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Disease burden and related costs of cryptosporidiosis and giardiasis in the Netherlands

SMC Vijgen, MJM Mangen, LM Kortbeek,
YTHP van Duijnhoven, AH Havelaar

Contact: A.H. Havelaar
Laboratory for Zoonoses and Environmental Microbiology
e-mail: arie.havelaar@rivm.nl

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

Abstract

Disease burden and related costs of cryptosporidiosis and giardiasis in the Netherlands

The disease burden and the costs-of-illness associated with *Cryptosporidium spp*. are relatively small in comparison to other (foodborne) pathogens. The disease burden and the costs related to giardiasis are comparable to those related to the noro- and rotaviruses.

Those conclusions can be drawn from the current study, a continuation of previous work on the disease burden and related costs of seven other (foodborne) pathogens. Both studies are part of a larger project aiming to support the setting of priorities in food safety policy.

Key words: foodborne illnesses, priority setting, disease burden, cost-of-illness, gastro-enteritis, Cryptosporidium, Giardia.

Rapport in het kort

Ziektelast en kosten van cryptosporidiosis en giardiasis in Nederland

De parasieten *Giardia lamblia* en *Cryptosporidium spp*. veroorzaken bij mensen darminfecties met diarree en buikgriep als gevolg. De ziektelast en de kosten van giaridiasis zijn groter dan die van cryptosporidiosis. Beide parasitaire ziekten veroorzaken echter minder schade dan bijvoorbeeld de bacterie Campylobacter.

Dit blijkt uit een vervolg op een eerdere studie naar gezondheidseffecten van zeven ziekteverwekkende micro-organismen (pathogenen), die onder andere door voedsel kunnen worden overgedragen. Het onderzoek helpt het ministerie van VWS prioriteiten te stellen bij het voedselveiligheidsbeleid.

Trefwoorden: voedselinfecties, prioritering, ziektelast, ziektegebonden kosten, gastro-enteritis, cryptosporidium, giardia.

Contents

Abbreviations

General

GE	Gastroenteritis
AIDS	Acquired immunodeficiency syndrome
HAART	Highly active antiretroviral therapy
PHL	Public Health Laboratory
ICD	International Classification of Diseases
GP	General practitioner

Health Status measures

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

Economic terms

COI	Cost-of-illness
DHC	Direct health care costs
DNHC	Direct non-health care costs
INHC	Indirect non-health care costs
CER	Cost effectiveness ratio
NPV	Net present value

Studies

ISIS	Infectious diseases Surveillance Information System
NIVEL study	GP-based study on gastroenteritis, 1996-1999
SENSOR	Community-based study on gastroenteritis, 1999

Organisation

CBS	Statistics Netherlands (Centraal Bureau voor de Statistiek)

Summary

Human health is threatened by a wide variety of foodborne and zoonotic pathogens. The major objective of this project was to develop a model that helps the Dutch Ministry of Public Health, Welfare and Sports to prioritize pathogenic micro-organisms as a decision tool in their food safety policy.
In a study published in 2006 the disease burden and/ or costs of seven pathogens were estimated. The current study, in which we estimated the disease burden and costs for *Cryptosporidium spp.* and *Giardia lamblia*, is a follow-up of this earlier work. We hereby apply the same methods as in the previous study.
For *Cryptosporidium spp.* the most likely disease burden was 123 and 110 DALYs, undiscounted and discounted, respectively. Cost-of-illness of community-acquired Cryptosporidium-associated gastroenteritis (GE) was approximately 5 million euros in 2004. Because protozoa are mostly not recognized in standard laboratory testing, a scenario analysis was performed, in which it was assumed that physicians would have to request more tests. Costs increased only with 0.6% of total costs. Besides scenario analysis was performed in which the impact of recurrent gastrointestinal illness was examined. In a population based scenario costs increased to 7 million euros. The disease burden increased with 14 (lab only based scenario) and 37 (population) DALYs.
The most likely disease burden for *Giardia lamblia* was 364 DALYs undiscounted. Cost-of-illness of community-acquired Giardia-associated GE was approximately 18 million euros in 2004, more than 85% due to indirect non-health care costs. In a scenario analysis the potential impact of chronic giardiasis on disease burden and related costs was examined. Costs increased with 0.5 million euros and DALYs increased to 377 per year.
The two pathogens studied in this report were compared to the seven pathogens as studied earlier. Cryptosporidium had the lowest disease burden and costs compared to five other pathogens and Giardia costs were in the middle of the range. The same can be concluded for disease burden results. However, it has to be mentioned that little information was available on hospitalization rates.

1. Introduction

1.1 Background

Human health is threatened by a wide variety of foodborne and zoonotic pathogens. In order to provide an objective basis for policy decisions the Dutch Ministry of Public Health, Welfare and Sports asked RIVM to develop a model that helps them to establish the priority of pathogenic micro-organisms that can (also) be transmitted by food, as a basis for effective and efficient policy-making on control, prevention and surveillance.

A first study was published in 2006, estimating the disease burden for five enteric and two non-enteric pathogens, and the related sequelae. The selected pathogens were norovirus, rotavirus, thermophilic *Campylobacter spp*., *Salmonella spp*., Shiga-toxin producing *Escherichi coli* O157, *Listeria monocytogens* and *Toxoplasma gondii*. For four of these pathogens, namely norovirus, rotavirus, thermophilic *Campylobacter spp*. and *Salmonella spp*. the associated cost-of-illness were also estimated. The focus was on community-acquired infections (i.e. excluding infections caused in health-care settings). Full details were reported by Kemmeren et al.[35].

The current report is a follow-up of this earlier work. In this report we describe the disease burden and associated costs for the pathogens: *Cryptosporidium spp.* and *Giardia lamblia* based on incidence data for the year 2004.

1.2 Outline of report

The methodology applied for disease burden and cost-of-illness estimates is shortly described in chapter 2. In chapter 3 and 4 the pathogen specific results are described. Chapter 5 ends with a general discussion.

2. Disease burden and cost-of-illness - methodology

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

Disease burden, one of the two criteria considered, is expressed in Disability Adjusted Life Years (DALYs). By using the DALY methodology, morbidity, expressed in years lived with disability (YLD), and mortality, expressed in years of life lost (YLL), are summed up into one metric unit. A detailed description of the DALY methodology and the general assumptions made with respect to disease burden is given in chapter 2 of Kemmeren et al.[35] and detailed methodological choices made are summarized in Appendix I. The used disability weights are summarized in Table 1.

Table 1. Disability weights used

	Acute annual disability weight	Source
Death	1.00	
Gastroenteritis		
Not visiting GP	0.067	Havelaar et al.[29, 30]
Visiting GP	0.393	Havelaar et al.[29, 30]
Hospitalized	0.393	Havelaar et al.[29, 30]

Cost-of-illness, the second valuation criterion, is calculated by accumulation of: a) direct health care costs (DHC), which are costs for e.g. the consultation of general practitioners (GP) and specialists, hospitalization, drugs and rehabilitation; b) direct non-health care costs (DNHC), which include e.g. the travel costs by patients and other co-payments by patients; and c) indirect non-health care costs (INHC), such as the productivity losses of patients and/or care-givers. Productivity losses were estimated according to the friction cost method. In order to keep our results comparable with the earlier estimations, costs were estimated using cost prices of the year 2004. The cost vectors used in the current study are summarized in Table 2. Pathogen specific assumptions, if available/necessary, are given in the specific chapters hereafter.

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

Uncertainty analysis was restricted to using low, most likely and high values for uncertain parameters, and some scenario analyses were applied (for details see Kemmeren et al.[35]).

Table 2. Cost vectors in the Netherlands for the year 2004 (in euros), most likely point estimate and if applicable, minimum and maximum point estimate.

Cost vectors	Costs per unit (in euros) Most likely point estimate (minimum and maximum)
Direct medical costs	
Over-the-counter medicine of patients not requiring medical help per day of illness	0.16
Over-the-counter medicine of patients requiring medical help per day of illness	0.53
Cost for medication including prescription charges	37.1
Cost per average GP visit	32.3 (20.4 – 32.3) [a]
Costs for pathogen diagnostic in feces/sample submitted	67
Hospitalization adults/day	367
Hospitalization child/day	461
Outpatient clinic/consultation	64[b]
Short subscription fee for internist	62
Short subscription fee for pediatrician	88
Direct non-medical services	
Travel cost per average GP consultation	0.8 (0.14 – 1.5) [c]
Travel cost per hospitalization	3.5
Cost per diaper	0.3
Indirect costs	
Average costs of absence from paid work/hour	36,5
Average costs of third person taking care of sick person/hour	22.5 (8.5 - 36.5) [d]

a) Of the considered GP consultations, approximately 90% were GP practice visits (€ 21/visit) and the remaining 10% were house calls from the GP to the patient (€ 41/visit). Furthermore, per registered GP consultation, an additional 0.97 GP telephone consultations of the doctors' assistant took place (€ 10/call). For the minimum estimate we assumed 100% GP practice visits and no phone calls.

b) Calculated as the weighted average of visiting a general hospital (84% of patients and €57 per consultation) and a university hospital (16% of patients and €101 per consultation).

c) Depending on the assumption made of an average GP consultation and depending of the travel form used (e.g. public transport, car or cycling/walking). For details see Kemmeren et al.[35].

d) It could not be assessed whether work absence was from paid work or from unpaid work. We therefore assumed as most likely point estimate that the average of productivity losses for an average working person, € 36.5/hour, and the opportunity costs for informal care, € 8.5/hour, which was equal to an average of € 22.5/hour. In our low cost estimate and high cost estimate, however, we assumed that productivity losses were equal to € 8.5/hour and € 36.5/hour, respectively.

3. *Cryptosporidium spp.*

Protozoa of the genus *Cryptosporidium spp*. are small coccidian parasites that infect the gastrointestinal and respiratory tracts of a wide variety of animals and humans [13]. From the public health perspective, the two major pathogens are *Cryptosporidium parvum* and *Cryptosporidium hominis.* However, *Cryptosporidium meleagridis, Cryptosporidium felis, Cryptosporidium canis, Cryptosporidium muris, Cryptosporidium suis* as well as the monkey and corvine genotypes of Cryptosporidium also cause infections in humans [10]. Cryptosporidium is transmitted by ingestion of fecally contaminated food or water (water swallowed while swimming included), by exposure to fecally contaminated environmental surfaces, and by the fecal-oral route from person to person[1]. Cryptosporidium causes a diarrhea that is self-limited in immunocompetent persons but potentially life-threatening in immunocompromised persons, especially those with acquired immunodeficiency syndrome (AIDS)[13]. Infection accounts for up to 6 percent of all reported diarrheal disease in immunocompetent persons worldwide[13]. And from all the persons with both AIDS and diarrhea worldwide, 24 percent is infected with *Cryptosporidium spp* [28]. In this section the estimated disease burden and cost-of-illness of *Cryptosporidium spp*. in the Netherlands are described.

3.1 Outcome tree, incidence and duration of illness

3.1.1 Outcome tree and incidence

Gastroenteritis caused by *Cryptosporidium spp*. is often self-limited in immunocompetent persons, but can become chronic in immunocompromised persons, especially those with AIDS [10]. There is strong evidence that the risk of fecal carriage, severity of illness and development of unusual complications of cryptosporidiosis are related to the $CD4^+$ cell count [53]. In the Netherlands nearly all AIDS patients are treated with highly active antiretroviral therapy (HAART) since 1996. This therapy has a remarkable impact on, among others cryptosporidium infections, resulting in a marked reduction in the occurrence [10]. Several clinical trials were performed to examine the relation between HAART and cryptosporidium in AIDS patients. They all conclude that AIDS-related cryptosporidiosis can be cured following successful antiretroviral therapy [10 46 11]. Two other studies reported that the HAART-induced recovery from cryptosporidiosis is not associated with a consistent increase in the $CD4^+$ T-cell count. So even patients with a $CD4^+$ T-cell count of less than 100 were able to recover from the infection [27 43]. For this reason we decided to make no difference between AIDS patients and those without AIDS in the outcome tree (see Figure 1) and in the estimation of disease burden and cost-of-illness.

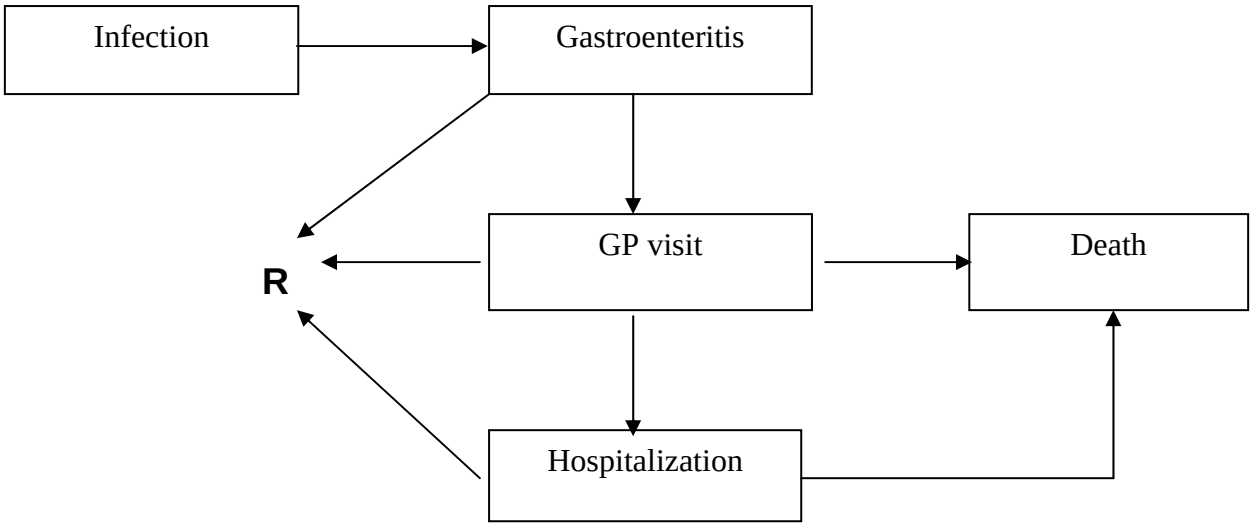

Figure 1. Outcome tree Cryptosporidium spp.-associated GE.

Based on SENSOR [17], a community based cohort study in 1999, the estimated incidence of community- acquired *Cryptosporidium spp*. cases in the population was estimated to be 71,000 cases in 2004, with an uncertainty range ranking from 34,000 (5% estimate) to 165,000 (95% estimate), see Table 3. Of these approximately 5,200 would visit a GP [15], both hospitalized and not hospitalized cases according to the Dutch health-care system, where the GP is the gatekeeper for any further medical specialization. The hospitalization rate for community-acquired Cryptosporidium cases in the Netherlands is unknown. A literature search was performed to find studies with useful data on Cryptosporidium. The results of that search can be found in Appendix II.

For the *most likely* and *maximum* estimation of hospitalizations among patients with a Cryptosporidium infection we used the estimates provided by Mead et al.[45] and the incidences as calculated from SENSOR data [17](see Appendix I in Kemmeren et al. [35]). Based on data from ISIS labs and a laboratory surveillance study by Adak et al.[6] we estimated the *minimum* number of hospitalizations[6]. The case fatality rate for community-acquired Cryptosporidium patients in the Netherlands is unknown. Mead et al.[45] estimated for the US that Cryptosporidium would be fatal in 0.005% of the entire population of ill patients. Dietz et al. [19] estimated a case fatality rate of 0.6% of laboratory-confirmed cases. In our *most likely* estimate we assumed that 0.6% of our reported laboratory-confirmed cases died, which resulted in a total of three fatal cases (see Appendix II). For the *minimum* and *maximum* estimate, we assumed a case-fatality rate of 0.005% multiplied with the minimum and maximum estimates for the entire population of ill patients, respectively.

Data from fourteen Dutch public health laboratories (PHL), all participating in the Infectious diseases Surveillance Information System (ISIS) database, were examined to find out the

number of reported laboratory-confirmed cases. Only four of these fourteen PHLs reported positive Cryptosporidium cases in all the years (2001-2006) studied. And only three of them registered the institution that requested the test (GP or hospital) in nearly all cases. The ISIS-data have to be viewed with caution because detection of Cryptosporidium requires non-routine approaches of sample treatment and analysis. When physicians in the Netherlands ask for testing, in most cases a stool culture for Salmonella, Shigella and Campylobacter is performed [44]. Mank et al. [44] showed that GPs underestimate the role of intestinal protozoa as a potential cause of diarrhea. The routine parasitological examination of the stool specimen (microscopic examination of a direct wet smear and of the sediment resulting from formalin-ether sedimentation) mostly does not recognize Cryptosporidium, but at a physician's specific request for other parasite-specific techniques for stool examination can be added. However, often a physician does not know that a specific request is needed to detect Cryptosporidium as a cause of gastro-enteritis[44]. So the ISIS data are probably an underestimation of the real amount of Cryptosporidium cases among fecal samples submitted for laboratory diagnosis. That is the reason we only used the data in combination with information from other studies.

Table 3. Incidence and duration of illness of community-acquired Cryptosporidium-associated GE for 2004[a]

	Incidence estimate (cases per year)			No. of days of illness
	Most likely	Low	High	
Gastroenteritis	71,000	34,000	165,000	-
No GP	65,800	31,100	156,200	3.5
GP	5,093	2,890	8,552	7
Hospitalization	107	10	248	18.4
Fatal	3	2	8	-

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

In Table 3 we have summarized the most likely estimates, and the attendant uncertainty, for the incidence of community-acquired cryptosporidium GE in the total population and split up according to the different disease severity states related to this pathogen.

There was only one study examining recurrent events from cryptosporidiosis [33]. In this analysis we therefore assume no recurrent gastrointestinal symptoms at baseline. Scenario analysis was performed assuming recurrent symptoms.

3.1.2 Duration of illness and age-distribution

When estimating the associated disease burden and cost-of-illness, information on duration of illness was required. No Dutch information was available with respect to duration of illness. Therefore several outbreak studies were used. Corso et al. [14] distinguished duration of illness in patients not visiting a GP (4.7 days), patients visiting a GP (5.8 days) and patients hospitalized (18.4 days). Other outbreak studies mentioned median durations between 4 and

6 days [2-5]. In Dietz et al. [19] the duration of illness was 7 to 14 days. The combination of these data and additional data as shown in Appendix II resulted in 3.5 days for patients not visiting a physician (taking the mean of all the lowest estimations, see Appendix II), 7 days for patients visiting a physician and 18.4 days for patients being hospitalized (see Table 3).

The age distribution of community-acquired Cryptosporidium-associated GE for the different health states is summarized in Table 4. We assumed that the age distribution of Cryptosporidium cases as found in SENSOR [17] would be representative for Cryptosporidium cases not visiting a GP (no GP). The age distribution of Cryptosporidium cases visiting a GP was based on NIVEL [16]. The age distribution for hospitalized Cryptosporidium cases was based on a study by Dietz *et al.* [19]and the ISIS data. For the age distribution of fatal cases we took the general age distribution for GE by Statistics Netherlands in the year 2004, because of lack of specific data.

Table 4. Age distribution of community-acquired Cryptosporidium-associated GE.

	Age classes				
	0-4 years	5-9 years	10-14 years	15-64 years	> 65 years
Gastroenteritis					
No GP	42%	6%	3%	47%	2%
GP	49%	18%	18%	13%	1%
Hospitalization [a]	12%	12%	8%	49%	19%
Fatal [b]	1%	0%	0%	22%	76%

a) No Dutch information available. We extracted data from Dietz et al. (2000) and ISIS as a proxy.
b) No pathogen specific information available. We extracted data from Statline (CBS) about age distribution GE

3.2 Disease burden

Most likely values for incidences, used disability weights per case per year, and estimated YLD, YLL and DALYs, undiscounted and discounted at 4%, are shown in Table 5 for the different health states associated with Cryptosporidium. Most likely estimates and attendant uncertainty for disease burden, undiscounted (0%) and discounted (4%), are shown in Figure 2. Given that the years of life lost due to premature death would be spread over several years, discounting the disease burden had a small impact on the disease burden associated with fatal cases. No discounting of the disease burden of non-fatal Cryptosporidium cases was required, as these cases recovered within a few days. The disease burden of cryptosporidiosis was 123 DALYs per year. Discounting had little effect on the total DALY estimate due to the relatively low number of fatal cases, mostly elderly patients (see Table 5 and Figure 2).

Table 5. Incidence and disease burden of community-acquired Cryptosporidium spp.-associated GE for 2004 (most likely estimates) [a]

(Discounting)	Incidence	Disability weight per case/year	YLD (0%)	YLL (0%)	DALY per year (0%)	DALY per year (4%)
Gastroenteritis	71,000	-	83	40	123	110
No GP	65,800	0.0006	42	-	42	42
GP	5,093	0.0075	38	-	38	38
Hospitalization	107	0.0198	2	-	2	2
Fatal	3	1	-	40	40	27

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

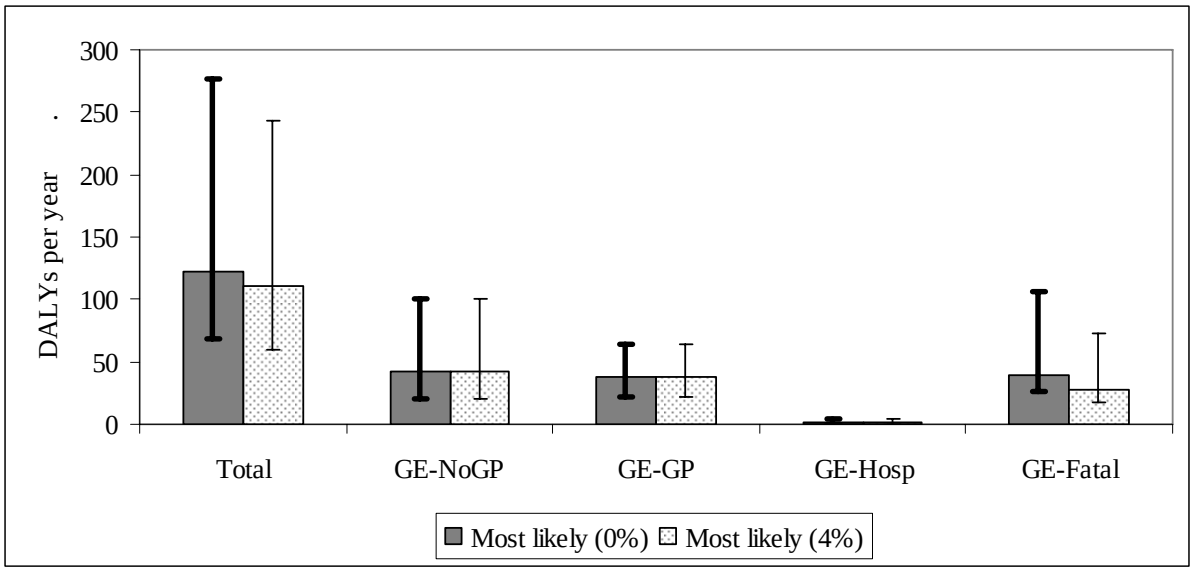

Figure 2. Disease burden of community-acquired Cryptosporidium-associated GE for 2004, using most likely estimates, undiscounted (0%) and discounted 4%). Error bars express an uncertainty interval that results from using low and high estimates.

3.3 Cost-of-illness

Based on the incidence and duration of illness shown in Table 3, and following the assumptions described in section 2 and in the previous report [35], we estimated the direct health care costs for the different non-fatal health states. An average hospital stay of eight days was assumed for community-acquired Cryptosporidium cases. [14] This is the average length of stay of patients (both with and without underlying conditions). Direct Health Care costs (DHC) of fatal cases were not considered separately. These patients were already considered in one of the other sub-groups of community-acquired Cryptosporidium patients. DHC results of community-acquired Cryptosporidium cases are summarized in Table 6 for the most likely estimate only.

Table 6. DHC of community-acquired Cryptosporidium-associated GE in million euros for 2004 (most likely estimates) [a,b]

	Drugs & medicine	GP consultations	Hospitalization	Other [c]	Σ DHC
Gastroenteritis	0.25	0.20	0.34	-	0.79
No GP	0.04	-	-	-	0.04
GP	0.21	0.19	-	-	0.40
Hospitalization	0.01	0.01	0.34	-	0.35

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

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

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

Productivity losses due to paid employment lost was considered in the current study due to work absence of patients as well as due to work absence of third persons taking care of sick persons, according to the assumptions described in section 2 and Appendix I. The estimated overall work absence for Cryptosporidium patients not visiting a GP, and Cryptosporidium patients visiting a GP only, were estimated to be 0.31 days, and 0.97 days, respectively. In Table 7 we have summarized the estimated number of days paid employment lost for adult patients and for third persons taking care of a sick person. We further present in Table 7 the most likely estimate of Indirect Non Healthcare Costs (INHC).

Table 7. Number of days paid employment lost and INHC of community-acquired Cryptosporidium spp.-associated GE in million euros for 2004 (most likely estimates)[a]

	No. of days paid employment lost		Productivity losses		Σ INHC
	Patient	3rd person	Patient	3rd person	
Gastroenteritis	-	-	3.1	1.0	4.1
No GP	0.31	1	2.7	0.8	3.6
GP	0.97	2	0.2	0.2	0.4
Hospitalization	6.52	4	0.1	0.0	0.1
Fatal	154	n.a.[b]	0.03	-	0.0

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

b) Not applicable (n.a.)

In Table 8 and Figure 3 we have summarized the most likely estimate and the most likely estimate with attendant uncertainty, respectively, for the total costs of community-acquired Cryptosporidium-associated GE cases. Given that all costs occur within one year, discounting costs is not an issue.

Table 8. Cost-of-illness of community-acquired Cryptosporidium-associated GE in million euros for 2004 (most likely estimates) [a,b]

(Discounting)	DHC (0%)	DNHC (0%)	INHC (0%)	Σ Costs (0%)
Gastroenteritis	0.79	0.06	4.1	4.9
No GP	0.04	0.05	3.6	3.7
GP	0.4	0.01	0.4	0.8
Hospitalization	0.35	0.00	0.1	0.5
Fatal	n.a.[c]	n.a.[c]	0.0	0.0

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

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

c) Not applicable (n.a.)

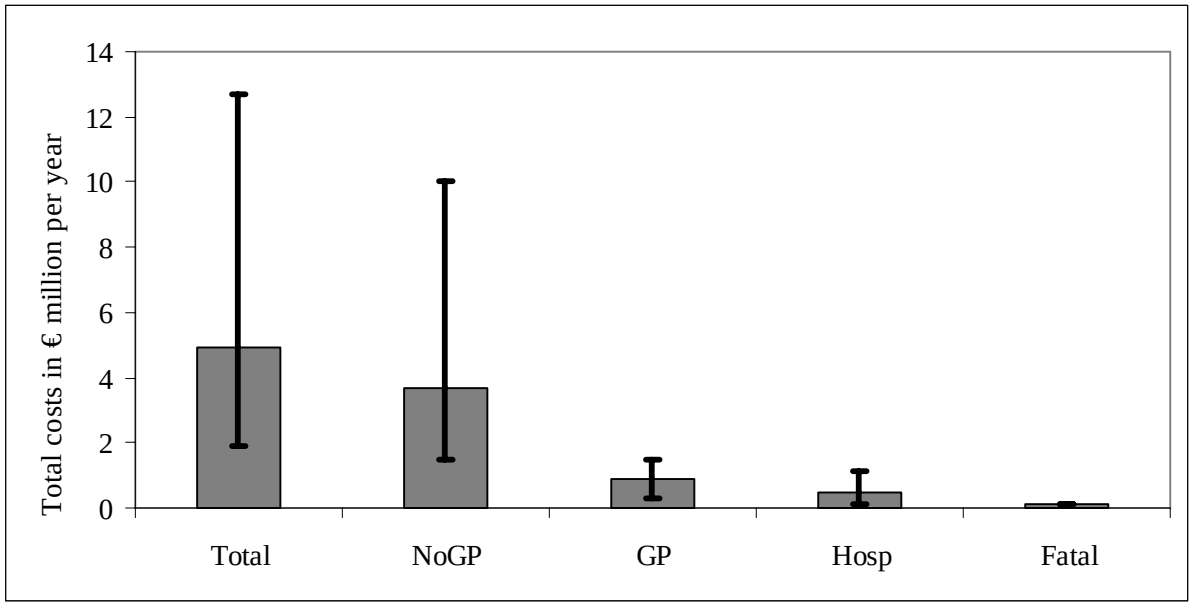

Figure 3. Cost-of-illness of community-acquired Cryptosporidium spp.-associated GE, using most likely estimates. Error bars express an uncertainty interval that results from using low and high estimates. Discounting was not required as all costs occur within the first year.

3.4 Scenario analysis

As mentioned before a problem with Cryptosporidium is that it needs additional laboratory methods that are not routinely performed by most laboratories. GPs underestimate the role of intestinal protozoa as a potential cause of diarrhea. The routine examination of the stool specimen (microscopic examination of a direct wet smear and of the sediment resulting from formalin-ether sedimentation) mostly does not recognize Cryptosporidium, but at the physician's request, other parasite-specific techniques for stool examination can be added. For this reason we calculated cost-of-illness using as a proxy twice the laboratory test costs.

As a result DHC would increase with 30,000 euros, but total costs would increase only slightly with about 0.6%, and can therefore be neglected.

Hunter et al. [33] examined, among others, the medium-term health effects of human cryptosporidiosis. This study concluded that the impact of cryptosporidiosis on public health extends beyond that of the acute diarrheal illness and can lead to significant health sequelae. Recurrence of gastrointestinal-related symptoms (e.g. loss of appetite, recurrent vomiting, abdominal pain, and diarrhea) were frequently (40.9%) found in cases after recovery from Cryptosporidium infections compared to control subjects (13.4%). The relatively small numbers of case patients who reported joint pains (13 control subjects and 36 case patients) meant that firm conclusions about the nature and distribution of joint symptoms could not be made[33]. In the current study we assumed in the baseline no recurrent events, because of scarce information on recurrent gastrointestinal symptoms in the literature. But given the uncertainty of this latter assumption and the findings of Hunter et al.[33], we applied scenario-analyses assuming 1) recurrent gastrointestinal symptoms in 27.5% of the laboratory confirmed cases (*lab only*); and 2) recurrent gastrointestinal symptoms in 27.5% of all the Cryptosporidium-associated GE cases (*population*). It was assumed that most patients with recurrent symptoms in the 'lab only' scenario would all need medical help, 98% of laboratory confirmed cases would visit a doctor and 0.3% of them would be hospitalized. In the population scenario 7% of total Cryptosporidium-associated GE cases would visit a GP and 0.3% of them would be hospitalized. In Table 9 we have summarized the incidence and the DALY, total and split up per health state, for the baseline as well as for the two alternative scenarios, but only the most likely estimate for incidence and disease burden are shown. The cost-of-illness would change from 4.9 million euros to 5.1 million euros if recurrent GE would affect 27.5% of laboratory confirmed cases; and to 7 million euros if recurrent GE would affect 27.5% of total ill cases in the population.

Table 9. Incidence and DALY of Cryptosporidium-associated GE and sequelae for baseline and alternative scenarios (most likely estimates)[a,b]

	Incidence of Cryptosporidium-associated GE episodes			DALY (0%)		
	BASE	Lab only	Population	BASE	Lab only	Population
Gastroenteritis	71,000	71,147	90,525	123	137	160
No GP	65,800	65,803	83,958	42	42	54
GP	5,093	5,234	6,295	38	39	47
Hospitalization	107	110	272	2	2	5
Fatal	3	4	4	40	53	53

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

b) In the baseline we assume no recurrent cases of Crypto-associated GE, in the lab only scenario we assume that 27.5% of the laboratory confirmed cases get recurrent GE symptoms within two months after recovery and in the population scenario we assume that 27.5% of all the crypto-associated GE cases get recurrent symptoms within 2 months after recovery.

3.5 Discussion

About 71,000 community-acquired Cryptosporidium cases occur each year in the entire Dutch population. Hospitalized Cryptosporidium cases are mainly found in adults between 15 and 64 years, which represent the working population. Community-acquired Cryptosporidium cases result each year in a loss of 123 DALYs, with an uncertainty range of 68 DALYs to 276 DALYs per year (undiscounted). Total costs associated with community-acquired Cryptosporidium-associated GE totaled to 4.9 million euros (uncertainty range 1.9 euros million to 12.7 million euros). Despite the fact we had not explicitly considered opportunity costs for the number of days lost for unpaid jobs, INHC accounted for about 85% of all costs associated with community-acquired Cryptosporidium-associated GE cases, the majority from patients, or their caretaker, not requiring any medical services.

A problem with Cryptosporidium is that it needs another laboratory test than is usually used in laboratories. GPs therefore underestimate the role of intestinal protozoa as a potential cause of diarrhea, and often more laboratory tests are needed to identify Cryptosporidium as a cause of GE. It could have a large impact on the disease burden, because the number of cases infected by Cryptosporidium is underestimated. On the other hand, for severe cases the cause will probably be found eventually. From a scenario analysis, we were able to conclude that total costs will not increase significantly due to higher laboratory costs per laboratory-confirmed Cryptosporidium case.

In our baseline we assumed no recurrent symptoms for Cryptosporidium. When assuming that 27.5% of all Cryptosporidium infected patients were at risk to develop recurrent symptoms an impact on the estimated disease burden was found. The total estimated disease burden increased from an estimated total of 123 to 160 DALYs per year and the estimated cost-of-illness would increase from 4.9 million euros to 7 million euros per year. The lab-only-scenario had little impact on both disease burden and cost-of-illness.

4. Giardia lamblia

4.1 Outcome tree, incidence and duration of illness

Giardiasis is the gastrointestinal illness caused by the flagellated protozoan *Giardia intestinalis*, also known as *G. lamblia* or *G. duodenalis* [12]. Giardia is spread from person to person and probably also from animals to humans through fecal-oral transmission. During the past two decades, Giardia infection has become recognized as one of the most common causes of waterborne diseases (found in both drinking and recreational water). In general practices, *Giardia lamblia* is by far the most commonly found enteric protozoan pathogen. It can cause a spectrum of symptoms including a mild self-limiting illness, acute diarrhea and a chronic diarrheal disease [60]. In otherwise healthy persons, symptoms of giardiasis may last two to six weeks. Occasionally symptoms last longer and in young children the infection can lead to a failure to thrive and chronic diarrhea with malabsorption due to villous atrophy. In Figure 4 the assumed outcome tree for Giardia is shown.

4.1.1 Outcome tree and incidence

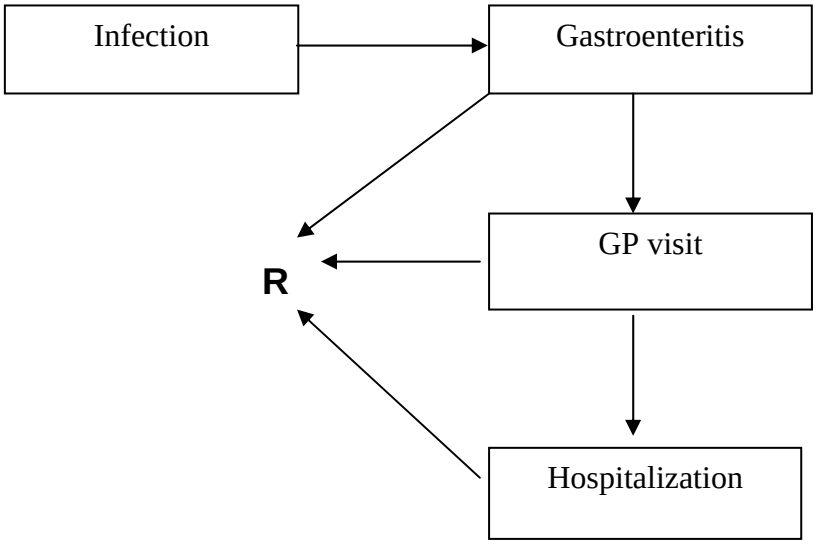

Figure 4. Outcome tree Giardia-associated GE.

Based on SENSOR [17] the estimated median incidence of community-acquired Giardia cases in the population was estimated to be 136,000 cases per year, with an uncertainty range ranking from 90,000 (low estimate) to 233,000 (high estimate), see Table 10. Of these, approximately 12,000 cases would visit a GP[15], both hospitalized and non-hospitalized cases.

However, it has to be notified that in SENSOR, the number of cases found with Giardia was similar to that in the control group. This could be partly due to the moment of sampling in the SENSOR study. The excretion of *Giardia lamblia* often starts only one week after the beginning of symptoms, and first samples were collected as soon as possible after onset[17]. On the other hand the absence of any difference between cases and controls could be caused by the phenomenon that a part of the population will become partially immune depending on the state of the host.

The hospitalization rate for community-acquired Giardia cases was based on data from ISIS and extrapolated to the entire Dutch population. We examined data from fourteen Dutch PHLs, all included in the ISIS surveillance database (ISIS labs) to find out the hospitalization rate. Nine of the fourteen PHLs reported laboratory-confirmed Giardia cases from 2001-2006, of which seven PHLs reported Giardia cases in a minimum of three of the analyzed six years. Six of those seven PHLs registered the institution, specialist or department that requested the test in nearly all cases. We used the data to estimate the incidences of laboratory-confirmed cases and to estimate the number of hospitalizations. We assumed that most likely, 355 cases were hospitalized, with an uncertainty range ranking from 315 (low estimate) to 395 (high estimate) cases hospitalized. Until now, the Dutch Association of Parasitology does not know any persons that died due to Giardia. Studies by Adak et al. [6] and Levy et al. [42] support that conclusion. Therefore we assumed in the current study that the case fatality rate due to Giardia was zero.

Table 10. Incidence and duration of illness of community-acquired Giardia-associated GE for 2004[a, b]

	Incidence estimate (cases per year)			No. of days of illness
	Most likely	Low	High	
Gastroenteritis	136,000	90,000	233,000	-
No GP	124,000	82,800	213,000	10
GP	11,600	6,900	19,600	10
Hospitalization	360	320	400	30

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

b) Assuming a case-fatality of zero

4.1.2 Duration of illness and age-distribution

Information on duration of illness was required for both the disease burden and the costs-of-illness calculations. Based on several studies we assumed a 10-day duration of illness for cases not visiting a GP. The Food Standards Agency reports[24] an overall duration of illness for Giarda of 8 days for 75% of the GP cohort cases, and 13 days for 25% of the GP cases. We therefore assumed that patients that visited a GP but not treated at the hospital would be ill for 10 days (0.75*8+0.25*13). According to the studies by Adak et al.[6] and Lengerich [41] the mean duration of hospitalization is 3.6 and 4 days, respectively. The assumed length of hospitalization was therefore 4 days in our analysis. For Giardia cases visiting a GP and

hospitalized, we assumed a maximum duration of illness of 30 days as found in the literature. Results are reported in Table 10.

The age distribution of community-acquired Giardia-associated GE for the different health states is summarized in Table 11. Given that the majority of Giardia cases would not need a doctor, we assumed that the average age distribution of Giardia cases as found in SENSOR [17] would be representative for Giardia cases not visiting a GP (No GP). The age distribution of Giardia cases visiting a GP was based on NIVEL[15]. The age distribution for hospitalized Giardia cases was based on the ISIS data (lab-confirmed cases with 'hospital' requesting the test, theoretically these might include outpatient consultations). As shown in Table 11, most Giardia cases occur in the age category 0 to 4 years.

Table 11. Age distribution of community-acquired Giardia-associated GE.

	Age classes				
	0-4 years	5-9 years	10-14 years	15-64 years	> 65 years
Gastroenteritis					
No GP	49%	16%	4%	30%	1%
GP	34%	16%	16%	25%	9%
Hospitalization [a]	27%	27%	3%	34%	8%

a) No information available. We used the ISIS age distribution as a proxy.

4.2 Disease burden

Most likely values for incidences used disability weights per case per year, and estimated YLD, YLL and DALYs are shown in Table 12 for the different health states associated with *Giardia lamblia.* The health effects were not discounted, because of the short duration of illness, - all within one year-, and the absence of mortality caused by Giardia. In Figure 5 results of community-acquired Giardia-associated GE are summarized for the most likely estimate and the attendant uncertainty. Discounting was not required as all ill persons recover within the same year of illness onset.

Table 12. Incidence and disease burden of community-acquired Giardia-associated GE for 2004 (most likely estimates) [a, b]

	Incidence	Disability weight per case/year	YLD	YLL	DALY
Gastroenteritis	136,000	-	364	-	364
No GP	124,000	0.0018	228	-	228
GP	11,600	0.0108	125	-	125
Hospitalization	360	0.0323	11	-	11

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

b) Assuming a case-fatality ratio of zero.

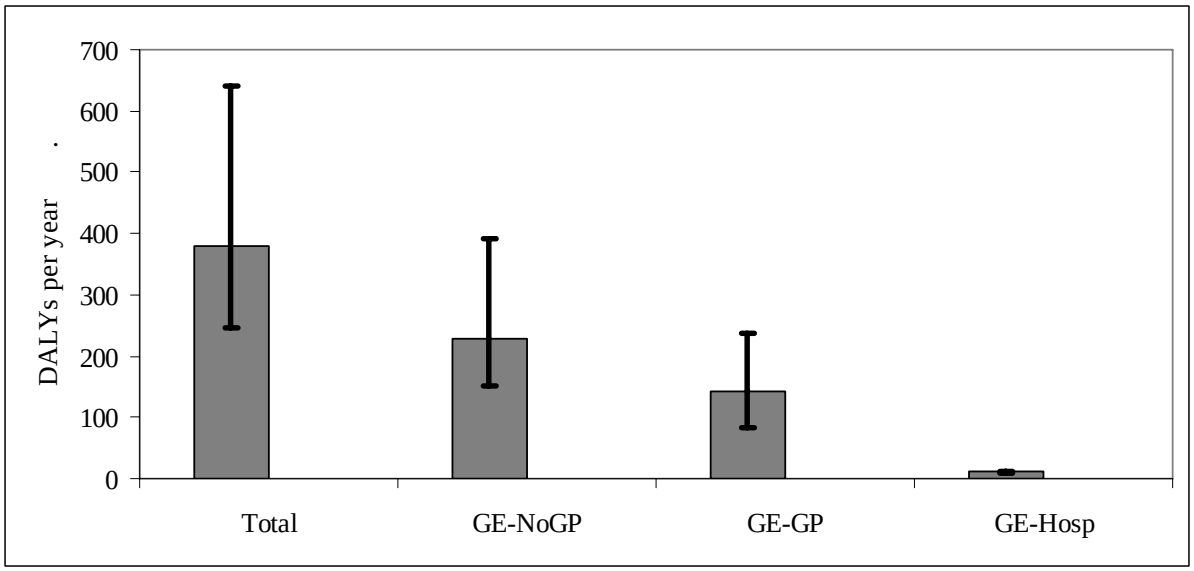

Figure 5. Disease burden of community-acquired Giardia-associated GE for 2004, using most likely estimates, undiscounted (0%). Error bars express an uncertainty interval that results from using low and high estimates. No fatal cases occur. No discounting required, ill persons recover within the same year.

4.3 Cost-of-illness

Based on the incidence and duration of illness shown in Table 10, and following in general the assumptions described in section 2 and in the previous report [35], we estimated the direct health care costs for the different non-fatal health states. An average hospital stay of four days was assumed for community-acquired Giardia cases [41] . DHC results of community-acquired Giardia cases are summarized in Table 13 for the most likely estimate only.

Table13. DHC of community-acquired Giardia-associated GE in million euros for 2004 (most likely estimates) [a, b]

	Drugs & medicine	GP consultations	Hospitalization	Other[c]	Σ DHC
Gastroenteritis	0.70	0.6	0.61	-	1.92
No GP	0.19	-	-	-	0.19
GP	0.49	0.57	-	-	1.06
Hospitalization	0.02	0.03	0.61	-	0.66

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

b) No fatal cases.

c) Apart from costs for drugs and medicine, GP consultations and hospitalization, no other direct health care costs were made for Giardia-associated GE cases.

Productivity losses due to paid employment lost was considered in the current study due to work absence of patients as well as due to work absence of third persons taking care of sick persons, according to the assumptions described in section 2. The estimated overall work absence for Giardia patients not visiting a GP and Giardia patients visiting a GP only, were estimated to be 0.88 days and 1.39 days, respectively. In Table 14 we have summarized the estimated number of days paid employment lost for adult patients and for third persons taking care of a sick person. We further present in Table 14 the most likely estimate of Indirect Non Health Care Costs (INHC).

Table 14. Number of days paid employment lost and INHC of community-acquired Giardia-associated GE in € million for 2004 (most likely estimates)[a]

	No. of days paid employment lost		Productivity losses		Σ INHC
	Patient	Third person	Patient	Third person	
Gastroenteritis	-	-	10.0	6.1	16.1
No GP	0.88	2	8.5	5.6	14
GP	1.39	2	1.2	0.5	1.7
Hospitalization	10.64	7	0.4	0	0.4

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

In Table 15 and Figure 6 we have summarized the most likely estimate and the most likely estimate with attendant uncertainty, respectively, for the total costs of community-acquired Giardia-associated GE cases. Given that all costs occur within one year, discounting costs is not an issue.

Table 15. Cost-of-illness of community-acquired Giardia-associated GE in million euros for 2004 (most likely estimates) [a,b]

(discounting)	DHC (0%)	DNHC (0%)	INHC (0%)	Σ Costs (0%)
Gastroenteritis	1.92	0.33	16.1	18.4
No GP	0.19	0.30	14.0	14.5
GP	1.06	0.03	1.7	2.7
Hospitalization	0.66	0	0.4	1.1

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

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

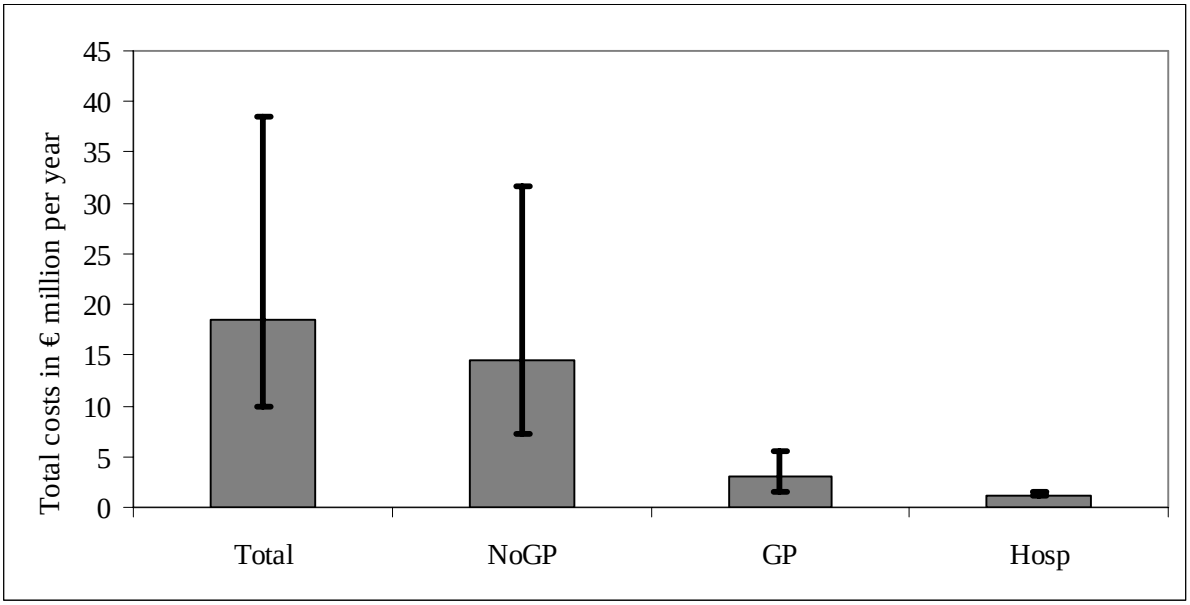

Figure 6. Cost-of-illness of community-acquired Giardia-associated GE, using most likely estimates. Error bars express an uncertainty interval that results from using low and high estimates. No fatal cases occur. Discounting was not required as all costs occur within the first year.

4.4 Scenario analysis

As mentioned before *Giardia lamblia* is also reported to cause a chronic diarrheal disease [60]. Occasionally symptoms last longer and in young children the infection can lead to a failure to thrive and chronic diarrhea with malabsorption due to villous atrophy. Unfortunately, less information is available on the frequency and duration of chronic giardiasis. But it could have a great impact on the disease burden and costs. Therefore, the potential impact of chronic giardiasis was analyzed in a scenario analysis.

The hospitalization rate for community-acquired Giardia cases was based on data from ISIS and extrapolated to the entire Dutch population. Besides the number of hospitalizations these ISIS labs might also include cases visiting outpatient clinics. We assumed that patients with chronic giardiasis were not hospitalized but were referred by their GP only to the outpatient clinic. One consultation in an outpatient clinic amounts to approximately 64 euro, which is the calculated average of consultations in general hospitals and university hospitals[51]. For estimating the extra productivity loss due to chronic giardiasis we assumed the same duration of illness as the hospitalized patients and third persons (i.e. 30 days). This may be a conservative assumption. Although chronic patients would probably be less severely affected than hospitalized patients, the illness, however, relapses probably a few times within one year-time, making our assumption more acceptable.

We examined data from fourteen Dutch PHLs, all included in the ISIS surveillance database (ISIS labs) to find out the outpatient clinic rate. We estimated from these data that most likely, 405 cases per year developed chronic giardiasis, with an uncertainty range ranking from 398 (low estimate) to 411 (high estimate) cases. When adding the chronic cases to our base case, the cost-of-illness increased from18.4 million euros to 18.9 million euros and the disease burden from 364 to 377 DALYs each year.

4.5 Discussion

About 136,000 community-acquired Giardia cases may occur each year in the entire Dutch population. The exact number is unknown because Giardia is also frequently isolated from healthy controls. Severe community-acquired Giardia cases are mainly found in children between 0 and 9 years. This is confirmed by the literature, because many outbreaks published occurred in day care centers. Community-acquired Giardia cases result each year in 364 DALYs, with an uncertainty range of 236 DALYs to 615 DALYs per year (undiscounted). Total costs associated with community-acquired Giardia-associated GE totaled to18.4 million euros (9.8 million euros to 38 million euros), more than 85% due to INHC.

Giardiasis may become chronic, especially in young children. Due to the lack of detailed information available on this topic, we assumed that patients visiting outpatient clinics would be the ones with chronic disease. A scenario analysis showed that extra costs and disease burden only marginally increase by including chronic giardiasis.

5. General discussion

The aim of this report was to describe the disease burden and cost-of-illness of two specific pathogens: *Cryptosporidium spp*. and *Giardia lamblia,* in order to help decision makers to establish the priority of pathogenic micro-organisms that can (also) be transmitted by food, as a basis for effective and efficient policymaking on control, prevention and surveillance. The current results and the results of the previous study by Kemmeren et al. [35] are a first step in the process of priority setting that helps to integrate complex information in a structured framework so that it is easily accessible to decision makers. We focused on two indicators, disease burden and cost-of-illness. The methods used to calculate both indicators are based on a broad range of practical and theoretical studies. Pathogen specific information for the Netherlands was not always available for Cryptosporidium and Giardia. Therefore, several assumptions had to be made. We tried to evaluate the uncertainties due to those assumptions by performing scenario analyses. The results are not completely transferable to other countries because of a) the Dutch health care system itself, for example in the Netherlands the GP is the gatekeeper for every further medical service, and b) due to the use of specific Dutch guidelines.

Table 16 Disease burden and cost estimates (in million euros) of the nine studied pathogens

Pathogen (discounting)	DALY (0%)	DALY (4%)	Σ Costs (0%)	Σ Costs (4%)
Bacteria-infections				
Campylobacter	1,300	830	22.3	19.6
Escherichi coli O157	110	-	-	-
Salmonella	670	500	8.8	7.8
Perinatal listeriosis	320	90	-	-
Acquired listeriosis	70	60	-	-
Viruses				
Norovirus	450	430	25.0	25.0
Rotavirus	370	290	21.7	21.7
Protozoa				
Cryptosporidium	123	110	4.9	4.9
Giardia lamblia	364	-	18.4	18.4
Congenital Toxoplasmosis	1200	360	-	-
Acquired Toxoplasmosis	1200	640	-	-

Table 16 presents a summary of disease burden and cost estimates of the two pathogens studied in this report, and the seven pathogens that were evaluated in the previous report. The results in this table show that the costs of Giardia-associated GE are high in comparison with Cryptosporidium-associated GE and Salmonella. However, the costs of Campylobacter, norovirus and rotavirus are somewhat higher. Figure 7 shows the disease burden of the two pathogens that were evaluated in this report in relation to the seven other pathogens.

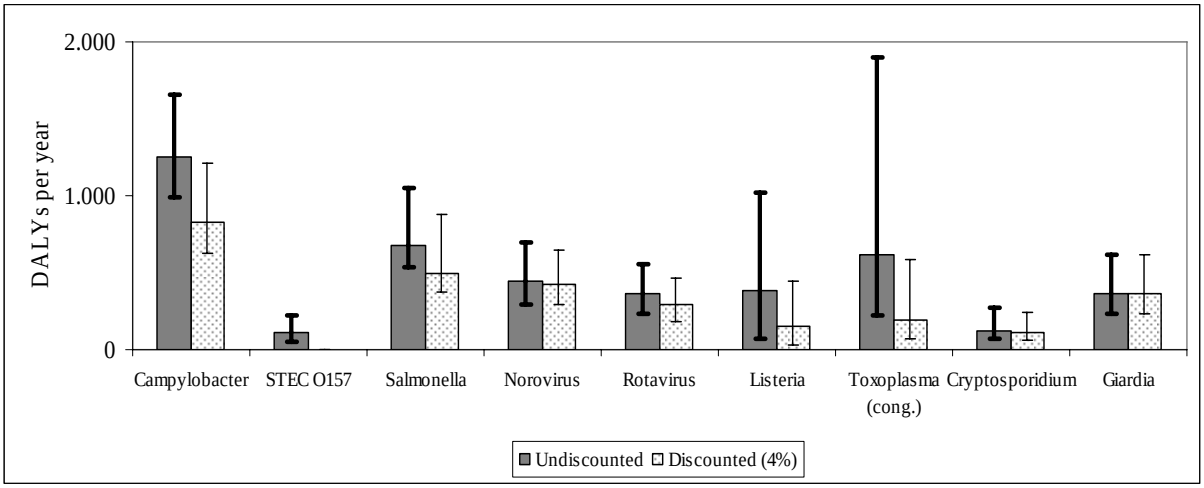

Figure 7. Disease burden of nine pathogens

Figure 8 shows a summary of cost-of-illness estimates of the two pathogens that were evaluated in this report in relation to the four previously studies pathogens.

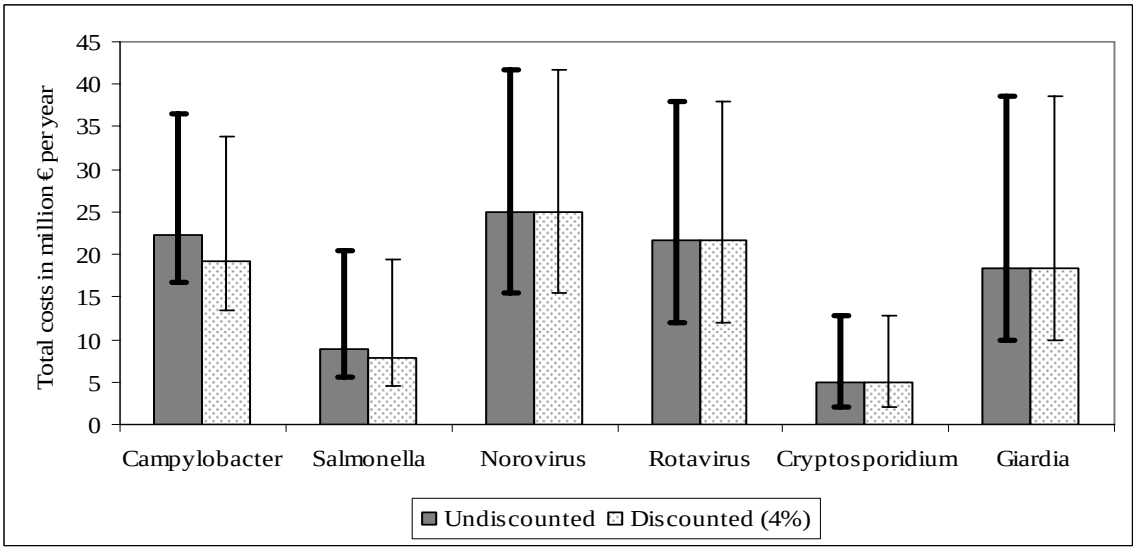

Figure 8 Cost-of-illness of six pathogens studied

A limitation in estimating the disease burden and cost-of-illness of Cryptosporidium is the fact that the laboratory confirmed cases (and thus our hospitalization rates) are often underestimated because they can not be found by using normal tests. The routine examination of the stool specimen (microscopic examination of a direct wet smear and of the sediment resulting from formalin-ether sedimentation) mostly does not recognize protozoa, but at the physician's request other parasite-specific techniques for stool examination can be added.

Therefore we performed a scenario analysis that doubled the test costs. But with only a minor effect on the total costs.

The estimations of both Cryptosporidium and Giardia might be an underestimation. On the other hand, the hospitalizations due to Giardia might be overestimated, because of the data used. From the ISIS data the first diagnosis for hospitalization can not be checked. And although Giardia was confirmed by laboratory testing, it is unknown if that might have been the reason for hospitalization.

Besides, we did not include potential recurrent Cryptosporidium-associated GE in our base case analysis because of limited information. Hunter et al. [33]studied the medium term health effects of cases of cryptosporidiosis, but could not tell anything about health effects after three months. We performed a scenario analysis to include recurrent GE symptoms. This resulted in little increase of costs and disease burden. Chronic or debilitating gastrointestinal illness caused by Giardia has been reported[57 58], but the frequency with which this occurs is not known [41]. In our analysis we tried to estimate the impact of chronic Giardia on disease burden and costs in a scenario analysis. Further research has to be done on the occurrence of long term health sequelae, their impact on quality of life and resources used, both medical and others due to both protozoan pathogens.

Little information is known on the hospitalizations due to Cryptosporidium and Giardia. Research is recommended to provide insight in this topic. The Dutch Ministry of Public Health, Welfare and Sports has asked RIVM to initiate a study to assess the amount of hospitalizations due to GE and to elucidate associated pathogens. With those results, a better estimation could be made of disease burden and costs of Cryptosporidium- and Giardia-associated GE.

In the current study, we used a 4% discount rate for both costs and health effects as suggested in the Dutch guidelines for public health economic evaluation previous to medio-2005 [51]. Since medio-2005, however, the Dutch guidelines for public health economic evaluation have changed and recommend to use a discount rate of 1.5% for health effects and 4% for costs [9]. We decided however, in the current report to follow the earlier recommendation, which was 4% for both costs and effects[51], to be able to compare with results of the previous study by Kemmeren et al. However, we show also the undiscounted estimates. This allowed us to analyze the impact of discounting on the results. If we had followed the new recommendation, the estimated discounted disease burden would have been somewhere in between the undiscounted and 4% discounted figures presented, whereas the cost estimates would remain unchanged. But, by following the earlier recommendations we do not only have the advantage that our results can be compared with earlier work done before 2005 in the Netherlands, but also with the work done in other countries where it is common practice to use the same discount rate for both monetary and health effects. In Appendix IV this matter is further explained.

In the present report and the report by Kemmeren et al. [36] the disease burden and/or cost-of-illness for nine pathogens were calculated. To support the setting of priorities in food safety policy, the disease burden and cost-of-illness have to be calculated for other pathogens that meet the inclusion criteria (see section 2.3 in Kemmeren et al.[36]). Therefore this project will be continued next year.

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Appendix I – Detailed methodological choices

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

Incidence or prevalence approach

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

In this study, we chose the incidence approach for several reasons. Firstly, most communicable diseases have such a rapid course that prevalence is not very informative. Secondly, because the incidence approach is based on current events it is more sensitive to current epidemiological trends than the prevalence approach. Thirdly, the incidence approach is more informative on health gains and related savings of avoided cost-of-illness expenses that can be obtained now and in the future by current control programs that aim to prevent new cases (= incidence). Lastly, with the incidence approach calculation of time lived with disability is more consistent with the calculation of time lost due to mortality: the burden is ascribed to the age of onset (instead of to the age at which the disability is lived) or the age at which death occurs[49]. This applies also to the cost-of-illness estimation. Using the incidence approach costs-of-illnesses made due to chronic and long-lasting diseases in the remaining life time are ascribed to the age of onset, similar to the estimations of productivity losses due to premature mortality that are ascribed to the age at which death occurs.

Outcome or agent-based approach

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

and the expected impact of preventive measures on both public health costs and associated costs. Therefore, the agent-based approach is chosen in this project.

Outcome trees

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

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

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

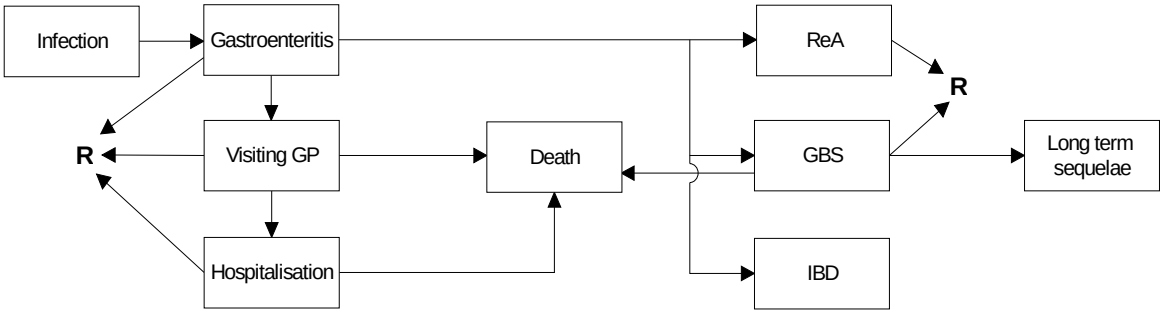

Figure A.1-1 Outcome tree Campylobacter-associated GE and sequelae (R: recovery).

Perspective of economic evaluation

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

Discounting

In most programs financial costs and revenues occur on different points over time. In order to be able to value and compare different projects, the net present values (NPV) of each single program is estimated taking into account all investments and revenues made over time. This is achieved by calculating the *net* cash flow in each period, and then discounting this stream back to the present. According to Drummond et al. [21] the applied rate is often the real rate of return on long-term government bonds. This concept is not only applied to financial costs and revenues, but, although not undisputed, is also commonly applied in economic analysis of medical or other public health interventions for the non-monetary health effects. When the principle of discounting is applied in disease burden estimates, it means that future life years are assigned less value than those lived today. This is based on the economic concept that immediate profits are generally preferred over benefits later in time [50]. In general, health today is valued higher than health in the future because there is uncertainty about future possibilities to 'better' treat diseases and about possible future co-morbidity.

Discounting of health benefits is disputed because its application results in a lower efficiency of prevention programs, whereas not discounting, or the use of a low discount rate - lower than the discount rate used for the costs - favour preventive measures due to benefit in the far future. We use in the current report a discount rate of 4% for both costs and effects[51], and also show the undiscounted estimates. This allows a comparison of our results with other work using discounted or undiscounted health effects, but also to analyze the impact of discounting on the results.

Data needs

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

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

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

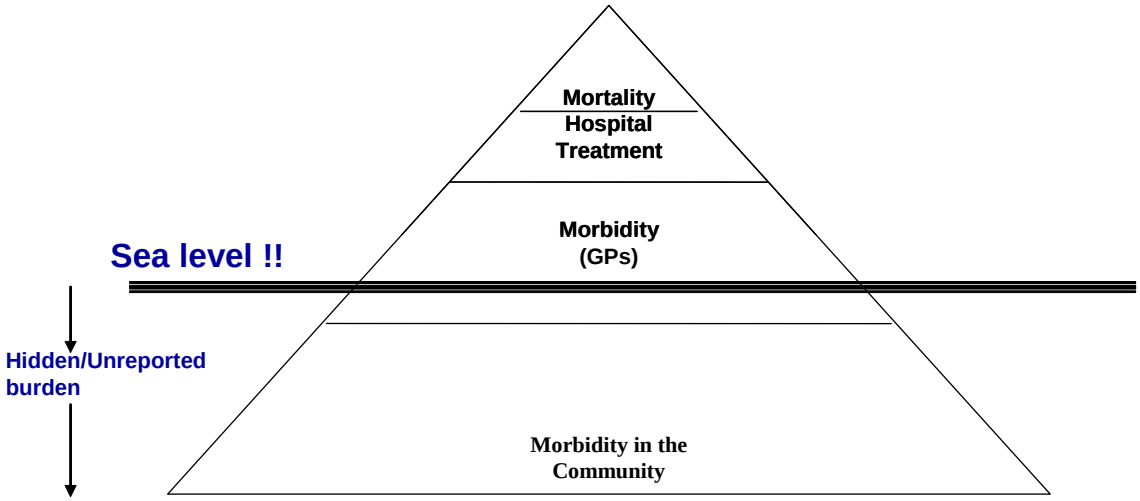

Figure A.1-2. The surveillance pyramid of communicable diseases [7]

Incidence of non-fatal health outcomes

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

Ideally, data are available for all relevant levels of the surveillance pyramid: non-consulting cases, cases consulting a GP and hospitalized cases. In this order, data availability may be expected to increase, but will seldom be complete. In this project, incidental studies such as

for example SENSOR and NIVEL, but also case-control studies and surveillance data readily available from the Basic Surveillance Network or Dedicated Surveillance Networks will be used, relying wherever possible on Dutch studies that will be complemented, where necessary, by published international literature studies. Data include all community-acquired infections in the Netherlands in the chosen time period, including travel-related cases but excluding illness contracted in closed settings such as hospitals and nursing homes.

Duration of non-fatal health outcomes

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

Number of fatal cases

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

Life expectancy of fatal cases.

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

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

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

Disability weights for non-fatal outcomes

Disability weights reflect the health impact of a condition and they are based on the preferences of a panel of judges. Ideally, the disability weights used in DALY calculations

reflect the preferences of the society under study. In the elicitations of disability weights, there are several aspects to consider, including:

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

Whose values? Ideally, disability weights based on preferences of the general public are used in burden of disease studies aimed to inform policy making at the national or international level. Disability weights based on elicitation panels consisting of lay persons are increasingly becoming available. Previous work has depended on panels of medical professionals. Preferences of patients who actually suffer from the disease are biased because of coping behaviour. The international transferability of disability weights is also of concern. A study in Western Europe[55] concluded that there was 'a reasonably high level of agreement on disability weights in Western European countries with the VAS and TTO methods, but a lower level of agreement with the PTO method'. However, a recent study [34] concluded that 'meaningful differences exist in directly elicited TTO valuations of EQ-5D health states between the US and UK general populations'. Hence, disability weights are ideally based on specific elicitations for the population under study, but this may be very difficult to realize for the EU.

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

Annual or period profiles. For chronic diseases, most descriptions are based on the impact of a disease in the course of a year. However, many infectious diseases have a rapid course, and consequently the disability weight can be assessed by focusing on the phase of acute disease only (period profile) or by focusing on a year in which an episode of acute illness is experienced (annual profile). Both methods have been used and using the annual profile may overvalue disability weights [59]. In practice, large differences may be found between these two methods for diseases that have a high incidence but low severity (e.g. norovirus-associated gastroenteritis). For such diseases, using annual profiles may lead to very high estimates of disease burden. Following earlier work on foodborne infections, in this project period profiles were used.

Age-weighting

In the original GBD project, age-weighting was applied to reflect the fact that individuals have different roles and changing levels of dependency and productivity with age. Therefore it may be appropriate to consider valuing the time lived at a particular age unequally [23 47 48].

Age-weighting is highly debated. Although the principle of age-weighting makes sense, the exact quantitative implementation is controversial [8]. In this project, age-weighting will not be applied. The disease burden estimate of the current study reflects solely the impact of illness and premature death on public health, independent of any other factors. However, the fact that individuals have different roles and changing levels of dependency and productivity with age is nevertheless not neglected in this study, but is taken into account in the cost-of-illness estimate, which we consider more relevant. Furthermore, the cost-of-illness estimates allow, in comparison to disease burden, not only a distinction of changing levels of dependency and productivity with age, but they allow also to distinguish, if required, age-dependent resource requests of any kind.

Cost categories

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

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

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

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

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

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

Differences in cost-of-illness valuations

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

In the case of productivity loss, there are currently two methods in use, the human capital approach and the friction cost approach. The human capital approach, which is based on neoclassical labour theory, estimates the value of *potential* lost production (or the potential lost income) as a consequence of disease. In the case of permanent disability or premature death at a specific age the total productivity value (or income) from that age until the age of retirement is counted as productivity loss. But according to Koopmanschap et al. [38], the real production losses for society are smaller. The aim of the friction cost approach is to adjust the human capital estimates of productivity costs for the compensations that are likely to occur as a result of a labour market [56]. The friction cost method considers only production losses for the period needed to replace a sick, invalid or dead worker, the 'friction period'[22]. The friction cost method takes explicitly into account the economic processes by which a sick, invalid or dead person can and will be replaced after a period of adaptation [39]. The length of the friction period depends on the situation of the labour market. A high unemployment rate generally allows fast replacement of a sick, invalid or dead person, whereas in the case of a low unemployment rate, on average more time is needed. The friction cost method places a zero value on persons outside the labour market, such as children aged 15 or younger and retirees of 65 years and older.

In the current project we chose the friction cost method, following the Dutch guidelines for farmaco-economic evaluation[51 52].

Productivity loss

Apart from the age at death, additional information on work relation and salary of the individuals is required. However, this information is often not available. Therefore, in the current project we used estimated productivity losses for an average Dutch (working) person in the working life of a specific age as given in Oostenbrink et al. [51] for the year 2005, increasing these costs by using the Dutch consumer price index.

Resources used, the quantity demanded and the cost per resource unit used

Ideally, data with respect to resources used, their quantity demanded, and the costs per resource unit should be available for all relevant levels of the surveillance pyramid. In this project information on resources used and the quantity demanded were collected from incidental studies such as SENSOR and NIVEL and case-control studies, as well as from

surveillance data. If there were no Dutch data available, information was gathered from published literature, and if these data were not available either, experts were consulted and scenario analysis was conducted. In this project, we used solely Dutch prices for the cost price per resource unit, following wherever possible the recommended prices given in the Dutch guidelines[51]

Appendix II- Literature and other data on hospitalizations, fatal cases and duration of illness of *Cryptosporidium spp*.

Table A.2-1 Summary of literature review on Cryptosporidium spp.

Source	Study	Outcome	Calculation outcome	Result	Conclusion
ISIS data	Lab-confirmed cases 11 laboratories tested positive crypto cases from 2001-2006, of which 4 laboratories tested positive crypto cases every year (useful labs). 3 of the useful labs registered the institution, specialist or department that inquired the test constantly.	1) Lab-confirmed cases, extrapolation to the NL., by including only the labs that tested crypto cases, 2) Hospitalised cases, extrapolation to the NL., by including only the labs that tested crypto cases, 3) Lab-confirmed cases, extrapolation to the NL. by including only the labs that tested crypto cases in all the years 2001-2006 (excluding Goes because no good registration of requesting physician), 4) Hospitalised cases, extrapolation to the NL., by including only the useful labs, Goes excluded. 5) Age distribution including all the labs with crypto cases 6) Age distribution hospitalisations including all the labs with crypto cases 7) Age distribution GP including all the labs with crypto cases 8) Age distribution including only the useful labs	1) ((crypto cases year 1-6/ coverage rate labs)* population NL)/6, 2) no hospitalized cases in all the labs/ total cases 3) ((crypto cases year 1-6/ coverage rate labs)* population NL.)/6, 4) no hospitalized cases in useful labs/ total cases in useful labs	1) 478 crypto cases, 2) 7% hospitalisation rate, 3) 536 crypto cases, 4) 19% hospitalisazion rate 5) 0-4 y: 24% 5-9 y: 24% 10-19 y: 6% 20-60 y : 39% 60+ y : 8% 6) 0-4 y: 12% 5-9 y: 12% 10-19 y: 0% 20-60 y : 45% 60+ y : 30% 7) 0-4 y: 26% 5-9 y: 26% 10-19 y: 4% 20-60 y : 41% 60+ y : 4% 8) 0-4 y: 22% 5-9 y: 22%	Minimum lab-confirmed cases = 478 Minimum hospitalisations= 7% of 478= 34 Maximum lab-confirmed cases= 536, Maximum hospitalisations= 19% of 536= 102

				10-19 y: 2% 20-60 y : 45% 65+ y : 9%	
		9) Age distribution hospitalizations including only the useful labs		9) 0-4 y: 11% 5-9 y: 11% 10-14 y: 0% 15-65 y : 52% 65+ y : 25%	9) only 18 cases
		10) Age distribution GP including only the useful labs		10) 0-4 y: 23% 5-9 y: 23% 10-14 y: 0.5% 15-65 y : 49% 65+ y :3.5%	
Corso et al. [14]	Outbreak study, Milwaukee, Wisonsin	1) no GP or hospital: 88% 2) GP: 11% 3) hospitalisation: 1% 4) duration of illness no GP: 4.7 5) duration of illness GP: 5.8 6) duration of illness hosp.: 18.4 7) persons in hospital with AIDS: 14% of hosp. 8) average length of stay in hospital, no underlying conditions: 5 days 9) average length of stay in hospital, underlying conditions other than AIDS: 7 days 10)) average length of stay in hospital, AIDS: 16 days 11) average length of stay in hospital, all conditions: 8 days	1) 88%*71,000 2) 11% *71,000 3) 1% * 71,000 7) 14%*710	1) 62480 cases no GP 2) 7810 GP cases 3) 710 hospitalisations 7) 99 hosp. cases with AIDS	
CDC[3]	Outbreak study, New York, drinking apple cider	median duration of symptoms: 6 days (1-21 days)			
CDC[5]	Outbreak study, Minnesota, water sprinkler fountain	1) median duration of illness was 7 days 2) 2% of the patients was hospitalized	2) 2%* 71,000	2) 1420 hospitalized cases	
CDC[4]	Outbreak study, Washington, foodborne	1) median length of illness: 5 days (1-13 days) 2) 2 of the 62 cases were hospitalized 3) 6 of the 62 cases GP	2) 2/62* 71,000 3) 6/62* 71,000	2) 2290 hospitalized cases 3) 6870 GP cases	

CDC[2]	Outbreak study, Minnesota, foodborne	Median length of illness was 4 days (0.5 day- 14 days)			
Dietz et al.[20]	Review of the first four years (1995-1998) of US surveillance crypto	Age distribution: 0-4 y: 20.6% 5-9 y: 10.1% 10-19 y: 8.0% 20-60 y : 54.5% 60+ y : 5.2%			
Adak et al.[6]	Trend study 1992-2000 in England and Wales using lab-surveillance data	1) duration hosp. 2) case fatality rate 3) hospitalisation rate	1) hosp. bed days/hosp. admissions= 145/39 2) deaths/total cases= 3/2063 3) hospital admissions/total cases= 39/2063	1) 3.7 days 2) 0.1% of total (478-536)= 0,5 deaths 3) 2% of lab (478-536)= 10-11 hospitalized cases	
Dietz et al.[19]	Laboratory based surveillance	1) duration of illness: 7-14 days 2) lab-confirmed cases by age1997-1998: 0-4 y: 19% 5-9 y: 9% 10-19 y: 13% 20-60 y : 53% 60+ y : 5% 3) hospitalisation rate is 15.7% of lab-confirmed cases (32% for HIV cases) 4) case fatality rate is 0.6% (3% for HIV cases) 5) hosp. cases by age: 0-4 y: 12% 5-9 y: 12% 10-19 y: 17% 20-60 y : 51% 60+ y : 8%	3) 15.7% * 478 15.7% * 536 4) 0.6%*478 0.6%* 536	3) 75 cases 84 cases 4) 3 cases 3 cases	
Mead et al. [45]	Surveillance	1) hospitalization rate: 0.150% of total crypto cases 2) case-fatality rate: 0.005% of total crypto cases	1) 0.150%*71,000 0.150%*34000 0.150%*165000 2) 0.005*71,000 0.005*34000 0.005*165000	1) 107 hospitalizations 51 hosp. 248 hosp. 2) 4 fatal cases 2 fatal cases 8 fatal cases	

Summarizing the hospitalization data:

- 34- 102 hospitalizations (ISIS data)
- 710 hospitalizations, and 99 for cases with AIDS (Corso et al[14]., outbreak study)
- 1420 hospitalizations (CDC [5] outbreak study)
- 2290 hospitalizations (CDC [4]outbreak study)
- 10-11 hospitalizations (lab-surveillance data England/Wales[6], Adak et al.)
- 75-84 hospitalizations (Dietz et al.[19] and ISIS data)
- 51-248 hospitalizations (Mead et al. [45]and incidence rates)

Conclusion: assume as most likely 107 hospitalizations (Mead et al.[45]), as a minimum 10 hospitalizations (Adak et al.[6] and ISIS data) and as a maximum 248 (Mead et al. [45]).

Summarizing the case-fatality data:

- 0,5 fatal cases (lab-surveillance data England and Wales[6])
- 3 fatal cases (labbased surveillance[19] and ISIS data) 14-16 (in HIV patients)
- 2-8 fatal cases (Mead et al.[45] and incidence rates)

Conclusion: assume as the most likely case fatality rate 3 (Dietz et al. [19] and ISIS), the minimum was 2 (Mead et al.[45] and incidence rates) and the maximum was 8 cases (Mead et al.[45] and incidence rates).

Summarizing the length of illness data:

- no GP: 4.7 days, GP: 5.8 days, hosp.: 18.4 days (Corso et al.[14], outbreak study)
- median duration of symptoms: 6 days (1-21 days) (CDC [3] outbreak study)
- median duration of illness was 7 days (CDC [5]outbreak study)
- median length of illness: 5 days (1-13 days) (CDC [4]outbreak study)
- median length of illness was 4 days (0.5 day- 14 days) (CDC[2], outbreak study)
- Duration of illness: 7-14 days (lab surveillance by Dietz et al.[19])

Conclusion: length of illness no GP 0.5- 7 days, GP 4-10 days, hosp. 13-21 days, thus for no GP we assumed a duration of 3.5 days, for GP 7 days and for hosp. 18.4 days.

Summarizing the length of hospitalisation:

- 8 days (5- 16 days depending on underlying conditions) (Corso et al.[14] , outbreak study)
- 3.7 days (surveillance data England and Wales[6])

Conclusion: length of hospitalization 3.7-8 days (HIV conditions higher). We assumed 8 days, like the Corso study[14].

Summarizing age distributions general (only for comparison because in our analysis we used data from SENSOR[17]):

SENSOR[17]	**Dietz et al[19] [20]**	**ISIS all labs**	**ISIS useful labs**	**Conclusion**
0-4 y: 42%	20.6% 19%	24%	22%	**21.5%**
5-9 y: 6%	10.1% 9%	24%	22%	**16.5%**
10-19 y: 3%	8.0% 13%	6%	2%	**8%**
20-60 y : 47%	54.5% 53%	39%	45%	**47%**
60+ y : 2%	5.2% 5%	8%	9%	**7%**

Hospitalizations by age :

Dietz et al. [19]	**ISIS all labs**	**ISIS useful labs**	**Conclusion**
0-4 y: 12%	12%	11%	**12%**
5-9 y: 12%	12%	11%	**12%**
10-19 y: 17%	0%	0%	**8.5%**
20-60 y: 51%	45%	52%	**49%**
60+ y: 8%	30%	25%	**18.5%**

GP by age (only for comparison because in our analysis we used data from NIVEL[18]):

	NIVEL[18]	**ISIS all labs**	**ISIS useful labs**	**Conclusion**
0-4 y:	34%	26%	23%	**24.5%**
5-9 y:	16%	26%	23%	**24.5%**
10-19 y:	16%	4%	0.5%	**2%**
20-60 y:	25%	41%	49%	**45%**
60+ y:	9%	4%	3.5%	**4%**

Age distribution case fatality rates, taken from general GE age distribution (CBS)

	CBS
0-4 y:	1%
5-9 y:	0%
10-19 y:	0%
20-60 y:	22%
60+ y:	76%

Appendix III- Literature and other data on hospitalizations, fatal cases and duration of illness of *Giardia lamblia*

Table A.3-1 Summary of literature review on Giardia lamblia

Source	Study	Outcome	Calculation outcome	Result	Conclusion
ISIS data	Lab-confirmed cases 9 laboratories tested Giardia cases from 2001-2006, of which 7 laboratories tested Giardia cases three years or more (useful labs). 6 of the useful labs registered the institution, specialist or department that inquired the test constantly.	1) Lab-confirmed cases, extrapolation to the NL., by including only the labs that tested Giardia cases,	1) ((Giardia cases year 1-6/ coverage rate labs)* population NL)/6,	1) 3154 Giardia cases,	Minimum lab-confirmed cases = 3154
		2) Hospitalised cases, extrapolation to the NL., by including only the labs that tested Giardia cases,	2) no. hospitalized cases in all the labs/ total cases	2) 10% hospitalization rate,	Minimum hospitalisations= 10% of 3154= 315
		3) Lab-confirmed cases, extrapolation to the NL., by including only the labs that tested Giardia cases three years or more (excluding Goes because no good registration of requesting physician),	3) ((Giardia cases year 1-6/ coverage rate labs)* population NL)/6,	3) 3290 Giardia cases,	Maximum lab-confirmed cases= 3290
		4) Hospitalised cases, extrapolation to the NL. by including only the good labs, Goes excluded.	4) no. hospitalized cases in useful labs/ total cases in useful labs	4) 12% hospitalization rate	Maximum hospitalisations= 12% of 3290= 395
		5) Age distribution including all the labs with Giardia cases		5) 0-4 y: 19% 5-9 y: 19% 10-19 y: 6% 20-60 y : 46% 60+ y : 10%	
		6) Age distribution hospitalisations including all the labs with Giardia cases		6) 0-4 y: 28% 5-9 y: 28% 10-19 y: 7% 20-60 y : 28% 60+ y : 9%	
		7) Age distribution GP including all the labs with Giardia cases		7) 0-4 y: 17% 5-9 y: 17% 10-19 y: 10% 20-60 y : 52% 60+ y : 10%	

		8) Age distribution including only the useful labs 9) Age distribution hospitalizations including only the useful labs 10) Age distribution GP including only the useful labs		8) 0-4 y: 20% 5-9 y: 20% 10-19 y: 6% 20-60 y : 44% 60+ y : 10% 9) 0-4 y: 27% 5-9 y: 27% 10-14 y: 3% 15-65 y : 34% 65+ y : 8% 10) 0-4 y: 17% 5-9 y: 17% 10-14 y: 2% 15-65 y : 58% 65+ y :6%	
Prismant	hospital discharge diagnoses	Mean number of hospitalizations 1996-2005	hosp.1996-2005/6	1) 134 hospitalizations in 2004, 145 (2003) and 90 (2002)	
Furness *et al.* [25]	Surveillance U.S., CDC	Mean annual incidence of hospitalization: 2.0 per 100.000 persons	extrapolation to the Netherlands	1) 326 hospitalizations	
IID study[24]	Surveillance in England	Duration of illness GP		1) 8-13 days	
Gardner *et al.* [26]		Duration of illness		7 to 10 days at presentation	
Homan et al. [31]		Duration of illness		8-28 days	n=18
Kortbeek *et al.* [40]		Duration of illness		>7 days	
Adak *et al.*[6]	Trend study 1992-2000 in England and Wales using lab-surveillance data	1) duration hosp. 2) case fatality rate 3) hospitalisation rate	1) hosp. bed days/hosp. admissions= 18/5 2) deaths/total cases= 0/1673 3) hospital admissions/total cases= 5/1673	1) 3.6 days 2) 0.0% of total lab= 0 deaths 3) 0.3% of lab (3154-3290)= 9-10 hospitalized cases	
De Wit *et al.*		Duration of symptoms until consultation		1) most in 15-28 days	

Lopez *et al.*	Outbreak study, Berlin, New Hampshire	1) median duration of diarrhoea 2) 13% of lab-confirmed cases hospitalized	2) 13%* 3154 13%* 3290	1) 10 days 2) 410 428	
Rauch *et al.* [54]	Longitudinal study in a day care center population	Mean duration of Giardia (SD)		2 weeks (+/- 1.5 weeks)	
Kent *et al.*[37]	Outbreak study US	Mean duration of diarrhea		11.3 days (with a range of 1-34 days)	
Lengerich *et al.* [41]	Review	1) US incidence of hospitalization is 2.0 per 100.000 persons 2) median length of hospitalization	extrapolation to the Netherlands	1) 326 hospitalizations 2) 4 days	
Hopkins *et al.* [32]	Review outbreakstudies	Duration of illness		3-30 days	
Levy *et al.*[42]	Surveillance	fatal cases		No deaths reported	

Summarizing the hospitalization data:

- 315- 395 hospitalizations (ISIS data)
- 134 hospitalizations in 2004 (90-145) (Prismant)
- 9-10 hospitalizations (lab-surveillance data England/Wales[6])
- 326 hospitalizations (surveillance U.S.[25])
- 326 hospitalizations (review[41])
- 410-428 hospitalizations (Lopez and ISIS data)

Conclusion: Assume as a most likely estimation 355 hospitalizations (mean of ISIS-data) and as a high estimate 395 hospitalizations (ISIS) and as a low estimate 315 hospitalizations (ISIS).

Summarizing the case-fatality data:

- 0 fatal cases (lab- surveillance data England and Wales[6])
- 0 fatal cases (Levy[42])

Conclusion: We assumed that no people die from Giardia.

Summarizing the length of illness data:

- GP: 8 days (13 days for 25% of persons)(IID-study[24])
- Duration of illness: 7-10 days (Gardner et al.[26])
- Duration of illness: 8-28 days (Homan et al.[31])
- Duration of illness: >7 days (Kortbeek et al. [40])
- Median duration of illness: 10 days (Lopez et al.)
- Mean duration of Giardia: 2 weeks (+/- 1.5 weeks) (Rauch et al.[54])
- Mean duration of illness: 11.3 days (1-34 days) (Kent et al. [37])
- Duration of illness: 3-30 days (Hopkins et al. [32])

Conclusion: Total range of duration is 3 to 30 days according to studies found. One study gives duration of illness for GP patients: 8 days. For no GP we assumed a duration of 10 days, for GP we assumed a duration of 10 (0.75*8+0.25*13) days and for hospitalization we assumed a duration of illness of 30 days.

Summarizing the length of hospitalisation:

- 3.6 days (surveillance data England and Wales[6])
- median length of hospitalization: 4 days (Lengerich et al. [41])

Conclusion: We assumed a length of hospitalization of 4 days.

Summarizing age distributions general (only for comparison because in our analysis we used data from SENSOR):

SENSOR[17]	**ISIS all labs**	**ISIS useful labs**
0-4 y: 49%	19%	20%
5-9 y: 16%	19%	20%
10-19 y: 4%	6%	6%
20-60 y : 30%	46%	44%
60+ y : 1%	10%	10%

Hospitalisations by age :

	ISIS all labs	**ISIS useful labs**
0-4 y:	28%	27%
5-9 y:	28%	27%
10-19 y:	7%	3%
20-60 y:	28%	34%
60+ y:	9%	8%

GP by age (only for comparison because in our analysis we used data from NIVEL):

	NIVEL[15]	**ISIS all labs**	**ISIS useful labs**
0-4 y:	34%	17%	17%
5-9 y:	16%	17%	17%
10-19 y:	16%	10%	2%
20-60 y:	25%	52%	58%
60+ y:	9%	10%	6%

Appendix IV- The used discount rates and their impact on the results

In most programs financial costs and revenues occur on different points over time. In order to be able to value and compare different projects, the net present values (NPV) of each single program is estimated taking into account all investments and revenues made over time. This is achieved by calculating the *net* cash flow in each period, and then discounting this stream back to the present. According to Drummond et al. [21]the applied rate is often the real rate of return on long-term government bonds. This concept is not only applied to financial costs and revenues, but, although not undisputed, is also commonly applied in economic analysis of medical or other public health interventions for the non-monetary health effects. Whereby applying a discount rate generally is used to account for the fact that health today is valued higher than health in the future, and for the fact that there is uncertainty about future possibilities to 'better' treat diseases.

In the Netherlands, the Dutch guidelines for public health economic evaluation recommended the use of a common discount rate. This was until medio-2005 4% for both costs and health effects [51]. Other countries and other analysts use slightly different discount rates, but mostly [52]varying between 3% to 5%. Since 2005, however, the Dutch guidelines for farmaco-economic evaluation have changed and recommend to use a discount rate of 1.5% for health effects and 4% for costs [9]. This recommendation, however, is not based on any economic theory, and is also not current practice in other countries or other sectors. The only reason to change them was to favour preventive measures that do realize benefit in the far future. In the case of preventive measure costs are made today, but most benefits, both health and financial benefits, will only be made in the far future, with as consequence a huge impact on health effects if high discount rates are applied (see example in Figure A.4-1). Whereas, for curative measures, both costs and benefits are made in most cases in a far narrower time span, with as consequence that discounting has only a little effect on the health effects.

Table A.4-1 – Example: estimated cost-effectiveness ratios (CER) expressed in euros per life-years gained (LYG) for an avoided premature death of an infant with an expected life-expectancy of 80 years for which net costs of 1 million euros were made, using different discount rates for health effects

Net costs (NPV) in euros	Remaining life-years	Remaining years if discounted at %		Estimated CER (in euros per LYG)
		Discount rate	Years	
1.000.000	80 years	0%	80	12.500 euro/LYG
1.000.000	80 years	1.5%	46.6	21.459 euro/LYG
1.000.000	80 years	2%	39.9	25.063 euro/LYG
1.000.000	80 years	4%	24	41.667 euro/LYG
1.000.000	80 years	6%	16.5	60.606 euro/LYG

By using no discount rates, or a lower discount rate, foodborne associated pathogens infections that result largely in premature death and/or long-lasting chronic disease with huge impacts on the quality of life of affected people in their remaining life years, would indeed result in higher disease burden estimates, than if using high discount rates. Consequently, potential programs to control such pathogens would result in better CERs due to a higher denominator, than if using higher discount rates. Therefore, with the new applied Dutch guidelines some of the previous evaluated and not cost-effective programs might become cost-effective by the only fact that a lower discount rate would be applied. Given that less experienced users of cost-effectiveness studies might not easily recognize this positive effect of using lower discount rates, we would strongly recommend that for each cost study applied and for each cost-effectiveness study applied extensive scenario analysis should be conducted. Here, costs and consequences should be presented in their undiscounted form as well as in their discounted form, whereby different discount rates are employed. This move allows others to investigate the impact of discounting easily.

In the current report we followed the earlier recommendation, which was 4% for both costs and effects[51], however, we do show also the undiscounted estimates. This allowed us to analyze the impact of discounting on the results. If we had followed the new recommendation, the estimated discounted disease burden would have been somewhere in between both presented figures, whereas the cost estimates would remain unchanged. But by following the earlier recommendations we do have the advantage that our results can be compared with earlier work done before 2005 in the Netherlands, as well as with the work done in other countries where it is common practice to use the same discount rate for both monetary and health effects.