%	21%
F-score 3 to 4	4%	17%

Severely affected GBS patients with an F-score of 3 and higher and older than 75 years were assumed to be directly transferred from hospital to a nursing home and would remain there for their remaining life (Mangen et al., 2004; 2005). Patients admitted to a nursing home were assumed to get physiotherapy once per week during one year. Furthermore, it was assumed that three additional consultations with the neurologist by the patients would occur as follow-up (Mangen et al., 2004; 2005).

For fatal cases costs were calculated the GP visit, the diagnostics, the medication and the hospitalization.

4.2.6.2 Direct non-healthcare costs

Travel costs to the GP, to the hospital for outpatient and inpatient visits, to the revalidation centre and for physiotherapy were the only DNHC costs considered, applying the assumptions described in section 4.1.4.1.1.

Travel costs to the GP and to the hospital were the only DNHC costs considered for fatal cases.

4.2.6.3 Indirect non-healthcare costs

There was no information about sickness leave of potential caregivers. We therefore estimated productivity losses for caregivers of children with GBS younger than 15 years. We assumed caregivers would be absent from work for GP visits, outpatient visits and during hospitalization stay of their child, applying the assumptions described in section 4.1.4.2. For patients 65 and older we assumed, in case of hospitalization, a caregiver would be absent for 0.4 hours per episode (see section 4.1.4.1.2). For fatal GBS cases younger than 15 years, sick leave of caregivers during hospitalization was considered. For fatal GBS cases 15 years and older we assumed caregivers would be absent for 0.4 hours during hospitalization.

For GBS patients between 15 and 64 years productivity losses due to absence from paid work were considered. Some of the mild GBS cases can return immediately to work, whereas for others it takes a few weeks to months before they can return to work. We therefore modelled as a Uniform (0:1) distribution that *p*% would return immediately to work after leaving hospital, whereas (1-*p*)% would experience problems for more than 23 weeks, which is the current friction period, similar to Mangen et al. (2004; 2005). For this latter category, we then considered the friction period, using a standard tariff for an average person in the corresponding age-class, see Table 4. For the other 50%, sickness leave corresponds to the hospital stay, applying the assumptions described in section 4.1.4.1.2. Furthermore, we assumed that doctors' consultations and physiotherapy consultation would result in some additional four hours and two hours' work absence per visit respectively, applying the assumptions described in section 4.1.4.1.2.

Most severely affected non-fatal GBS cases would need a long time to recover, which in majority would be longer than the friction period. We therefore considered here the friction period, similar as Mangen et al. (2005). However, not all GBS cases recover completely from the disease. About 20% are declared to be disabled and will therefore not return to work, whereas the other GBS cases will return to work. For these GBS cases we did assume doctors consultations and physiotherapy consultation in the second year and thereafter would result in some additional four hour and two hour work absence per visit respectively, applying the assumptions described in section 4.1.4.1.2.
In concordance with the Dutch guidelines, the estimate of work loss in case of death, is based on the friction cost methods.
Productivity losses from paid work of patients were valued using standard tariff according to the corresponding age-classes (see Table 4). We further assumed a productivity loss of € 27.20 for caregivers of children and of € 31.11 for caregivers of adults, who would be absent from paid work in order to take care of a sick child/person.

4.2.7 Hemolytic uraemic syndrome (HUS)

4.2.7.1 Direct healthcare costs

Direct healthcare costs of HUS were based on Tariq et al. (2011) and indexed to the year 2011. They were estimated at € 25,866. As these costs are mainly hospitalization costs, we assumed fatal cases would incur the same DHC costs as non-fatal cases.

4.2.7.2 Direct non-healthcare costs

No information was available on DNHC. We therefore assumed HUS patients would visit a GP before being admitted to hospital. Travel costs to the GP and to and from the hospital were also the only DNHC costs considered for both non-

fatal and fatal HUS patients, applying the assumptions described in section 4.1.4.1.1.

4.2.7.3 Indirect non-healthcare costs

There was no information about sickness leave of potential caregivers. We therefore estimated productivity losses for caregivers of children with HUS younger than 15 years. We assumed caregivers would be absent from work during illness, applying the assumptions described in section 4.1.4.1.2. The duration of HUS symptoms was assumed to be 21 days according to Havelaar et al. (2004). For patients 65 and older we assumed that, in case of hospitalization, a caregiver would be absent for 0.4 hours per episode (see section 4.1.4.2). For fatal HUS cases younger than 15 years, sick leave of caregivers during illness was considered. For fatal HUS cases 15 years and older we assumed caregivers would be absent for 0.4 hours during hospitalization.

For HUS patients between 15 and 64 years productivity losses due to absence from paid work was considered. Duration of sick leave from paid work was estimated based on the duration of illness, in total 21 days, and the assumptions described in section 4.1.4.1.2.

In concordance with the Dutch guidelines the estimate of work loss in case of deaths is based on the friction cost methods.

Productivity losses from paid work of patients were valued using standard tariff according to the corresponding age-classes (see Table 4). We further assumed a productivity loss of € 27.20 for caregivers of children and of € 31.11 for caregivers of adults who would be absent from paid work in order to take care of a sick child/person.

4.2.8 End-stage renal disease (ESRD)

4.2.8.1 Direct healthcare costs

Direct healthcare costs for ESRD are costs for full care centre haemodialysis or peritoneal dialysis, as well as costs for kidney transplantation (see Table 14), whereby the age of the patient is a determinant for the kind of dialysis delivered (see Table 15). These costs were based on Tariq et al. (2011), who used a microsimulation model developed by Havelaar et al. (2004), to estimate the costs of ESRD cases triggered by STEC O157 in the Netherlands.

Table 14. ESRD direct healthcare costs in 2011

	Unit cost (€)	Source
Full care centre haemodialysis – 1st year	94,183	Tariq et al. (2011)
Full care centre haemodialysis – 2nd year and following years	89,119	Tariq et al. (2011)
Peritoneal dialysis – 1st year	80,005	Tariq et al. (2011)
Peritoneal dialysis – 2nd year and following years	70,890	Tariq et al. (2011)
Kidney transplantation – 1st year	55,699	Tariq et al. (2011)
Kidney transplantation – 2nd year and following years	11,140	Tariq et al. (2011)

Table 15. Distribution over full care centre haemodialysis and peritoneal dialysis for the different age-classes (Source: Havelaar et al. (2004) and Tariq et al. (2011))

	Full care centre haemodialysis	Peritoneal dialysis
0-15 years	42%	58%
16-64 years	69%	31%
65-75 years	78%	22%
75+ years	89%	11%

4.2.8.2 Direct non-healthcare costs

No information was available on DNHC. We expect them to be only marginal, and did not consider them in the current study, similar to Tariq et al. (2011).

4.2.8.3 Indirect non-healthcare costs

There was no information available on potential sick leave in the case of ESRD. These costs were therefore also based on Tariq et al. (2011), who used a micro-simulation model developed by Havelaar et al. (2004), to estimate the costs of ESRD cases triggered by STEC O157 in the Netherlands.

4.2.9 Acquired listeriosis

4.2.9.1 Direct healthcare costs

According to the Dutch healthcare system where the GP is the gatekeeper for any other healthcare service, we assumed each symptomatic acquired listeriosis (AL) case would first visit his GP before being admitted to the hospital. The majority of cases is asymptomatic or has only mild symptoms (flu-like) and will not visit the GP (Anonymous, 2011). Given the severity of symptoms, we assumed all acquired listeriosis cases would be admitted to hospital. The average duration of hospitalization was assumed to be 23 days based on Ruzante et al. (2011). For 45% of the cases with either a sepsis and/or meningitis (Haagsma et al., 2009), we assumed a 5-day stay in the intensive care unit.

We assumed, as for GE cases (see section 4.2.1.1), about 1%, 19% and 71% of AL patients younger than 18 years, AL patients between 18-64 years and elderly AL patients (≥ 65 years) respectively, were transported to hospital by ambulance (Friesema et al., 2012).

Ruzante et al. (2011) reported that in Canada about 12% of all listeriosis cases would be sent home with support service and 23% would be transferred to another institution (i.e. long-term care facility; another facility providing in-patient hospital care or another type of institution). No information for the Netherlands was available. We therefore assumed, as for GE (see section 4.2.1.1), that approximately 5.9% (modelled as Beta-distribution 1 of 17) of the non-fatal and elderly (≥ 65 years) hospitalized AL patients would be transferred to a nursing home for 60 days (Friesema et al., 2012).

Following Bos et al. (2001) we assumed there are two additional consultations with a specialist after having left hospital.
For fatal AL cases we considered the same costs as for non-fatal AL cases, except for the admission to a nursing home after hospital discharge.

4.2.9.2 Direct non-healthcare costs

Travel costs to the GP and other medical specialists and to the hospital were the only direct non-healthcare costs considered, thereby making the same assumptions as for GE patients (see section 4.2.1.2).

4.2.9.3 Indirect non-healthcare costs

There was no information about sickness leave of potential caregivers. We therefore estimated productivity losses for caregivers of children younger than 15 years with AL. We assumed caregivers would be absent during the hospitalization of their children, in total 23 days (Ruzante et al., 2011), by applying the assumptions described in section 4.1.4.1.2. For patients 65 and older we assumed that in case of hospitalization, a caregiver would be absent for 0.4 hours per episode (see section 4.1.4.1.2). For fatal AL cases younger than 15 years sick leave of caregivers during hospitalization was considered, and for fatal AL cases 65 years and older we assumed caregivers would be absent for 0.4 hours during hospitalization.

For AL patients between 15 and 64 years productivity losses due to absence from paid work was considered. Duration of sick leave from paid work was estimated based on the assumed hospitalization stay, in total 23 days (Ruzante et al., 2011), and the assumptions described in section 4.1.4.1.2.
In concordance with the Dutch guidelines the estimate of work loss in case of death is based on the friction cost methods.

Productivity losses from paid work of patients were valued using standard tariff according to the corresponding age-classes (see Table 4). We further assumed a productivity loss of € 27.20 for caregivers of children and of € 31.11 for caregivers of adults who would be absent from paid work in order to take care of a sick child/person.

4.2.9.4 Scenario analysis

There is evidence that in particular elderly AL patients are at risk of being transferred from hospital into a nursing home before returning home (Ruzante et al., 2011), but information on the duration of stay was scarce. In our baseline we assumed an average stay in a nursing home to be 60 days, but this assumption was based on one single GE case (Friesema et al., 2012). We therefore conducted scenario analyses by multiplying the duration of the nursing stay by 50% (Scenario analysis: AL: shorter stay in nursing home) and 150% (Scenario analysis: AL: longer stay in nursing home) respectively.

4.2.10 Perinatal listeriosis

4.2.10.1 Direct healthcare costs

Infants born with a perinatal listeriosis (PL) have in 100% of the cases meningitis (Haagsma et al., 2009) and would be admitted to hospital if they are not already in hospital. Hospitalization stay was assumed to be 15 days (Bos et al., 2001), of which 5 days are spent in the Intensive Care Unit. For fatal PL cases we assumed about 100% of the hospitalization costs were incurred before dying.
Following Bos et al. (2001) we assumed further there are two additional outpatient visits in the first year to consult a specialist after hospital discharge.

4.2.10.2 Direct non-healthcare costs

Travel costs to the hospital and for outpatient visits were the only DNHC considered, making the same assumptions as for a GE patients (see section 4.2.1.2). For fatal PL cases travel costs to the hospital were considered.

4.2.10.3 Indirect non-healthcare costs

Given that PL cases are younger than 1 year and their mothers are most probably still on maternity leave, we assumed there would be no productivity losses from paid work for the primary caregiver for infants with PL. Following the friction cost approach, no productivity losses were considered for fatal PL cases, as all children are younger than 1 year.

4.2.11 Neurological sequelae after listeriosis

4.2.11.1 Direct healthcare costs

Listeriosis cases who had meningitis, both acquired listeriosis cases and perinatal listeriosis cases, do have a risk of developing neurological sequelae with remaining lifelong symptoms.

Independent of the age of disease onset, about 25% of the listeriosis survivors who develop neurological sequelae (Bos et al., 2001) are expected to require lifetime care in an institute for mentally and physically disabled people. These were the only DHC costs considered for this health outcome.

4.2.11.2 Direct non-healthcare costs

Given there was no information available we did not consider DNHC costs.

4.2.11.3 Indirect non-healthcare costs

For patients between 15 and 64 years who develop severe neurological sequelae requiring life-long institutional care for mental and physical disability, in accordance with the Dutch guidelines, we calculated once at disease onset the friction period for the corresponding age-group, see Table 4. No productivity losses were considered for PL cases developing neurological sequelae.

However, in the case of PL with neurological sequelae as a complication, we assumed about 50% of the survivors (Bos et al., 2001) would require special education throughout their school life, starting at the kindergarten, primary school as well as secondary school, see Table 4.

4.2.12 Acquired toxoplasmosis

Most cases of acquired toxoplasmosis (AT) are asymptomatic and self-limiting (Rorman et al., 2006). Symptomatic infections often have as only clinical findings focal lymphadenopathy, mostly often involving a single site around the neck (Rorman et al., 2006) and eventually resulting in a clinical biopsy (Anand et al., 2012). But a small fraction of infected persons will also develop chorioretinitis (Burnett et al., 1998; Gilbert et al., 2008; Commodaro et al., 2009), depending on the *Toxoplasma gondii* genotype. Although less common, acute infection in immune-competent patients can lead to fever, malaise, sore throat, headache and atypical lymphocytosis on peripheral blood smear (Rorman et al., 2006; Anand et al., 2012), but seldom leads to hospitalization. In areas other than Europe and North America other *Toxoplasma gondii* genotypes have been reported. In particular more virulent genotypes circulate in Latin America, leading to more severe clinical outcomes in infected patients than the European genotype (Demar et al., 2012).

In immuno-compromised patients, *T. gondii* may cause a severe central nervous system disease, resulting in brain lesions or diffuse encephalitis (Rorman et al., 2006). However, a US-study has shown that with the introduction of highly

active antiretroviral therapy in 1995, toxoplasmosis hospitalizations in HIV patients has dropped markedly (Jones and Roberts, 2012).

In the underlying disease burden model only incident cases of AT cases developing chorioretinitis were taken into consideration when estimating the disease burden (Havelaar et al., 2012). Information on incidences of symptomatic infections with focal lymphadenopathy and of hospitalized acquired toxoplasmosis cases were both missing. Therefore these costs were disregarded in the current study. We estimated only the costs related to chorioretinitis for acquired toxoplasmosis.

4.2.12.1 Direct healthcare costs

Chorioretinitis results in ocular lesions with symptoms ranging from asymptomatic lesions to clinical lesions whereby individuals can eventually have profound vision loss, even with treatment (Jones and Holland, 2010). In some cases ocular toxoplasmosis (OT) is recurrent.
Treatment of OT is generally recommended when lesions are large or threaten the central part of the retina (Jones and Holland, 2010). In a survey conducted among US uveitis specialists 15% would treat all cases regardless of clinical findings (Holland and Lewis, 2002). For the remaining respondents 'disease-associated factors such as location of lesions and presence of vitreous tumor inflammatory reactions determine if medical treatment is applied or not' (Holland and Lewis, 2002).

Based on a retrospective observational case series of 154 patients having visited UMC Utrecht between 1990-1999, Bosch et al. (2002a) observed that macular lesions were more common in the eyes of patients with a congenital infection, whereas peripheral lesions were more common among patients with postnatal acquired toxoplasmosis. Nearly one quarter of their patients with OT developed legal blindness in at least one eye (Bosch-Driessen et al., 2002a). In 2 of the 154 patients both eyes became legally blind. Both patients had congenital ocular toxoplasmosis (2 of 13 congenital ocular toxoplasmosis versus 0 of 141 acquired ocular toxoplasmosis) (Bosch-Driessen et al., 2002a). These authors reported that 79% of their patients developed recurrences. The same authors reported complications in 67 of the 154 (44%) patients. Twenty-seven of 154 (18%) required at least one (intra)ocular surgical procedure. Cataracts developed in 20 of 154 patients (13%), 14 of whom underwent a cataract extraction. Retinal detachment occurred in nine (6%) patients. Surgical removal of subretinal neovascularisation was performed in one case and enucleation because of a painful atrophic eye in another (Bosch-Driessen et al., 2002a).

According to the Dutch healthcare system, where the GP is the gatekeeper for any other healthcare service, we assumed that acquired toxoplasmosis cases developing chorioretinitis would always first visit their GP before being transferred to a specialist, in this case an ophthalmologist.

The specialist would test for toxoplasmosis and simultaneously also for other potential pathogens (in the current study we assumed 3 other potential pathogens) using serology (see Table 16). We assumed results would be discussed during a second consultation with the specialist and when necessary treatment would be started.

Based on Bosch-Driessen et al. (2002a) we assumed that in about 80% of the cases medical treatment would be applied, assuming that the current Dutch guidelines (SWAB, 2012) are followed and a combination of pyrimethamine,

sulfadiazine and folinic acid would be used. The assumed doses were based on the clinical trial of Bosch-Driessen et al. (2002b) with 100 mg pyrimethamine on day 1, followed by 50 mg pyrimethamine per day, 4000 mg/day of sulfadiazine and 15 mg/day folinic acid for at least 4 weeks (see Table 16).

Acquired toxoplasmosis cases presenting in an outbreak had a mean follow-up of 113.7 weeks (range 38-170 weeks) (Burnett et al., 1998). We therefore assumed follow-up consultations would occur by the end of treatment (month 1), in month 3 and one year later in month 15.

44% of the patients were assumed to develop complications leading to additional outpatient visits. Whether those complications were related to the first diagnosis or to a recurrence was unclear. For simplification we therefore assumed all of these cases would occur within the first year of infection. We assumed one additional outpatient visit per complication. Further we assumed that in 19% of all ocular toxoplasmosis patients a surgical procedure such as (intra)ocular surgical procedure or a surgical removal of subretinal neovascularisation would be required and in 9% a cataract extraction would be required (Bosch-Driessen et al., 2002a). For the costs see Table 16. We assumed none of these complications would require inpatient hospitalization.

Further we assumed that 79% of the patients would develop recurrences (Bosch-Driessen et al., 2002a) requiring one additional outpatient visit. Where necessary, medical treatment would be (re)started (~80% of the cases). For simplification we assumed all of these cases would occur within the first year of infection.

Table 16. Acquired toxoplasmosis-specific Unit Costs in 2011 €

	Unit cost (€)	Source
Diagnostic tests		
Serology: testing for IgG/pathogen	12.86	Nederlandse Zorgautoriteit (2012)
Serology: testing for IgM/pathogen	16.24	Nederlandse Zorgautoriteit (2012)
Serology: confirmation for IgM/pathogen	55.22	Nederlandse Zorgautoriteit (2012)
Medication cost[a]		
Sulfadiazine 100 mg[a]	2.88	CVZ (2012a)
Pyrimethamine 25 mg[a]	0.11	CVZ (2012a)
Folinic acid 15 mg (1 tablet)[a]	2.87	CVZ (2012a)
Surgerical procedures		
(Intra)ocular surgical procedure	332.61	Nederlandse Zorgautoriteit (2012)
Cataract extraction	108.48	Nederlandse Zorgautoriteit (2012)

a) Medication costs, including VAT, but exclusive pharmacy fee (see Table 4)

4.2.12.2 Direct non-healthcare costs

Travel costs to the GP and medical specialists were the only direct non-healthcare costs considered, by using the general assumptions as described in section 4.1.4.1.1.

4.2.12.3 Indirect non-healthcare costs

Although, according to Bosch et al. (2002a), some of the acquired ocular toxoplasmosis patients might develop legal blindness in one eye, these authors found no AT patients who had developed blindness in both eyes. Blindness in one eye, however, seldom results in permanent work disability. There was no information available as to whether legal blindness of one eye might result in a temporary sick leave or not. We therefore did not consider such costs in the current study. There was also no information available as to whether acute chorioretinitis might lead to absence from paid work, so we disregarded these costs. However, we did assume that doctors' consultations and outpatient visits would result in some additional four hours and eight hours work absence per visit respectively, applying the assumptions described in section 4.1.4.1.2.

There was no information about sickness leave of potential caregivers. We therefore estimated productivity losses for caregivers of children younger than 15 years with chorioretinitis. We assumed caregivers would be absent for GP visits and outpatients visits, applying the assumptions described in section 4.1.4.1.2.

Productivity losses from paid work of patients were valued using standard tariff according to the corresponding age-classes (see Table 4). We further assumed a productivity loss of € 27.20 for caregivers of children who would be absent from paid work in order to take care of a sick child/person.

4.2.13 Congenital toxoplasmosis

Vertical transmission from a recently infected pregnant woman to her fetus may lead to congenital toxoplasmosis (Rorman et al., 2006). Congenital

toxoplasmosis (CT) can result either in asymptomatic infections, with or without developing symptoms later in life, mostly chorioretinitis, or mild to severe clinical symptoms at birth i.e. chorioretinitis, intracranial calcifications, hydrocephalus and central nervous system (CNS) abnormalities, some of them being fatal (Rorman et al., 2006; Havelaar et al., 2007; Kortbeek et al., 2009; Havelaar et al., 2012). Fetal infection may also result in natural abortion and stillbirth (Rorman et al., 2006).

For the mother, the toxoplasmosis infection generally does not result in clinical manifestations, although some may have regional lymphadenopathy or occasionally acquired chorioretinitis (Rorman et al., 2006). Potential disease burden and associated costs of affected mothers, if existing, are therefore considered as acquired toxoplasmosis (see section 4.2.12).

We could identify several cost studies (Roberts and Frenkel, 1990; Roberts et al., 1994; Buzby and Roberts, 1997) and economic evaluations including costs for congenital toxoplasmosis (Wilson and Remington, 1980; Henderson et al., 1984; Joss et al., 1990; Stray-Pedersen and Jenum, 1992; Mohammed et al., 1994; Lappalainen et al., 1995; Sagmeister et al., 1995; Stillwaggon et al., 2011). All except one of the identified studies were conducted before 2000 and are included in the literature review on cost-effectiveness of preventive congenital toxoplasmosis programs by Binquet et al. (2002). The more recent study was published in 2011 by Stillwaggon et al. (2011). Apart from one (Mohammed et al., 1994), all studies were conducted in European or North-American countries. Given there are different genotypes in the world, some of which lead to more severe clinical outcomes in infected patients than the European genotype (Demar et al., 2012) does, we have concentrated on the European and North-American studies, and have summarized the underlying assumptions and resource utilization for the European and North-American studies in Appendix I.

There were also a few cohort studies with follow-up reporting on observed health outcomes and/or resource utilizations of congenital toxoplasmosis cases over the years (see Appendix II). Depending on screening policies in the different countries, prenatal and/or postnatal treatment of congenital toxoplasmosis cases might have taken place. According to the findings of Cortina-Borja et al. (2010), an observational prospective cohort study, ‘prenatal treatment seems to reduce the risk of severe neurologic sequelae in infants’, whereas prenatal treatment does not seem to reduce the risk for chorioretinitis (Freeman et al., 2008; Peyron et al., 2011). In previous systematic reviews conducted by EUROTOX, an European consortium, the authors concluded there was not sufficient evidence treatment would have an effect on outcomes, either for postnatal treatment (Thiébaut et al., 2005) or for prenatal treatment (Thiébaut et al, 2006).

In the underlying disease burden model incident cases of CT were considered, taking into account the health outcomes: chorioretinitis, either diagnosed in the 1st year of life (hereafter referred to as ‘chorioretinitis’), or later in life (hereafter referred to as ‘post-1-year chorioretinitis’); intracranial calcifications; hydrocephalus and central nervous system (CNS) abnormalities (Havelaar et al., 2012). The disease burden model does not make a distinction if a congenital infected infant with *T. gondii* develops only one symptom (e.g. post-1-year chorioretinitis) or several symptoms simultaneously (e.g. infant with hydrocephalus and chorioretinitis). Additionally, the disease burden model

considers stillbirth and neonatal death as a consequence of congenital toxoplasmosis (Havelaar et al., 2012).

4.2.13.1 Direct healthcare costs

4.2.13.1.1 Diagnostic

In order to treat congenital toxoplasmosis accurately, we assumed that for all congenital toxoplasmosis (CT) cases with symptoms at birth, including neonatal deaths, serological diagnostic tests are conducted in both mother and child, as well as diagnostic testing in the placenta (see Table 17; Malgosia Verboon, UMCU Utrecht; personal communication August 2012). We assumed testing is applied for toxoplasmosis and simultaneously also for other potential pathogens (in the current study we assumed 3 other potential pathogens). We further assumed that identified newborns would be examined by a pediatrician for hearing, and undergo ophthalmoscopy and cerebral ultrasound (Schmidt et al., 2006; Roser et al., 2010). In the case of severe CNS damage eventually also an MRI-scan would be conducted (Malgosia Verboon, UMCU Utrecht; personal communication August 2012), see Table 17.

In case of stillbirth-abortion, serological tests of the mother (see Table 17) would be applied to determine potential reasons for the stillbirth. For post-1-year chorioretinitis cases diagnosed later in life, serological diagnostic tests (see Table 17) would only be conducted for the affected child when first symptoms occur.

4.2.13.1.2 Follow-up in the case of stillbirth

For stillbirth/spontaneous abortion we assumed the woman concerned would first, according to the Dutch system, consult their GP, who would refer her to a gynaecologist. In order to make a proper diagnosis, the gynaecologist would request some serological tests of the mother to determine potential reasons for the stillbirth. We assumed testing is applied for 4 potential pathogens that might result in stillbirths, if acquired during pregnancy (e.g. toxoplasmosis, cytomegalovirus, rubella, listeriosis).
Test results are assumed to be discussed in a follow-up visit with the gynaecologist.

Table 17. Congenital toxoplasmosis-specific unit costs in 2011 €

	Unit cost (€)	Source
Diagnostic tests		
Serology: testing for IgG/pathogen	12.86	Nederlandse Zorgautoriteit (2012)
Serology: testing for IgM/pathogen	16.24	Nederlandse Zorgautoriteit (2012)
Serology: confirmation for IgM/pathogen	55.22	Nederlandse Zorgautoriteit (2012)
Testing placenta	22.87	Nederlandse Zorgautoriteit (2012)
Diagnostic procedures by pediatrician for infants with symptoms at birth		
Ophthalmoscope examination	48.39	Nederlandse Zorgautoriteit (2012)
Hearing examination	23.41	Nederlandse Zorgautoriteit (2012)
Cerebral ultrasound	263.93	Halkes et al. (2006)
MRI-scan	294.73	Halkes et al. (2006)
Medication cost[a]		
Sulfadiazine 1 mg[a]	0.04	CVZ (2012a)
Pyrimethamine 100 mg[a]	5.78	CVZ (2012a)
Folinic acid 5 mg[a]	0.97	CVZ (2012a)
Therapeutic help		
Cost/sitting	32.65[b]	Hakkart-van Roijen et al. (2010)
Surgerical procedures		
(Intra)ocular surgical procedure	332.61	Nederlandse Zorgautoriteit (2012)
Cataract extraction	108.48	Nederlandse Zorgautoriteit (2012)
Placing a drain	6,838.20	Nederlandse Zorgautoriteit (2012)

a) Medication costs, including VAT, but exclusive pharmacy fee (see Table 4)
b) Average costs of speech therapy, physiotherapy, remedial therapy and occupational therapy.

4.2.13.1.3 Treatment and hospitalization of CT after birth

For all CT cases with symptoms at birth, including neonatal deaths, we assumed they would be admitted to hospital for 4 weeks (Henderson et al., 1984; Roberts and Frenkel, 1990; Lappalainen et al., 1995). We further assumed, in case of hydrocephalus, a drain by a specialist in neurosurgery is necessary (Malgosia Verboon, UMCU Utrecht; personal communication August 2012), see Table 17. We further assumed all these cases would receive medical treatment during one-year with sulphadiazine (100 mg/kg/day) in two divided doses, and pyrimethamine (2 mg/kg/day on the first and second day in 2 doses, thereafter 1 mg/kg/day in 1 dosis), supplemented with folinic acid (5 mg) administered twice a week, based on the current practice as applied within UMCU (Malgosia Verboon, UMCU Utrecht; personal communication Augustus 2012), see Table 17. Average body life-weights from the WHO[7] were used to estimate the age-specific doses.

[7] Source: For children from 0-5 years: www.who.int/childgrowth/standards/en/; accessed on October 2012

Neonatal deaths receive medical treatment until their death, which is assumed to occur on average four weeks after birth.

4.2.13.1.4 Follow-up of cases with intracranial calcification, hydrocephalys and CNS abnormalities

We assumed CT cases with intracranial calcification, hydrocephalus and CNS abnormalities would have repeated neurological examination during an outpatient visit at 3, 6, 9 and 12 months of age, and a yearly follow-up until 20 years of age (Schmidt et al., 2006; Roser et al., 2010). The extent of other medication prescribed is questionable. The complication of epilepsy, controlled by medication, is a finding reported in follow-up studies (Wallon et al., 2004; Berrebi et al., 2010), but detailed information with respect to applied dose and treatment duration is missing, thus we disregard these costs in our estimates. In case of hydrocephalus additional drains placed by a specialist in neurosurgery might be required during the whole lifetime. Having no information at hand, we assumed hydrocephalus patients would experience on average 10-day hospital periods per year for therapeutic intervention; however, only until the age of 20 (Lappalainen et al., 1995).

Most of the studies with a longer-follow-up period summarized in Appendix II reported that congenital infected children were not mentally retarded and the education level was comparable with that of the general population (Koppe et al., 1986; Peyron et al., 2011). The rare cases which showed some retarded development, often could catch up in later years; e.g. Berrébi et al. (2010) reported 1 of 112 infected cases had a slight language delay at 40 months, for which this child received motor rehabilitation and speech therapy in his earlier life years, allowing him to catch up with his peers. 'He has been attending school normally since the age of 7 years' (Berrebi et al., 2010). Wallon et al. (2004) reported that of 327 children with a CT infection, 3 children with hydrocephalus had moderate psychomotoric retardation. Lebech et al. (1999) reported that of 27 children 1 child was blind in one eye and had retarded development. Having no better information, we assumed 1 of 112 (Betadistribution) CT cases with intracranial calcification, hydrocephalus and CNS abnormalities would require therapeutic help (between age 2 and 7 years) twice a week.

4.2.13.1.5 Follow-up of cases with chorioritinitis

For CT cases developing chorioretinitis in their first year of life, we assumed follow-up consultations during an outpatient visit occur at 1, 3, 6, 9 and 12 months of age and a yearly follow-up until 20 years of age.

Recurrences of ocular toxoplasmosis, requiring additional treatment is a finding reported in literature and ranges from 11.8% (Peyron et al., 2011) to 29% (Wallon et al., 2004) up to 79% (Bosch-Driessen et al., 2002a). Presuming prenatal treatment does not reduce the risk for congenital chorioretinitis (Freeman et al., 2008; Peyron et al., 2011), we assumed 29% (most likely estimate; 11.8%-79%) would have recurrent ocular toxoplasmosis, requiring an additional treatment with medication in the following years after their diagnosis, where the majority (~80%) is assumed to occur within the first year after the primary diagnosis. For simplicity reasons we assumed that remaining recurrences develop within the second year after the primary diagnosis.

Between 44% to 59% of the chorioretinitis patients (Bosch-Driessen et al., 2002a; Tan et al., 2007) developed complications leading to additional

outpatient visits. Whether those complications were related to the first diagnosis or to a later occurring recurrence was unclear. We assumed on average 50% would have complications, requiring one additional outpatient visit per complication. Further we assumed that in 19% of all chorioretinitis patients a surgical procedure such as (intra)ocular surgical procedure or a surgical removal of subretinal neovascularisation would be required, and in 9% a cataract extraction (Bosch-Driessen et al., 2002a). For the costs see Table 17. We assumed none of these complications would require inpatient hospitalization.

Children developing unilateral blindness, but having no other health outcomes which cause mental retardation, seem to be able to cope with this handicap, as the findings of several long-term cohort studies (Koppe et al., 1986; Peyron et al., 2011) have shown. Children with bilateral blindness, with or without mental retardation, might require institutional care. Based on a Dutch study (Bosch-Driessen et al., 2002a), only congenital ocular toxoplasmosis resulted in legal blindness in both eyes, hence we assumed that minimum 0% (Wallon et al., 2004) and maximum 2% (Schmidt et al., 2006; Tan et al., 2007) of all chorioretinitis cases would develop bilateral blindness and would therefore require institutional care for their remaining life.

4.2.13.1.6 Post-1-year chorioretinitis cases

Based on Havelaar et al.(2012) we assumed that at 1-year post-infection and up to the age of 20 years, the hazard rate of developing post-1-year chorioretinitis cases is most likely 2% (range: 1%-3%).

For CT cases developing post-1-year chorioretinitis later in their life, we assumed, according to the Dutch healthcare system where the GP is the gatekeeper for any other healthcare service, these cases would first visit their GP before being transferred to a specialist, an ophthalmologist. The specialist would then test for toxoplasmosis using various diagnostic tests (see section 4.2.13.1.1). But as other diseases have similar symptoms, we assumed the tests are also conducted for three other pathogens simultaneously. Results would have to be discussed with the parents/patients and treatment would be started, leading to a second visit. A 4-week treatment was assumed consisting of sulphadiazine (100 mg/kg/day) in two divided doses, and pyrimethamine (2 mg/kg on the first day, thereafter 1 mg/kg/day), supplemented with folinic acid. Follow-up consultations are assumed to occur by the end of treatment (month 1), in month 3 and one year later in month 15. Average body life-weights[8] were used to estimate the age-specific doses.

Recurrences of ocular toxoplasmosis requiring additional treatment is a finding reported in the literature and ranges from 11.8% (Peyron et al., 2011) to 29% (Wallon et al., 2004) up to 79% (Bosch-Driessen et al., 2002a). Presuming prenatal treatment does not reduce the risk for congenital chorioretinitis (Freeman et al., 2008; Peyron et al., 2011), we assumed that 29% (most likely estimate; 11.8%-79%) would have recurrent ocular toxoplasmosis, requiring an additional treatment with medication in the following years after their diagnosis; the majority (~80%) is assumed to occur within the first year after the primary

[8] Source: For children from 0-5 years: www.who.int/childgrowth/standards/en/; for children from 5-10 years: http://www.who.int/growthref/who2007_weight_for_age_field/en/index.html; and for children/adolescents from 10-20 years: http://www.bibliofood.be/NL/Gezonde_voeding-Percentielen_en_groeitabellen-8-28-V.html. All accessed on October 2012

diagnosis. For reasons of simplicity we assumed the remaining recurrences develop within the second year after the primary diagnosis.

Between 44% to 59% of the chorioretinitis patients (Bosch-Driessen et al., 2002a; Tan et al., 2007) develop complications leading to additional outpatient visits. Whether those complications are related to the first diagnosis or to a later occurring recurrence is unclear. We assumed on average 50% would have complications, requiring one additional outpatient visit per complication. Further we assumed that in 19% of all ocular toxoplasmosis patients a surgical procedures such as (intra)ocular surgical procedure or a surgical removal of subretinal neovascularisation would be required and in 9% a cataract extraction (Bosch-Driessen et al., 2002a). For the costs see Table 17. We assumed none of these complications would require inpatient hospitalization.

We assumed, as for perinatal chorioretinitis cases (see section 4.2.13.1.5) post-1-year chorioretinitis cases developing unilateral blindness don't require institutional care. But the minimum of 0% (Wallon et al., 2004) and maximum of 2% (Schmidt et al., 2006; Tan et al., 2007) of all post-1-year chorioretinitis cases develop bilateral blindness and therefore require institutional care for their remaining life.

4.2.13.2 Direct non-healthcare costs

For hospitalized infants, including neonatal deaths, daily travel costs of parents were considered using the general assumptions described in section 4.1.4.1.1. Further we considered for all non-fatal congenital toxoplasmosis cases travel costs to the GP and to the medical specialists, by using the general assumptions as described in section 4.1.4.1.1.

In the case of stillbirth, travel costs of the mother to the GP and to the gynaecologist were considered, applying the assumptions described in section 4.1.4.1.1.

4.2.13.3 Indirect non-healthcare costs

4.2.13.3.1 Productivity losses

There was no information about sickness leave of potential caregivers of congenital toxoplasmosis cases. Given the fact that hospitalization of congenital toxoplasmosis infants mostly occurs within the first months after birth, including neonatal deaths, mothers would be on maternal leave. We therefore assumed no sick leave of caregivers during this period. For all outpatients visits and hospitalization stays later in life and up to the age of 18 years, productivity losses for caregivers were assumed. We assumed caregivers would be absent from work for GP visits, outpatients visits and during the hospitalization stay of their child, applying the assumptions described in section 4.1.4.1.2. We assumed a productivity loss of € 27.20/hour for caregivers of children. No productivity losses were considered for caregivers of patients 15 years and older.

Productivity losses from paid work for women having a stillbirth/abortion were considered and valued using a standard tariff (mean, all ages), see Table 4. Having no information on sick leave, we assumed a consultation of a GP would result in sickness leave of 4 hours, whereas a consultation of a gynaecologist would result in sickness leave of 8 hours and applying the assumptions described in section 4.1.4.1.2.

Chorioretinitis, with or without severe unilateral visual impairment in children, seems not to be a handicap for daily life, as such children, if having no other toxoplasmosis-associated symptoms, were able to follow regular schools and acquire a comparable education level as the general population (Peyron et al., 2011), whereas bilateral blindness might cause a handicap. As we use the friction approach to estimate the productivity losses, no productivity losses will be considered for children with bilateral blindness while not being able to enter a normal work life later in their life.

Productivity losses from paid work for toxoplasmosis patients between 15 and 64 years were considered. We assumed caregivers would be absent for GP visits, outpatients visits and during hospitalization stay, applying the assumptions described in section 4.1.4.1.2. Productivity losses from paid work of patients were valued using standard tariff, according to the corresponding age-classes (see Table 4).

4.2.13.3.2. Special education

Children with bilateral blindness were assumed to require special education throughout their whole school life, starting at the kindergarten, and continuing through primary and secondary education. No other CT cases would require special education in the baseline.

4.2.13.4 Scenario analysis

Most of the followed cohorts were congenitally infected children identified either pre- or post-natal. In the case of screening programs of pregnant women, pregnancies might be terminated because of suspected or proven fetal congenital toxoplasmosis infection. Wallon et al.(2004) reported that of 1506 consecutive pregnant women, 27 pregnancies were terminated as a result of suspected or proven fetal infection. But what happens with these pregnancies if there is no screening program as is the case in the Netherlands? Some of those cases would have resulted in either a spontaneous abortion, stillbirth or postnatal death. But for those surviving, would they have severe neurological damage, with or without severe visual impairment? And would they require lifelong institutional care for persons with severe neurological damage, as was assumed in most published cost and cost-effectiveness studies (see Appendix I)? Having no information at hand, we assumed in our baseline that all those terminated pregnancies would not have resulted in CT cases with bad outcomes and consequently in no additional medical costs than the ones assumed so far. However, in a scenario analysis we estimated all CT cases with CNS abnormalities would have severe neurological damage (Scenario analysis: CT: CNS abnormalities with bad outcomes), and they all (i.e. all CT cases with CNS abnormalities) would have required life-long institutional care and special education.

In this scenario analysis we assumed CT cases with CNS abnormalities would have additional DHC costs: the costs for lifetime care in an institute for mentally and physically disabled people. Further we assumed all CT cases with CNS abnormalities required special education throughout their whole school life, starting at the kindergarten, primary and secondary education.

4.3 Results

4.3.1 Costs per pathogen

4.3.1.1 Baseline

The total costs-of-illness of the fourteen food-related pathogens in 2011 were estimated at € 468 million, if undiscounted and at € 416 million, if discounted at 4% (see Table 18). DHC accounted for 24% and INHC for 74% of the total costs. DNHC is negligible at about 2% of the total costs (see Table 19 and Figure 3). Table 18 shows the undiscounted and discounted average costs by pathogen on a population level (costs in million euros per year) and on an individual basis (costs in euros per 1,000 cases). For international comparison, standardized data (costs in thousand euros per 100,000 inhabitants) are also reported. Figure 2 shows the discounted average costs by pathogen on a population level (costs in million euros per year) and the attendant uncertainty.

Table 19 shows the average costs by pathogen on a population level split up into direct healthcare costs (DHC), direct non-healthcare costs (DNHC) and indirect non-healthcare costs (INHC).

At population level, norovirus, *Campylobacter* spp. and rotavirus were associated with the highest costs, for both discounted and undiscounted costs. Norovirus was estimated at € 105.8 million per year, both discounted and undiscounted. *Campylobacter* spp. was estimated at € 81.5 million per year (undiscounted) and at € 76.1 million per year, if discounted at 4%. Rotavirus was estimated at € 73.3 million per year, both discounted and undiscounted. The cost-of-illness of hepatitis-E virus is with € 0.2 million per year, both discounted and undiscounted, the lowest (see Table 18).

Discounting has an impact on *Toxoplasma gondii*, *Listeria monocytogenes*, STEC O157, *Campylobacter* spp. and *Salmonella* spp., and affects ranking. The discounted costs of *Toxoplasma gondii*, *Listeria monocytogenes* and STEC O157 are equal to 36%, 49% and 52% of the undiscounted costs respectively, whereas the discounted costs of *Campylobacter* spp. and *Salmonella* spp. are equal to 93% of the undiscounted costs. *Toxoplasma gondii* has with € 55 million undiscounted costs, the fourth highest costs at the population level, but falls to the seventh rank when comparing discounted costs. *Listeria monocytogenes* has with € 9.4 million undiscounted costs, the ninth highest costs at the population level, but falls to the eleventh rank when comparing the discounted costs (see Table 18).

Cost-of-illness per case varied between € 275,282 for perinatal listeriosis to € 150 for *Clostridium perfringens.* Perinatal listeriosis, congenital toxoplasmosis, acquired listeriosis, acquired toxoplasmosis and hepatitis-E virus, all non-gastroenteric pathogens, are the ones with the highest cost burden per case. Protozoa- GE pathogens and virus-GE pathogens have the lowest cost burden per case (see Table 18).

Given that the majority of costs for gastroenteritis pathogens were indirect non-healthcare costs, the ranking of the gastroenteritis pathogens is similar to the one found for total costs, if ranked at the population level (see Table19). The non-gastrointestinal pathogens *Toxoplasma gondii* and *Listeria monocytogenes* have with less than 10% INHC of the total costs, the lowest proportion of INHC costs, and are therefore ranked lower. At the population level, the INHC of norovirus, rotavirus and *Campylobacter* spp. are with € 97 million, € 59.5 million

and € 47.5 million the highest per year. STEC O157 and hepatitis-E-virus are with € 0.4 million and € 0.1 million the lowest (Table 19).

Figure 2 – Average discounted costs and attendant uncertainty (in million euro per year) for the different pathogens under study in 2011

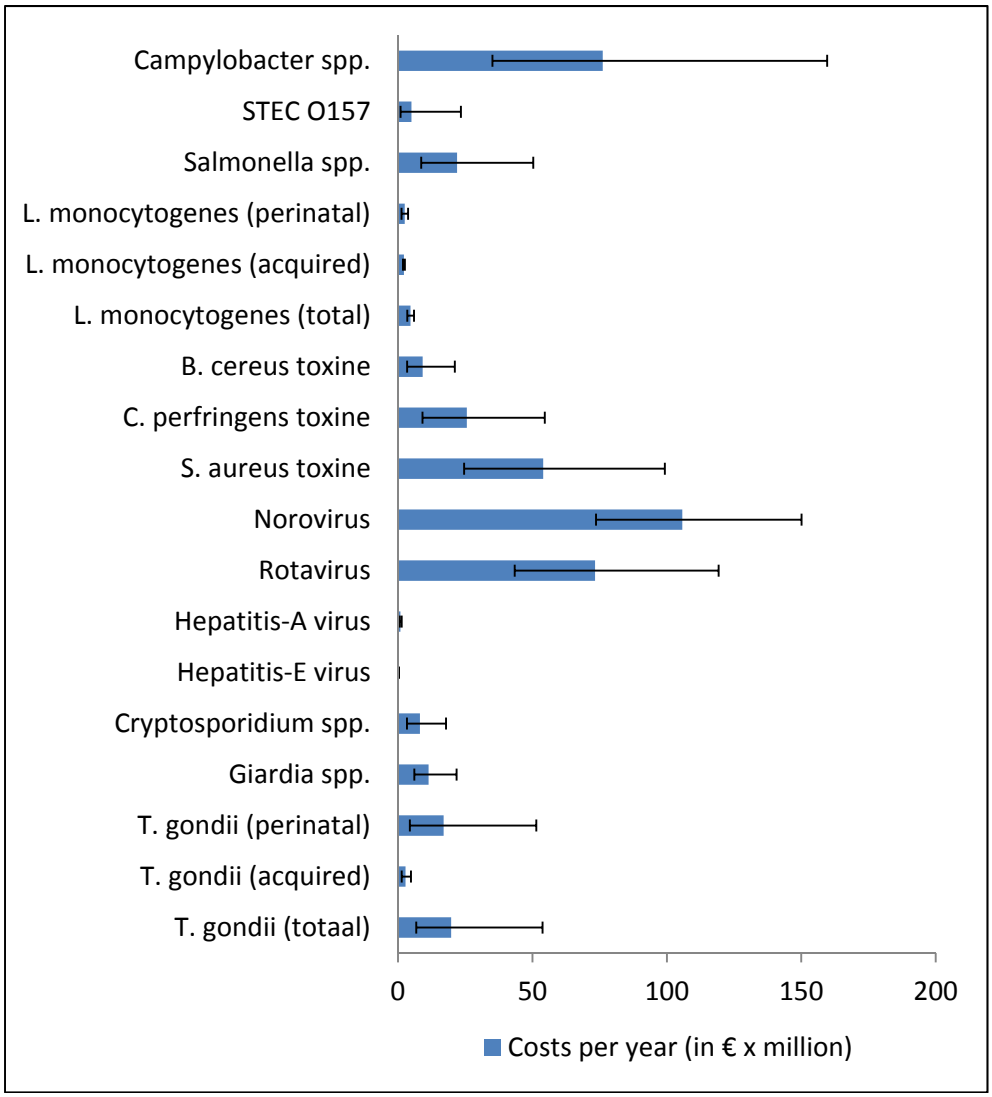


Table 18. Estimated average costs in 2011 for the different pathogens under study for the total population (x 1,000,000), per 100,000 (x 1,000) and per 1,000 cases. Results are presented undiscounted (0%) and discounted (4%)

Pathogen	**Costs per year (x 1,000,000)**		**Costs per 100,000 (x 1,000)**		**Costs per 1,000 cases (x 1,000)**	
	0%	4%	0%	4%	0%	4%
Bacteria infections						
Campylobacter spp.	81.5	76.1	489	457	757	706
STEC O157	4.8	2.1	29	13	4.555	2.342
Salmonella spp.	23.7	22.0	142	132	640	593
Listeria monocytogenes (perinatal)	7.1	2.5	42	15	786,070	275,282
Listeria monocytogenes (acquired)	2.3	2.2	14	13	29,551	27,430
Listeria monocytogenes (total)	9.4	4.6	56	28	106,922	52,779
Bacteria-toxin producing						
Bacillus cereus	9.2	9.2	55	55	181	181
Clostridium perfringens	25.6	25.6	154	154	150	150
Staphylococcus aureus	54.0	54.0	324	324	185	185
Viruses						
Norovirus	105.8	105.8	635	635	152	152
Rotavirus	73.3	73.3	440	440	244	244
Hepatitis A virus	0.9	0.9	5	5	1,426	1,426
Hepatitis E virus	0.2	0.2	1	1	4,224	4,224
Protozoa						
Cryptosporidium spp.	8.1	8.1	49	49	289	289
Giardia spp.	11.3	11.3	68	68	180	180
Toxoplasma gondii. (congenital)	52.1	17.0	313	102	143,182	46,596
Toxoplasma gondii.(acquired)	2.8	2.8	17	17	6,567	6,559
Toxoplasma gondii.(total)	54.9	19.8	330	119	69,514	25,006
Sum	**467.6**	**415.9**	**2,778**	**2,468**	**267**	**238**

Table 19. Average DHC, DNHC and INHC costs per year in € million in 2011, both undiscounted and discounted for the different pathogens under study

Pathogen	DHC		DNHC		INHC	
	0%	4%	0%	4%	0%	4%
Bacteria infections						
Campylobacter spp.	30.2	26.7	2.0	1.8	49.3	47.5
STEC O157	9.3	4.6	0.0	0.0	0.4	0.4
Salmonella spp.	11.5	10.3	0.7	0.6	11.5	11.1
Listeria monocytogenes (perinatal)	6.6	2.1	0.0	0.0	0.5	0.3
Listeria monocytogenes (acquired)	2.3	2.1	0.0	0.0	0.1	0.1
Listeria monocytogenes (total)	8.8	4.2	0.0	0.0	0.6	0.4
Bacteria-toxin producing						
Bacillus cereus	0.9	0.9	0.2	0.2	8.1	8.1
Clostridium perfringens	4.0	4.0	0.7	0.7	20.9	20.9
Staphylococcus aureus	4.6	4.6	1.2	1.2	48.1	48.1
Viruses						
Norovirus	6.5	6.5	2.3	2.3	97.0	97.0
Rotavirus	12.5	12.5	1.3	1.3	59.5	59.5
Hepatitis A virus	0.3	0.3	0.0	0.0	0.6	0.6
Hepatitis E virus	0.1	0.1	0.0	0.0	0.1	0.1
Protozoa						
Cryptosporidium spp.	2.7	2.7	0.1	0.1	5.3	5.3
Giardia spp.	1.8	1.8	0.3	0.3	9.2	9.2
Toxoplasmosis gondii (congenital)	50.9	16.5	0.1	0.0	1.1	0.5
Toxoplasmosis gondii (acquired)	2.4	2.4	0.0	0.0	0.4	0.4
Toxoplasmosis gondii (total)	53.3	18.9	0.1	0.1	1.5	0.8
Sum	146.5	98.1	8.9	8.6	312.1	309.0

Note: DHC= direct healthcare costs; DNHC= direct non-healthcare costs and INHC=indirect non-healthcare costs

Figure 3 – Distribution of total discounted costs in DHC, DNHC and INHC for the different pathogens under study

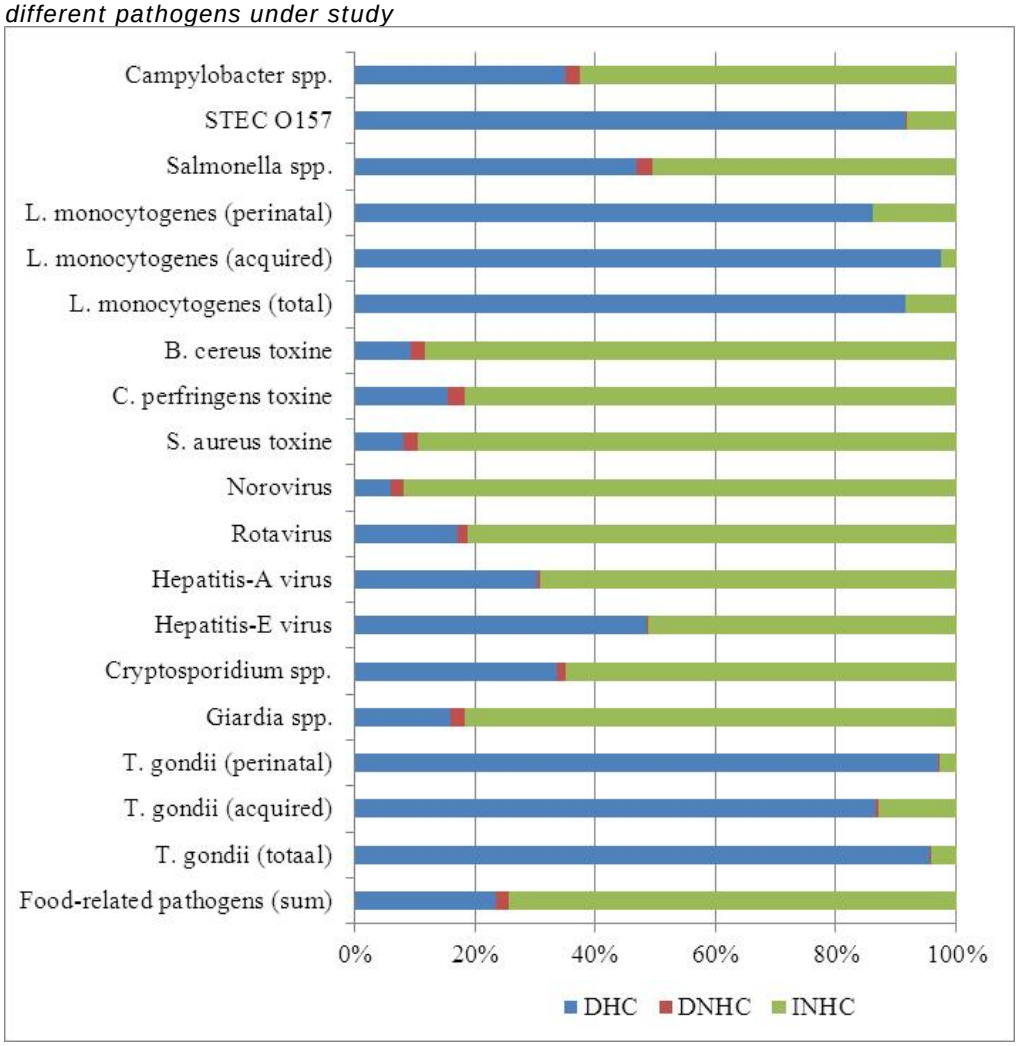


Table 20 and Table 21 show the discounted costs by pathogen and by health outcome on a population level. Costs are expressed in million euros.

For bacteria GE-associated pathogens such as STEC O157, *Campylobacter* spp. and *Salmonella* spp., GE-associated costs accounts for 8%, 49% and 58% of the total costs. IBS is a major driver of the costs for both, Campylobacter (38% of the total costs, and 76% from the costs associated with sequel) and Salmonella (37% of the total costs, and 89% from the costs associated with sequel). For more details see Table 20. HUS and ESRD are the major cost drivers in the case of STEC O157.

For non-gastroenteric pathogens the perinatal infection in particular drives the costs, both for *Listeria monocytogenes* (54% of the total costs) and *Toxoplasma gondii* (86% of the total costs).

Table 20. Estimated average discounted costs per pathogen and per health outcome for GE-associated pathogens for 2011

Pathogens	Health outcomes (in € mio)							Totals (in € mio)
	GE	ReA	IBD	IBS	HUS	ESRD	GBS	
Bacteria GE infections								
Campylobacter spp.	37.7	0.2	2.8	29.1	-	-	6.2	76.2
STEC O157	0.4	-	-	-	0.6	3.9	-	5.0
Salmonella spp.	12.8	0.0	1.0	8.1	-	-	-	22.0
Bacteria-toxin producing								
Bacillus cereus	9.2	-	-	-	-	-	-	9.2
Clostridium perfringens	25.6	-	-	-	-	-	-	25.6
Staphylococcus aureus	54.0	-	-	-	-	-	-	54.0
Viruses								
Norovirus	105.8	-	-	-	-	-	-	105.8
Rotavirus	73.3	-	-	-	-	-	-	73.3
Protozoa								
Cryptosporidium spp.	8.1	-	-	-	-	-	-	8.1
Giardia spp.	11.3	-	-	-	-	-	-	11.3

Note: GE=gastroenteritis; ReA= reactive arthritis; IBD=inflammatory bowel disease; IBS=irritable bowel syndrome; HUS= haemolytic uremic syndrome; ESRD=end-stage renal disease; GBS= Guillain-Barré Syndrome

Table 21. Estimated average discounted costs and attendant uncertainty per pathogen and per health outcome for non-GE-associated pathogens for 2011

Pathogens	Health outcomes (in € mio)	Totals (in € mio)
Bacteria GE infections		
Listeria monocytogenes		4.6
Acquired	1.5	
Sequelae due to acquired	0.7	
Perinatal	0.2	
Sequelae due to perinatal	2.3	
Viruses		
Hepatitis-A virus	0.9	0.9
Hepatitis-E virus	0.2	0.2
Protozoa		
Toxoplasma gondii		19.7
Acquired chorioretinitis	2.8	
Perinatal chorioretinitis	7.7	
Perinatal Post1year chorioretinitis	5.2	
Perinatal intracranial calcifications	2.1	
Perinatal hydrocephalus	1.6	
Perinatal CNS abnormalities	0.3	
Perinatal stillbirth	0.001	
Perinatal neonatal death	0.05	

4.3.1.2 Scenario analyses

Scenario analyses were applied for all pathogens with the health outcomes gastroenteritis (GE), for all pathogens with the health outcome IBS, for acquired listeriosis and for congenital toxoplasmosis cases developing CNS abnormalities.

We studied the impact of a shorter (longer) stay in a nursing home after discharge from the hospital of elderly GE patients (Scenario analysis: GE - shorter (longer) nursing home stay). But also elderly hospitalized cases with acquired listeria might be admitted temporarily to a nursing home after discharge from the hospital. We therefore studied also for acquired listeria cases the impact of a shorter (longer) stay in a nursing home after discharge from the hospital of elderly hospitalized persons (Scenario analysis: AL - shorter (longer) nursing home stay). We further studied the impact of higher direct healthcare costs (DHC) in the case of IBS (Scenario analysis: IBS - higher DHC). We also assumed in a scenario analysis congenital toxoplasmosis cases with CNS abnormalities would have a bad outcome with the consequences of life-long institutional care and special education for the affected cases (Scenario analysis: CT with bad outcome).

Only the scenario analyses IBS - higher DHC and CT with bad outcome had a significant impact on the costs. In particular CT with bad outcome with the underlying assumption that all congenital toxoplasmosis with CNS abnormalities would require life-long institutional care and special education would increase the total costs of congenital toxoplasmosis by almost 250% (see Table 22). But also higher direct healthcare costs of IBS would increase the total costs for *Campylobacter* spp. by 116% and the total costs for *Salmonella* spp. by 118%. Whereas a longer (shorter) temporary admission to a nursing home of elderly persons after hospital discharge has only a marginal impact on the costs, independent if admitted with either GE or listeriosis (see Table 22).

The conducted scenario analyses are summarized in Table 22. Results are shown for the baseline assumptions as well as for conducted scenario analyses.

Table 22. Average discounted costs per year in € million in 2011 for both baseline and scenario analyses.

Pathogen	**Costs per year (x 1,000,000)**				
	Baseline	GE / AL: Shorter nursing home stay	GE / AL: Longer nursing home stay	IBS: Higher DHC	CT with bad outcome
Bacteria infections					
Campylobacter spp.	76.1	76.0	76.2	88.1	-
STEC O157	5.0	5.0	5.0	-	-
Salmonella spp.	22.0	21.9	22.1	26.0	-
Listeria monocytogenes (acquired)	2.2	2.1	2.2	-	-
Listeria monocytogenes (total)	4.6	4.6	4.7	-	-
Bacteria-toxin producing					
Bacillus cereus	9.2	9.1	9.2	-	-
Clostridium perfringens	25.6	25.5	25.7	-	-
Staphylococcus aureus	54.0	53.8	54.2	-	-
Virus					
Norovirus	105.8	105.7	105.8	-	-
Rotavirus	73.3	73.3	73.3	-	-
Protozoa					
Cryptosporidium spp.	8.1	8.1	8.2	-	-
Giardia spp.	11.3	11.3	11.3	-	-
Toxoplasmosis gondii (congenital)	17.0	-	-	-	42.3
Toxoplasmosis gondii (total)	19.8	-	-	-	45.1

4.3.2 Attribution of costs to pathways and food groups

Attribution results based on expert elicitation described by Havelaar et al. (2008) are presented in Table 23 and Table 24. Table 23 shows the discounted attribution of costs to the main pathways and Table 24 the discounted attribution of costs to the main food groups.

More than 40% of all costs-of-illness can be attributed to food, in total € 168 million per year. The other costs can be attributed to exposure from humans (28%), the environment (15%) and animals (7%), while 9% were travel-related.

Staphylococcus aureus intoxications accounted for the highest share of costs attributed to food (€ 47.1 million), followed by *Campylobacter* spp. (€ 32.0 million) and norovirus (€ 17.7 million).

Products of animal origin account for € 86 million (or 51% of the costs attributed to food) per year. Fish, fruit and vegetables, beverages, grains and other foods account for 8%, 6%, 2%, 5% and 14% of the costs attributed to food respectively. Human and animal contamination of foods accounts for 13.6% of the costs attributed to food.

Table 23. Attribution of average costs in million euros (discounted) to the main pathways for the different pathogens under study in 2011

Pathogens	Food	Environment	Human	Animal	Travel	Total costs
Bacteria-infections						
Campylobacter spp.	32.0	15.7	4.8	14.5	9.1	76.2
STEC O157	2.0	0.9	0.5	1.0	0.6	5.0
Salmonella spp.	12.0	2.8	2.0	2.0	3.1	22.0
Listeria monocytogenes	3.2	0.3	0.2	0.3	0.6	4.6
Bacteria-toxin-producing						
Bacillus cereus	8.2	0.1	0.1	0.1	0.7	9.2
Clostridium perfringens	23.2	0.6	0.5	0.5	0.8	25.6
Staphylococcus aureus	47.1	1.9	1.7	1.2	2.1	54.0
Viruses						
Norovirus	17.7	15.0	58.6	5.3	9.2	105.8
Rotavirus	9.5	12.5	42.6	2.2	6.5	73.3
Hepatitis-A virus	0.1	0.1	0.2	0.0	0.5	0.9
Hepatitis-E virus	0.0	0.1	0.0	0.0	0.1	0.2
Protozoa						
Cryptosporidium spp.	1.0	2.3	2.2	1.1	1.6	8.1
Giardia spp.	1.5	2.7	3.9	1.2	2.0	11.3
Toxoplasma gondii	11.0	7.1	0.2	0.5	0.9	19.7
Sum	168.5	62.5	117.5	29.9	37.8	415.9

Table 24. Attribution of average discounted costs in € millions to the different food groups for the different pathogens under study in 2011

Pathogens	Beef & lamb	Pork	Chicken & other poultry	Eggs	Dairy	Fish & shellfish	Fruit & vegetables	Beverages	Grains	Other foods	Humans & animals	Total costs
Campylobacter spp	1.31	1.63	17.24	0.99	2.85	2.24	1.7	0.54	0.74	1.06	1.7	31.98
STEC O157	0.89	0.13	0.06	0.04	0.15	0.06	0.14	0.07	0.06	0.07	0.34	2.01
Salmonella spp.	1.51	1.71	1.77	2.66	0.79	0.49	0.75	0.37	0.52	0.72	0.68	11.98
Listeria monocytogenes	0.36	0.3	0.21	0.12	0.79	0.57	0.24	0.08	0.19	0.18	0.16	3.21
Bacillus cereus	0.59	0.29	0.13	0.29	0.47	0.16	0.16	0.14	1.38	4.36	0.2	8.19
Clostridium perfringens	11.08	1.95	1.65	0.65	0.95	1.51	1.6	0.58	0.6	1.78	0.83	23.17
Staphylococcus aureus	3.53	3.81	3.67	1.55	6.92	2.73	0.94	0.85	3.53	13.94	5.6	47.08
Norovirus	0.57	0.55	0.51	0.34	0.35	2.74	1.29	0.55	0.92	0.88	8.97	17.66
Rotavirus	0.00	0.27	0.00	0.00	0.16	1.85	2.27	0.42	0.72	0.43	3.42	9.53
Hepatitis-A virus	0.00	0.00	0.00	0.00	0.00	0.01	0.01	0.00	0.00	0.00	0.06	0.10
Hepatitis-E virus	0.00	0.02	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.03
Cryptosporidium spp.	0.25	0.04	0.03	0.03	0.09	0.21	0.2	0.03	0	0.03	0.06	0.97
Giardia spp.	0.29	0.07	0.05	0	0.11	0.19	0.49	0.05	0	0.05	0.18	1.47
Toxoplasma gondii	2.52	5.53	0.53	0.00	0.51	0.41	0.64	0.00	0.00	0.25	0.63	11.01
Sum	22.90	16.30	25.85	6.67	14.14	13.17	10.43	3.68	8.66	23.75	22.83	168.38

4.4 Discussion

The total cost-of-illness of the fourteen food-related pathogens under study resulted in a total of € 468 million if undiscounted, and € 416 million if discounted with 4%. Direct healthcare costs are € 147 million if undiscounted, € 98 million if discounted with 4%, and accounted for 24% of the total costs. The majority of the costs, about 74%, were indirect non-healthcare costs. Direct non-healthcare costs were only marginal, about 2% of the total costs.

At the population level, the cost-of-illness of norovirus, *Campylobacter* spp. and rotavirus are with € 105 million, € 83 million and € 73 million the highest per year. The cost-of-illness of hepatitis-E virus is with less than € 1 million per year the lowest. Discounting has an impact on *Toxoplasma gondii*, *Listeria monocytogenes*, STEC O157, *Campylobacter* spp. and *Salmonella* spp., and affects ranking. The discounted costs of *Toxoplasma gondii*, *Listeria monocytogenes* and STEC O157 are equal to 36%, 49% and 52% of the undiscounted costs respectively, whereas the discounted costs of *Campylobacter* spp. and *Salmonella* spp. are equal to 93% of the undiscounted costs. *Toxoplasma gondii* has with € 55 million undiscounted costs the fourth highest costs at the population level, but falls to the seventh rank when comparing the discounted costs. *Listeria monocytogenes* has with € 9.4 million undiscounted costs the ninth highest costs at the population level, but falls to the eleventh rank when comparing discounted costs.

Given that the majority of costs for gastroenteritis pathogens were INHC, the ranking of the gastroenteritis pathogens is similar to the one found for total costs, if ranked at the population level. The non-gastrointestinal pathogens *Toxoplasma gondii* and *Listeria monocytogenes*, with less than 10% INHC of the total costs, have the lowest proportion of INHC costs, resulting in lower rankings in comparison to the total cost ranking. At the population level, the INHC of norovirus, rotavirus and *Campylobacter* spp. are € 97 million, € 59.5 million and € 47.5 million respectively, the highest per year. STEC O157 and hepatitis E virus, are with € 0.4 million and € 0.1 million responsible for the lowest INHC among those estimated.

If considering only DHC at the population level, then *Campylobacter* spp. has the highest costs (€ 26.7 million) followed by *Toxoplasma gondii* (€ 18.9), rotavirus (€ 12.5 million), *Salmonella* spp. (€ 10.3 million) and norovirus (€ 6.5 million). Hepatitis E virus would have the lowest DHC cost burden (€ 0.1 million per year).

Cost-of-illness per case varied between € 275,282 for perinatal listeriosis to € 150 for *Clostridium perfringens*. Perinatal listeriosis, congenital toxoplasmosis, acquired listeriosis, acquired toxoplasmosis and hepatitis E virus, all non-gastroenteric pathogens, are the ones with the highest cost burden per case. Protozoa-GE pathogens and virus-GE pathogens have the lowest cost burden per case.

More than 40% of all costs-of-illness can be attributed to food, in total € 168 million per year. The other costs can be attributed to exposure from humans (28%), the environment (15%) and animals (7%), while 9% were travel-related.

Staphylococcus aureus intoxications accounted for the highest share of costs attributed to food (€ 47.1 million) followed by *Campylobacter* spp (€ 32.0 million) and norovirus (€ 17.7 million).

Products of animal origin account for € 86 million (or 51% of the costs attributed to food) per year. Fish, fruit and vegetables, beverages, grains and other foods account for 8%, 6%, 2% 5% and 14% of the costs attributed to food respectively. Human and animal contamination of foods accounts for 13.6% of the costs attributed to food.

Apart from updating the cost to the year 2011, we have also made in the current cost-of-illness study a few changes compared to the earlier studies done by Kemmeren et al. in 2006, Vijgen et al. in 2007 and by Haagsma et al. in 2009. These were:

- So far there were only disease burden estimates available for the pathogens *Toxoplasma gondii*, Hepatitis A virus and Hepatitis E virus, but no cost-of-illness estimates. Based on literature, by preferences Dutch literature, information on used resources was collected and multiplied by Dutch unit prices in order to obtain cost estimates.
- Furthermore, the health outcome IBS was not yet included in the cost-of-illness estimates for *Campylobacter* spp. and *Salmonella* spp. Based on literature, by preference Dutch literature, information on used resource costs was collected. By using Dutch unit prices, the costs were estimated. As a consequence, the costs presented in the current report for both *Campylobacter* spp. and *Salmonella* spp. are by far higher than in one of the earlier studies. IBS costs account for 38% and 37% of the total costs of *Campylobacter* spp. and *Salmonella* spp. respectively. Not considering them would strongly underestimate the costs.
- Further we reviewed the costs for *Listeria monocytogenes* using new available information from the literature (Ruzante et al., 2011).
- Also for ReA new information was available in literature (Söderlin et al., 2003; Townes et al., 2008). That is why the costs for ReA were updated.
- The costs for IBD were updated with data from a very recent Dutch study (Van der Valk et al., 2012).
- Based on a new Dutch publication (Van der Maas et al., 2011) we also reviewed the costs for GBS, where necessary.
- Most of the costs for hospitalized GE patients were updated with data from the recently published GEops-study (Friesema et al., 2012).
- Our estimates for indirect non-healthcare costs for the health outcome GE were based on recent studies, namely the Pienter 2 study (Mollema et al., 2009; Van der Klis et al., 2009) for mild and moderate GE cases, and the GEops study (Friesema et al., 2012) for severe GE cases. The new estimates result in higher INHC.
- Based on information from the GEops study (Friesema et al., 2012) we now also consider costs for temporary nursing after hospital discharge of both elderly GE patients and elderly acquired listeriosis cases.

For some of the considered health outcomes and/or pathogens good information on costs and/or used resources is available. However, for other health outcomes and/or pathogen information is scarce and assumptions had to be made. So we were not always able to find disease-specific information on potential

productivity losses. We therefore had to make some assumptions on potential productivity losses of caregivers and patients.

Presenteeism is another form of production loss and describes the situation of patients being at work but working at a reduced capacity due to health problems. However, information on presenteeism is scarce and is therefore seldom considered in COI studies (Hakkaart - van Roijen et al., 2010). We therefore excluded the condition from the current COI estimates too. Given that presenteeism is of more importance for chronic diseases such as migraine and depression, we probably only underestimated the productivity losses per case for health outcomes like IBD and IBS, whereas for other health outcomes such as GE and hepatitis, presenteeism might be less important, at least if expressed in cost per case.

Information on used resources of toxoplasmosis is scarce, in particular on congenital toxoplasmosis. Assumptions had to be made. In our baseline we assumed no one of the infected congenital toxoplasmosis cases would require life-long institutional care and/or special education. However, this might be an underestimation. To test this assumption, we therefore conducted a scenario analysis by assuming that all congenital toxoplasmosis with CNS abnormalities would require life-long institutional care and special education. In this scenario analysis the total costs of congenital toxoplasmosis would increase by almost 250%. This scenario analysis is probably a worst case scenario. More research is necessary on congenital toxoplasmosis cases and their required resources.

The available Dutch study on medical costs of IBS patients is probably an underestimation of the true IBS costs in the Dutch population. Cost studies conducted in neighbouring countries mostly report double the value. But when doubling the DHC of IBS, the total costs for *Campylobacter* spp. would increase by 116% and the total costs for *Salmonella* spp. by 118%.

The current study shows food-related pathogens cause high costs to the Dutch society, € 98 million DHC if discounted with 4%, or € 147 million if undiscounted. The impact is however only marginal when comparing to the total Dutch healthcare expenditure of € 74,447 million in 2007 (and € 87,596 million in 2010) (Slobbe et al., 2011). However, apart from perinatal infections, the majority of the costs of food-related pathogens are INHC rather than DHC. The INHC totalled to € 309 million if discounted with 4%, or € 312 million if undiscounted. In particular productivity losses due to absence from paid work are responsible for the majority of the total costs. Although there were some recent studies having information on sickness leave, information was lacking and assumptions had to be made. We therefore strongly recommend collecting data on sick leave from paid and unpaid work for patients and their caregivers for all pathogens under study, in all kinds of epidemiological and clinical studies to get more accurate data in the future, and as such also more accurate cost estimates.

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Appendices

Appendix I – Summary of published European and North-American cost and cost-effectiveness studies

We have summarized the underlying assumptions and resource utilization of the European and North-American studies in Appendix I in Table I-A and in Table I-B respectively.

Table I-A. Congenital toxoplasmosis cases and their distributions over severity classes in published European and North-American cost and cost-effectiveness studies

Study	Congenital toxoplasmosis with		Remarks
	Mild/asymptomatic	**Severely affected/death**	
Wilson et al. (1980); USA-study	82% asymptomatic at birth of surviving CT cases; Based on 13 asymptomatic children at birth, they assumed: • 15% would develop no symptoms • 61% develop chorioretinitis without developing blindness and for 37.5% also sensorineural hearing loss (not functionally significant) • 15% develop chorioretinitis with unilateral blindness • 8% develop chorioretinitis with unilateral blindness & severely retarded child	8% severely affected surviving CT cases; No information on neonatal deaths	Assumption of asymptomatic children were based on 13 cases.
Henderson et al. (1984); UK-study	67% asymptomatic whereby assuming that: • 40% develop chorioretinitis, whereof 25% being visual handicapped[a] • 8% are assumed to be mentally retarded[b] 15.4% mild clinical symptoms, whereby assuming that: • they all develop chorioretinitis whereof 25% being visual handicapped[a] • 8% are assumed to be mentally retarded[b]	7.7% neonatal deaths; 10.2% severe clinical symptoms, whereby assuming that: • they all develop chorioretinitis and being visual handicapped[a] • 90% are assumed to be mentally retarded[b]	Based on UK data
Joss et al. (1990); UK-study	71% asymptomatic whereby assuming that: • 10% will be visually handicapped • 5% would be blind	12% neonatal death 5% sever clinical symptoms, whereby assuming that: • 100% will be visually handicapped	Based on UK data and on Henderson et al. (1984)

	• 8% are assumed to be mentally retarded[b] 13% mild clinical symptoms, whereby assuming that: • 25% will be visually handicapped • 5% would be blind • 8% are assumed to be mentally retarded[b]	• 5% would be blind • 100% are assumed to be mentally retarded[b]	
Roberts et al. (1990)[c]; US-study		2% die; 11% survivors	US; 1st year assumptions were based on a French study from 1984 and to determine the impairments at 3 to 17 years they used an US-study published in 1980 (n=24)
Stray-Pedersen et al. (1992); Norwegian-study	88% asymptomatic at birth	12% of infected offsprings, the infection is so severe the diagnosis may be suspected at delivery; (4.8% would die in utero or during early childhood;7.2% would require institutional care)	Assumptions were based on several published studies
Lappalainen et al. (1995); Finnish-study	87% are subclinical infections	13% (3% would die; 10% would have a severe infection)	Derived from a prospective screening study conducted in pregnant women (studies published in 1992 & 1993)
Sagmeister et al. (1995); Swiss-study	75% were assumed to be subclinical • 15% would not develop symptoms • 85% would develop chorioretinits later in life; whereof 77% would have no visual impairment; 11.5% would develop unilateral visual impairment and 11.5% would develop bilateral (=severe) visual impairment 15% were assumed to have mild symptoms • 99% would develop chorioretinits; whereof 50% would have develop no visual impairment; 25% would develop unilateral visual impairment and 25% would develop bilateral (=severe) visual impairment	10% were assumed to be severely affected • All children would develop recurrent chorioretinitis resulting mostly in severe visual impairment • 15% prenatal death • 85% severe central nervous symptoms with an average life expectancy of 15 years	Assumptions were based on several published studies
Sahai et al.	80% are mild subclinically infections	20% severely affected	Based on published studies

(1996); Canadian-study			(Carter and Frank, 1979; Wilson et al., 1980; Koppe et al., 1986);
Villena et al. (2010); French-study	10% (27/272) with unknown clinical outcome; 76% (206/272) were asymptomatic at birth;	7.7% (21/272) had moderate symptoms (i.e. intracranial calcifications and/or peripherical chorioretinitis); 2.6% (7/272) had severe symptoms (i.e. three with hydrocephalus and four with macular chorioretinitis); 2.2% (6/272) abortions; 1.8% (5/272) fetal deaths.	Based on national laboratory-based surveillance in 2007; France and French overseas department.
Stillwaggon et al. (2011) [d]; US-study	5.7% probability of no fetal disease 4.1% probability of mild visual impairment 41.5% probability of moderate to severe visual impairment 16.% probability of mild visual and cognitive impairment	5% probability of fetal death due to CT 26.1% probability of moderate to severe visual and cognitive impairment 1% Probability of visual impairment, cognitive & hearing impairment	Based on US and French data

a) About 5% of the visually handicapped are assumed to be blind. The rest is assumed to be moderately impaired.
b) About 1/3 is assumed to be very severely mentally handicapped and also physically damaged while living only to a mean age of 10 years; 1/3 will be moderately handicapped and will have normal life expectancy; and 1/3 will be mildly handicapped with normal life expectancy.
c) Roberts et al. (1994) and Buzby and Roberts (1997) are both cost studies that base their assumptions on Roberts and Frenkel (1990), and are therefore not presented in the current table, and also not in Table I-B.
d) Stillwaggon et al. (2011) costs were derived from another study and presented as total cost per outcome, why no information on used resources in Table I-B.

Table I-B. Assumed utilization in percent of surviving congenital toxoplasmosis cases in published European and North-American cost and cost-effectiveness studies

Study	Assumed utilization (%) of surviving congenital toxoplasmosis (CT) cases	Assumed utilization of fatally ill CT cases
Wilson et al. (1980); US-study	• 2.4% aid to totally disabled • 15.1% institutional or state-supported foster care for severely retarded • 7.1% special schooling for moderately retarded • 14.2% special schooling for visually handicapped • 78.0% yearly ophthalmologic follow-up care	n.a.
Henderson et al. (1984); UK-study	• 11% of the cases requiring four weeks in an acute hospital • 2.8% in institutional care for severely mentally retarded CT (mean LE is 10 years) • 0.6% in institutional care for blind CT cases • 5.7% extra costs of special education of severely mentally retarded CT cases (mean LE is 10 years) • 5.7% extra cost of special education of moderately mentally retarded CT cases • 1.1% extra cost of special education of blind CT cases • 22.5% having visual handicap and therefore 6 extra ophthalmic outpatient attendances between 0 and 29 years • 11.2% having operation for strabismus between 0 and 4 • 2.8% extra expenses to family for severely mentally retarded CT (mean LE is 10 years) • 5.7% extra expenses to family for moderately mentally retarded CT cases • Assumed life expectancy for severely mentally retarded CT is 10 years	Four days in an acute hospital
Joss et al. (1990); UK-study	• 5% of the cases requiring four weeks in an acute hospital • 2% in institutional care for severely mentally retarded CT (mean LE is 10 years) • 0.4% in institutional care for blind CT cases • 4% extra costs of special education of severely mentally retarded CT cases (mean LE is 10 years) • 4% extra cost of special education of moderately mentally retarded CT cases • 0.8% extra cost of special education of blind CT cases	Four days in an acute hospital

	• 16.7% having visual handicap and therefore 6 extra ophthalmic outpatient attendances between 0 and 29 years • 8.3% having operation for strabismus between 0 and 4 • 2% extra expenses to family for severely mentally retarded CT (mean LE is 10 years) • 4% extra expenses to family for moderately mentally retarded CT cases • Assumed life expectancy for severely mentally retarded CT is 10 years	
Roberts and Frenkel (1990) [c]; US-study	• 11% of cases who survive severe illness, 2 weeks in intensive care and 2 weeks in regular hospital room were assumed, plus fees for physician services pharamaceuticals; as well as diagnostic test • For those with visual impairment (48%): annual eye examination for 20 years; Of those individuals 17% were assumed to need an operation for strabismus • Half of the severely retarded were assumed to be living in institutions and the other half to be living at home until the age of 18 years • Special education (12 years of education and 3 years preschool) for severely retarded (2.59x regular education); • Special education for children who are deaf (???%) or blind (???%)	2% of cases who die, 3 weeks of intensive care hospitalization were assumed
Stray-Pedersen et al. (1992); Norwegian-study	• 10% institutional care because of mental retardation (duration: 4-50 years) • 15% special education for children with impaired vision (duration: 7-20 years) • 15% moderately retarded but attending regular school with some additional support (duration: 7-15 years)	
Lappalainen et al. (1995); Finnish-study	• (~10%) Severely infected infants, who stay alive or eventually die, require approximately 30 days of care in the neonatal intensive care unit • (10%) The severely ill children require permanent institutional care for the whole of their lives i.e. 40 years; Direct cost due to special education, training and resource help were partly included, since they are being offered in institutions as an essential element of long-term care • (10%) The severely ill children require an average of three 30-day hospital periods for diagnostic and therapeutic interventions until the age of 20, due to unresolved diagnosis (~10%) • (87%) Subclinical infected children were assumed to require, on average, one annual outpatient visit • 74% (85% of subclinical infected) require five 10-day hospital periods at the ages of 10 to 30 at the Department of Ophthalmology due to reactivating retinochoroiditis	(~3%) Severely infected infants, who stay alive or eventually die, require approximately 30 days of care in the neonatal intensive care unit

	• Assumed life expectancy for severely ill children requiring permanent institutional care is 40 years	
Sagmeister et al. (1995); Swiss-study	• 87% costs for testing • 22% regular controls of eyes up till the age of 15 years • 31% having additional treatment for recurrence of chorioretinitis • 16% admitted to hospital during 4 weeks • 16% antibiotic treatment during one year • 11% in institution because of blindness • 8.65% additional operation due to central nervous symptoms • 8.65% in institution for mentally severely retarded persons	1.5% were assumed to die; diagnostic costs and hospital costs for 4 weeks
Sahai et al. (1996); Canadian-study	• 2.4% aid to totally disabled • 15.0% institutional or state-supported foster care for severely retarded • 7.1% special schooling for moderately retarded • 14.2% special schooling for visually handicapped • 78.0% Yearly ophthalmologic follow-up care	n.a.

Appendix II

Summary of European Cohort studies reporting information on observed health outcomes and/or resource utilizations of congenital toxoplasmosis

Table II. Summary of European cohort studies reporting on utilization and outcomes of (surviving) congenital toxoplasmosis cases

Study	Type, year & country	Screening policy	Results/findings
Peyron et al. (2011)[a]	Prospective study (n=102) with special focus on OT[b]; 20-year follow-up; France	Infection was confirmed during pregnancy or within the first months of life (March 1983-June 1991). Ante- and postnatal treatment had been undertaken	• At birth 12 of the patients had neurologic effects (intracranial calcifications: n=11; hydrocephalus: n=2; seizures: n=1) • Of the 102 patients, 60 (58.8%) showed ocular lesions • But only 12.7% of the cases were associated with reduced visual function (= Snellen score below 16 of 20) • 11.8% reported a recurrence • None of the 102 individuals were living in an institution for handicapped persons • No evidence of limited cognitive function as the educational level was comparable with that of the general population • At the age of 14 to 15 years school performances of the patients did not differ from those of other uninfected children
Berrébi et al. (2010)	Prospective study from 1985-2005; 20-year follow-up; France	Screening during pregnancy & treatment of mothers if sero-conversation and/or postnatal treatment of children with positive prenatal diagnosis	• 676 women (681 fetuses) with toxoplasmosis sero-conversion • Termination of pregnancy in 1.5% of woman (10/676) because of severe fetal malformations • Utero deaths in 0.7% (5 cases) • Of the 666 live born children, 112 (17%) were infected by T. gondii • Whereof 6 (5%) showed minor abnormalities in ultrasound screening; a) 4 had moderate ventricular dilatation associated with mild ascites and 2 had moderate intrauterine growth restriction b) All of them had normal psychomotor development except for 2: 1 had a slight language delay at 40 months and a second developed epilepsy

			c) 3 of the 6 had chorioretinitis; it was peripheral in 2, and both peripheral and macular in the third • Of the 112 children, five were lost to follow-up. Of the 107 children neurological and intellectual development was age appropriated. They attended school normally. a) 79 children (74%) were entirely asymptomatic with a normal ocular fundus b) 28 (26%) developed chorioretinitis. Peripheral and unilateral in 20 of these 28 children (72%), peripheral and bilateral in 2 (7%), and macular and unilateral in 6 (21%) c) 11 (39%) were diagnosed at birth, 24 children (85%) before the age of 5 years, and 27 children (96%) before the age of 10 years. • One child who developed chorioretinitis at the age of 1 year also developed epilepsy, well controlled with medication • Another child had severe clinical involvement with left peripheral and right macular chorioretinitis, convulsions, and delayed psychomotor development. He was treated with valproic acide for epilepsy and received motor rehabilitation and speech therapy. He has had no epileptic seizures since the age of 3 years, right eye vision is satisfactory, his speech has caught up with that of his peers, and rehabilitation has corrected his motor problems. He has been attending school normally since the age of 7 years
Freeman et al. (2008) [c]	Prospective cohort study (n=281); 4-years follow-up; Europe	Congential toxoplasmosis cases identified by prenatal or neonatal screening	• 50 had ≥ 1lesion (4 had ≥ 3 lesions) a) 5 had also intracranial abnormality • 20 had lesions detected at their first ophthalmoscopy
Tan et al. (2007) [c]	Prospective study (n=281); 3-years follow-up; special focus on OT; Europe	Congential toxoplasmosis cases identified by prenatal or neonatal screening	• 33 children (12%) had detected their first lesion in infancy • 49 children (17%) had at least one retinochoroidal lesion a) 32 (65%) had at least one lesion affecting the posterior pole b) 7 had bilateral posterior pole lesions • Or 104 lesions were detected in 69 eyes a) 46 (44%) lesions were at the posterior pole (affecting 39 eyes) b) 58 lesions were at the periphery (affecting 40 eyes)

			• Of the 7 children with bilaterial posterior pole lesions; 6 had acuity measured: 2 had normal vision; 3 were impaired unilaterally and one was blind bilaterally. • Ocular complications occurred in 29 children (10%): 1.8% microphtahalmia; 1.4% vitrael opacity; 7.5% strabismus; 0.7% ambyopia; 0.7% cataract; 0.4% retinal detachment; 1.1% acute symptoms • 4 children with ocular disease had bilateral visual impairment of worse than 6/12 • '3 of the 4 children with bilaterally impaired vision also had ventricular dilatation and neurologic deficits, raising the possibility that impaired vision in part may have been the result of intracranial pathologic characteristics'
Schmidt et al. (2006)	Retrospective study (n=47); follow-up of 1999-2002 cohort until 3 years; Denmark	Neonatal screening and if treatment if sero-conversation	• 47 newborns with CT (consented) • 12 (25.5%) had clinical signs at birth, which were: a) 5 had intracranial calcifications only b) 4 had intracranial calcifications and retinochoroiditis c) 1 intracranial calcifications, hydrocephalus, and bilateral retinochoroiditis d) 2 had retinochoroiditis only • Thus 7 (14.8%) of infants had retinal lesions when first evaluated; 8 at 1 year of age, and 4 at 3 years of age • Of the 94 eyes examined at birth, 9 showed clinical signs at the initial examination, all manifesting as central lesions a) 2 infants had macular involvement of both eyes b) 5 infants had macular involvement of one eye • 68 of the 94 eyes were examined when the children were 1 year old. New retinochoroidal lesions were found in three eyes (one child in a previous asymptomatic child; two with previous lesions) • At 3 years of age: a) Severe neurological signs, gross intracranial calcification, and hydrocephalus were found in one patient. Additionally this child had at birth macular involvement of both eyes. b) Pediatric neurologic examination did not reveal any abnormality in the remaining study children
Wallon et al. (2004)	(n=327 children);	Screening of mothers & treatment is seroconversion	• Of 1506 consecutive pregnant women 53 pregnancies ended with spontaneous abortion (n=22);

	follow-up; France		stillbirth (n=4); or termination as a result of suspected or proven fetal infection (n=27) • The remaining 1453 pregnant women gave birth to 1466 live-born infants (1384 (94%) of whom could be followed) • In 358 of 1384 congenital toxoplasmosis was confirmed; 31 were excluded because they had been followed up for <6 months at the study endpoint • The long-term study included 327 children being aged between 6 months and 14 years • 79 (24%) had at least 1 retinochoroidal lesion (187 lesion total): a) 55 had lesion in 1 eye b) 24 had lesion(s) in 2 eyes. NONE of the children had bilateral impairment • 50% of the initial lesions were diagnosed before 1 year of age, 58% before 2 years; 76% before 5 years and 95% before 10 years • Among the 79 children with at least 1 lesion, 23 (29%) had at least 1 new event: reactivation of an existing lesion (1 case), lesion in a previously healthy location (19 cases), or both (3 cases) • At the final pediatric examination: a) 232 of 327 children (71%) were free of any lesions b) 60 children (18%) manifested no sequelae except retinochoroiditis c) In the other 35 children (11%), at least 1 pathologic sign was detected: cranial calcifications were detected in 31 children, hydrocephalus was detected in 6 and microcephalus was detected in 1. i. Three children with hydrocephalus had moderate psychomotor retardation; ii. the other 3 had normal development and school progression. iii. Two children with calcifications had 1-time seizures that remained isolated despite the lack of long-term antiepileptic therapy
Lebech et al. (1999)	Retrospective study (n=27); follow-up until 12 months; Denmark	Screening of mothers & neonatal screening (was test study); no treatment of mothers	• 141 infants whereby maternal seroconversion was confirmed between first-trimester sample and delivery • 27 children with congenital toxoplasmosis • 23 (85%) had no signs of infection • 4 (15%) had clinical findings a) 1 had hydrocephalus and retinal scars

			b) 1 had intracranial calcifications and retinal scars c) 1 had intracranial calcifications and retarded development d) 1 was blind in one eye and had retarded development
Koppe et al. (1986)	20-year follow-up study; start of the study in 1964; the Netherlands	Selection based on pregnancy screened and positive seroconversion; no treatment of mothers; but treatments of children with symptoms at birth (n=5) and symptomless children (n=7)	• 5 children with symptoms at birth (4 had chiorioretinitis & 1 had parasites in his placenta and cerebrospinal fluid) and treated, at the age of 20 years a) 1: scar in left and right eye b) 1: paroxysmal tachycardia and scars in left eye with serious risk for blindness in this eye c) 1: scars in left and right eye with 1/60 vision in the left eye d) 1: no new scars e) 1: new scar in right eye • 7 children symptomless at birth; at the age of 20 years a) 1: Scars in left eye with severe impairment of vision b) 1: Scars in left and right eye with severe impairment of vision of right eye c) 1: Scars in right eye d) 1: Scars in right eye & severe behavioral problems (attempted suicide) e) 2: nothing abnormal f) 1: lost-to follow-up • The 11 congenitally infected children did not differ from the other 117 children (case) in their school performance • None of the 11 children is mentally retarded • 9/11 have chiorioreinitis and scars after 20 years of follow-up and that 5/11 have severe impairment of vision in one eye

a) Peyron et al. (2011) concluded 'that prenatal treatment does not appear to reduce the risk for chorioretinitis'.
b) OT stands for ocular toxoplasmosis. In the table we always refer to congenital-acquired ocular toxoplasmosis.

Tan et al. (2007) and Freeman et al. (2008) are the same prospective study, the EMSCOT study.

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