



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



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ABSTRACT

To inform risk management decisions on control and prevention of food-related disease, both the disease burden expressed in Disability Adjusted Life Years (DALY) and the cost-of-illness of food-related pathogens are estimated and presented. Disease burden of fourteen pathogens that can be transmitted by food, the environment, animals and humans was previously estimated by Havelaar et al. (2012). In this paper we complement these by cost-of-illness estimates. Together, these present a complete picture of the societal burden of food-related diseases.

Using incidence estimates for 2011, community-acquired non-consulting cases, patients consulting their general practitioner, hospitalized patients and the incidence of sequelae and fatal cases, estimates were obtained for DALYs, direct healthcare costs (e.g. costs for doctor's fees, hospitalizations and medicines), direct non-healthcare costs (e.g. travel costs to and from the doctor), indirect non-healthcare costs (e.g. productivity loss, special education) and total costs.

The updated disease burden for 2011 was equal to 13,940 DALY/year (undiscounted) or 12,650 DALY/year (discounted at 1.5%), and was of the same magnitude as previous estimates. At the population-level thermophilic *Campylobacter* spp., *Toxoplasma gondii* and rotavirus were associated with the highest disease burden. Perinatal listeriosis infection was associated with the highest DALY per symptomatic case.

The total cost-of-illness in 2011 of fourteen food-related pathogens and associated sequelae was estimated at € 468 million/year, if undiscounted, and at € 416 million/year if discounted by 4%. Direct healthcare costs accounted for 24% of total costs, direct non-healthcare costs for 2% and indirect non-healthcare costs for 74% of total costs. At the population-level, norovirus had the highest total cost-of-illness in 2011 with € 106 million/year, followed by thermophilic *Campylobacter* spp. (€ 76 million/year) and rotavirus (€ 73 million/year). Cost-of-illness per infected case varied from € 150 for *Clostridium perfringens* intoxications to € 275,000 for perinatal listeriosis.

Both incident cases and fatal cases are more strongly correlated with COI/year than with DALY/year.

More than 40% of all cost-of-illness and DALYs can be attributed to food, in total € 168 million/year and 5,150 DALY/year for 2011. Beef, lamb, pork and poultry meat alone accounted for 39% of these costs. Products of animal origin accounted for € 86 million/year (or 51% of the costs attributed to food) and 3,320 DALY/year (or 64% of the disease burden attributed to food). Among the pathogens studied *Staphylococcus aureus* intoxications accounted for the highest share of costs attributed to food (€ 47.1 million/year), followed by *Campylobacter* spp. (€ 32.0 million/year) and norovirus (€ 17.7 million/year).

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1. Introduction

Foodborne pathogens cause acute and chronic health outcomes of widely different durations, severity and mortality. In food safety policy the relevance of pathogens by quantitative comparison of their public health impact is key – although not the only – information required to make sound decisions. National estimates of annual number of illnesses, hospitalizations, and deaths are important but incomplete measures of the societal impact of foodborne disease. Comparison of relative burden

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of diseases having diverse outcomes is possible when using integrated measures of health such as Health-adjusted life years (HALY) or cost-of-illness. HALYs, including Disability-Adjusted Life Years (DALY) and Quality-adjusted life years (QALY), are population health measures integrating morbidity and mortality into one metric (Gold et al., 2002). Cost-of-illness (COI), using societal perspective, measures 1) the costs related to the resources used within the healthcare sector; 2) the resources used by patients and their families; and 3) productivity losses and other non-healthcare related resources used that are indirectly related to illness (e.g. special education). In contrast to initiatives such as a universal infant vaccination program, the control of foodborne pathogens has an impact on several stakeholders in the society and therefore implicitly requires the use of a societal perspective (Belli et al., 2001).

There is a growing number of publications considering COI and loss of HALYs due to multiple foodborne pathogens, for example from Canada (Ruzante et al., 2010), Korea (Shin et al., 2010), New Zealand (Lake et al., 2010) and the United States (Hoffmann et al., 2012).

In the Netherlands, the National Institute for Public Health and the Environment (RIVM) has published in the last 10 years a series of disease burden estimations (Haagsma et al., 2010; Havelaar et al., 2000, 2004, 2007) and publications considering both the disease burden and the cost-of-illness (Haagsma et al., 2009; Kemmeren et al., 2006; Mangen et al., 2005; Tariq et al., 2011; Vijgen et al., 2007).

This article presents the estimates of the cost-of-illness (Euros) and disease burden (DALYs) for fourteen foodborne pathogens in the Netherlands in 2011, building on Havelaar et al. (2012). We update illness incidence and DALY estimates to 2011. In addition we present, for the first time in the peer-reviewed literature, the methodology, data, and results of cost-of-illness estimates for these same pathogens including cost estimates for *Toxoplasma gondii* and irritable bowel syndrome. We attributed the costs of the fourteen pathogens to different exposure pathways and different food groups based on expert elicitation (Havelaar et al., 2008).

2. Materials and methods

2.1. Pathogens included

The fourteen pathogens were selected based on preliminary analyses of the burden caused by the pathogens in the Netherlands and on data availability (Havelaar et al., 2012). These pathogens include seven that cause gastroenteritis (GE) including three bacteria (thermophilic *Campylobacter* spp., Shiga-toxin producing *Escherichia coli* O157 (STEC O157), nontyphoidal *Salmonella* spp.), two viruses (norovirus and rotavirus) and two protozoa (*Cryptosporidium* spp., *Giardia* spp.); three GE toxin-producing bacteria (*Bacillus cereus*, *Clostridium perfringens* and *Staphylococcus aureus*), and four pathogens causing systemic infections (*Listeria monocytogenes*, hepatitis-A virus (HAV), hepatitis-E virus (HEV), and *T. gondii*).

2.2. Health outcomes and health states considered

Using an incidence- and pathogen-based approach to assess DALYs and COI estimates for the pathogens under study, the health outcomes following infection needed to be defined using outcome trees.³ To better represent the true burden (i.e. financial and disease burden) a health outcome was split further into subcategories, so-called 'health states'. The outcome trees used are presented in full detail in Havelaar et al.

(2012). Briefly, for GE, we distinguished four health states: mild (patient does not seek medical help, and recovers), moderate (patient visits a general practice (GP) and recovers), severe (patient is hospitalized and recovers), and death. Sequelae following disease caused by GE-bacteria were defined as:

- *Campylobacter* spp.: Guillain-Barré Syndrome (GBS) (health states: mild, severe, and fatal; furthermore we considered long-term sequelae after having had non-fatal severe GBS); reactive arthritis (ReA) (health states: mild, moderate and severe); Irritable Bowel Syndrome (IBS) and Inflammatory Bowel Disease (IBD).
- *Salmonella* spp.: ReA; IBS and IBD.
- STEC O157: Post-diarrheal Hemolytic Uremic Syndrome (HUS) (health states: severe and fatal), and End-Stage Renal Disease (ESRD) (health states: dialysis, transplantation, functioning graft, death).

In the case of HAV and HEV, hepatitis was the only health outcome considered. For listeriosis we distinguished between acquired listeriosis (AL) with or without meningitis (health states: severe and fatal), and perinatal listeriosis (PL) having meningitis with or without sepsis (health states: severe and fatal). Furthermore, we considered neurological sequelae after having had non-fatal listeriosis with meningitis. In the case of acquired toxoplasmosis (AT), the only health outcome considered was chorioretinitis. For congenital toxoplasmosis (CT) we considered as health outcomes: stillbirth, neonatal death, chorioretinitis, intracranial calcifications, hydrocephalus, and Central Nervous System (CNS) abnormalities. Furthermore, asymptomatic CT cases at birth were assumed to be at risk of developing chorioretinitis later in life (referred to as post-1-year chorioretinitis).

2.3. Incidence of illness

Following the methodology described in Havelaar et al. (2012), incidence of illness was estimated for the year 2011 using surveillance data and demographic information for this year. Briefly, incidence of GE in the entire Dutch population, the proportion of cases visiting their GP, and attribution of cases to pathogens were based on a population-based cohort study and associated case-control studies (de Wit et al., 2001a, 2001b). These estimates based on the original studies were updated to 2011 with trends based on laboratory surveillance, on hospitalized viral GE cases or on active surveillance. Estimates for GE hospitalization were based on data from the National Medical Register and attributed to pathogens using results from an observational study on the etiology of GE in six Dutch hospitals (Friesema et al., 2012a, 2012b). For systemic infections, incidence estimates were based on enhanced surveillance for *L. monocytogenes* (Friesema et al., 2011), continuous notifiable reporting system for HAV (Van de Laar et al., 2000), 2-year monitoring of lab-confirmed non-travel related cases for HEV (Borgen et al., 2008) and a large study on dried-blood spots of neonates for *T. gondii* (Kortbeek et al., 2009). For more details see web-appendix A.

2.4. Disease burden

Using incident cases for 2011 we estimated the disease burden in DALYs as described by Havelaar et al. (2012). The DALY estimates are presented undiscounted and discounted at a discount rate of 1.5% for health outcomes in accordance with Dutch guidelines for health economic evaluations (Hakkaart-van Roijen et al., 2010).

2.5. Cost-of-illness

2.5.1. General approach

A societal perspective was taken when estimating the COI, considering direct healthcare costs (DHC), direct non-healthcare costs (DNHC) and indirect non-healthcare costs (INHC). We also considered the

³ Developing an outcome tree, using the incident- and pathogen-based approach is not only the most appropriate approach for infectious diseases when estimating DALYs (see Mangen et al., 2013 and in particular Appendix A for the methodology), but is also the most appropriate approach when estimating COI.

third payer perspective (i.e. only DHC). The expected sum of current and future costs of acute illness and sequelae all triggered by the infections occurring in the year 2011 was estimated. Costs expressed in 2011 euros were presented undiscounted and discounted, using a discount rate of 4% in accordance with Dutch guidelines for health economic evaluations (Hakkaart-van Roijen et al., 2010).

2.5.1.1. Direct healthcare costs (DHC). DHC, or the costs related to the resources used within the healthcare sector, included valuation for medical services such as GP consultations, specialist consultations, hospitalization, drugs, rehabilitation, temporary or permanent admission to a nursing home for elderly/mentally retarded or handicapped people and other medical services. DHC costs were estimated for each pathogen separately; the total DHC costs were estimated by accumulating the costs for the different medical services for all illnesses including sequelae resulting from an infection and for all disease severity states related to this pathogen.

2.5.1.2. Direct non-healthcare costs (DNHC). DNHC are costs paid by the patients themselves ('out-of-pocket' costs). Travel costs of patients, costs for additional diapers, informal care and over-the-counter medication and other co-payments by patients are some examples of DNHC.

2.5.1.3. Indirect non-healthcare costs (INHC). INHC are mainly production losses to society due to disease, but costs for special education as a consequence of disease (i.e. for children disabled as a consequence of PL and CT, respectively) are also considered as INHC.

Production losses due to absenteeism (i.e. absence from work) of patients and of caregivers taking care of a sick patient were considered for both paid and unpaid work (e.g. charity work). Production losses could be the consequences of: a) temporary absence from work; b) permanent or long-term disability; and c) premature mortality. When information was available all three categories were considered, using the friction cost method as recommended by the Dutch guidelines. In this approach productivity losses due to absenteeism from paid work and due to fatal cases are only estimated for persons between 15 and 64 years (patients in the working age in the Netherlands) and only for a duration of 23 weeks (Hakkaart-van Roijen et al., 2010), which is the estimated average time needed to replace a person on the labor market.

2.5.1.4. General. In order to calculate the COI for the different health outcomes, data on the number of cases per age-group, the types of resources used, the volumes of resources used and the actual economic cost of each of these resource units were necessary (for formulas and further detail see Appendix B). Dutch prices were used where available (see Appendix B, Table B.1). Disease-specific assumptions with respect to used resources, volumes of resources used as well as disease-specific costs are described in detail in Appendix C.

In the absence of disease-specific traveling details we assumed: no traveling associated with buying medicines (Mangen et al., 2005); 77% and 97% of persons younger than 15 years and 15 years and older, respectively, used car/public transport (50/50) when visiting GP/healer/physical therapist (Friesema et al., 2012c); and 97% and 100% of persons younger than 15 years and 15 years and older, respectively, used car/public transport (50/50) for in- and outpatient visits (Friesema et al., 2012c). We used Dutch average distances for transport costs (Hakkaart-van Roijen et al., 2010). When no disease-specific details on sickness leave were available for patients and/or caregivers, we used the assumptions presented in Table B.2 in web-appendix B.

2.6. Uncertainty

Data necessary for the quantitative estimates of incident cases, disease burden and the costs are often limited or absent, which leads to a certain degree of uncertainty. Total uncertainty was therefore broken down into variability (i.e. inherent heterogeneity of a system) and

uncertainty (i.e. lack of perfect knowledge). Variable factors were represented by arithmetic means. Statistical uncertainty (e.g. due to small sample size) was evaluated by Monte Carlo simulation (Analytica Professional 4.4.1, Lumina Decision Systems, Los Gatos, CA, USA; 10,000 iterations). Results presented are the mean and the 95% credible intervals resulting from the stochastic simulations.

Scenario analysis was used to represent uncertainty due to lack of data and systematic uncertainty. Scenario analyses were applied for all pathogens having GE as a health outcome, for all pathogens causing IBS, for AL and for CT cases developing CNS abnormalities. There is evidence that elderly severe GE patients (Friesema et al., 2012c; Ruzante et al., 2011), and elderly severe AL cases (Ruzante et al., 2011) are at risk of being transferred from hospital into a nursing home before returning home. Information on the duration of stay was scarce. In scenario analyses we studied the impact of a shorter or longer stay in a nursing home after discharge from the hospital of elderly GE patients and of elderly AL cases independently. We further studied the impact of increased direct healthcare costs (DHC) in the case of IBS. The cost categories considered by Goettsch et al. (2004) – the only available Dutch cost study of IBS-associated DHCs (as of October 2013) – were rather restricted (NHG, 2011), and other COI studies conducted in neighboring countries such as Germany (Muller-Lissner and Pirk, 2002) and France (Le Pen et al., 2004) reported annual DHC per IBS patient that were more than twice as high. We therefore conducted a scenario analysis by doubling the baseline DHC related to IBS. Most of the cohorts affected by *T. gondii* were congenitally infected children identified either pre- or post-natal. Where screening programs exist, pregnancies might be terminated because of suspected or proven fetal congenital toxoplasmosis infection. In the absence of screening (as in the Netherlands) some of these cases might develop severe neurological damage, with or without severe visual impairment. In a scenario analysis we therefore assumed that all CT cases with CNS abnormalities would have severe neurological damage incurring costs for life-long institutional care (i.e. care in an institute for mentally and physically disabled people) and for special education throughout school-age, starting at kindergarten, and through primary and secondary education.

2.7. Correlation

Correlation between incident cases, fatal cases, disease burden and costs was studied in SPSS 20.0 using Spearman's rho. Additionally, we plotted the prepared scatterplots of annual mean costs/year with estimated mean DALY/year for all fourteen pathogens.

2.8. Attribution

Based on an expert elicitation study by Havelaar et al. (2008), we attributed the total disease incidence, burden and costs to different exposure pathways. There were five major pathways, namely food, environment, human, animal and travel. The food pathway was further subdivided into eleven food groups. Major pathways and food groups were mutually exclusive and the arithmetic mean proportions of cases attributed to major pathways, or to food groups within the food pathway summed to 1. For full details see Havelaar et al. (2008). Similar to Havelaar et al. (2012) we did not take the uncertainty in the attribution estimates into account in the stochastic simulations, but used the mean across all experts as we considered this the most reliable estimate.

3. Results

3.1. Incidence

Incidence estimates for 2011 in the Netherlands are presented in Table 1, and in more details in web-appendix D in Table D.1. The 2011 estimates formed the input for the disease burden and COI estimates. The 2011 estimates were similar to the incidence estimates of

Table 1

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

Pathogen and sequelae	Incidence	Fatal cases
Bacteria-infections		
<i>Campylobacter</i> spp.		
Gastroenteritis	108,000 (33,000–271,000)	34 (21–51)
Guillain–Barré Syndrome	79 ^a (0–149) ^b	2 ^a (0–5) ^b
Reactive arthritis	1,935 (829–3,919)	0
Irritable Bowel Syndrome	9,350 (2,668–24,150)	0
Inflammatory Bowel Disease	23 (16–31)	0
STEC O157		
Gastroenteritis	2,100 (220–8,800)	1 (0–3)
Hemolytic Uremic Syndrome	22 (15–30)	2 (1–5)
End-Stage Renal Disease	3 (1–5)	1 (1–1)
<i>Salmonella</i> spp.		
Gastroenteritis	37,000 (6,500–107,000)	35 (30–39)
Reactive arthritis	458 (163–954)	0
Irritable Bowel Syndrome	3,125 (468–9440)	0
Inflammatory Bowel Disease	8 (6–11)	0
<i>Listeria monocytogenes</i> (perinatal)		
Listeriosis	9 ^c	1 ^c
Meningitis	8 ^c	NA
Neurological sequelae of meningitis	4 (2–5)	0
<i>Listeria monocytogenes</i> (acquired)		
Listeriosis	79 ^c	4 ^c
Meningitis	22 (18–26)	NA
Neurological sequelae of meningitis	3 (2–5)	0
Bacteria-toxin producing		
<i>Bacillus cereus</i> toxin		
Gastroenteritis	51,000 (19,000–111,000)	0
<i>Clostridium perfringens</i> toxin		
Gastroenteritis	171,000 (63,000–357,000)	5 (0–19)
<i>Staphylococcus aureus</i> toxin		
Gastroenteritis	292,000 (135,000–531,000)	7 (0–30)
Viruses		
Norovirus		
Gastroenteritis	694,000 (481,000–988,000)	65 (29–121)
Rotavirus		
Gastroenteritis	301,000 (157,000–528,000)	45 (15–97)
Hepatitis A virus		
Hepatitis	612 ^a (391–989) ^b	2 (1–3)
Hepatitis E virus		
Hepatitis	53 (31–81)	1 (0–1)
Protozoa		
<i>Cryptosporidium</i> spp.		
Gastroenteritis	28,000 (10,000–67,000)	2 (0–8)
<i>Giardia</i> spp.		
Gastroenteritis	64,000 (36,000–118,000)	2 (0–7)
<i>Toxoplasma gondii</i> (perinatal)		
Toxoplasmosis	364 (189–637)	13 (7–22)
Chorioretinitis 1st year of life	49 (25–87)	NA
Chorioretinitis later years of life	59 (31–103)	NA
Intracranial calcifications	38 (19–69)	NA
Hydrocephalus	7 (3–14)	NA
Central Nervous System abnormalities	10 (2–29)	NA
<i>Toxoplasma gondii</i> (acquired) ^d		
Chorioretinitis	426 (203–727)	0

Note: NA, not applicable.

^a Mean.

^b 2.5–97.5 percentile.

^c No uncertainty because cases were acquired through active surveillance.

^d Chorioretinitis only.

Havelaar et al. (2012) for the year 2009. Observed changes were minimal, except for *Campylobacter* infections, where increased incidence is attributed to the increase use of proton pump inhibitors (Bouwknegt et al., 2014) and for perinatal listeriosis, where incidence is highly variable between years.

3.2. Disease burden

The updated disease burden of the fourteen food-related pathogens for the year 2011 was equal to 13,940 DALY/year (13,500 in 2009), if undiscounted, and 11,600 DALY/year (11,200 in 2009) when discounted at 1.5%. DALY estimates for 2011 were similar to the one presented in Havelaar et al. (2012) for the year 2009 (see Fig. D.1 in web-appendix D). At the population level *Campylobacter* spp., *T. gondii* and norovirus were associated with the highest disease burden, either discounted or undiscounted (Table 2 and Table D.2 in web-appendix D). Measured in DALY/year or in DALY/100,000, the estimated disease burden of hepatitis-E virus is the lowest, both discounted and undiscounted. DALYs per case was largest for *L. monocytogenes*, followed by *T. gondii* while the lowest values for DALYs per case were seen for the toxin-producing bacteria, for *Cryptosporidium* and *Giardia* infections, and for norovirus infections (Table 2 and Fig. D.2 in web-appendix D).

Discounting of DALYs has an impact on *T. gondii*, *L. monocytogenes*, STEC O157, *Salmonella* spp. and *Campylobacter* spp. and affects ranking. The discounted DALYs of *T. gondii*, *L. monocytogenes* and STEC O157 are equal to 65%, 65% and 79% of the undiscounted DALYs, respectively, whereas the discounted DALYs of *Salmonella* spp. and *Campylobacter* spp. are equal to 86% and 89% of the undiscounted DALYs (see Table 2).

3.3. Cost-of-illness per pathogen

The total COI of the fourteen food-related pathogens in 2011 was estimated at € 468 million per year, if undiscounted and at € 416 million per year, if discounted at 4% (see Table 2 and Table D.2 in web-appendix D). DHC accounted for 24% and INHC for 74% of the total costs. DNHC was negligible at about 2% of the total costs (see Fig. 1, and Table D.3 in web-appendix D). Table 2 shows the undiscounted and discounted average costs by pathogen on a population level (costs in million euros/year) and on an individual basis (costs in euros per 1000 cases). For international comparison, standardized data (costs in thousand euros/year per 100,000 inhabitants) were also reported. Fig. 1 shows the discounted average costs split into DHC, DNHC and INHC, by pathogen on a population level (costs in million euros per year) and the attendant uncertainty.

At the population level norovirus, *Campylobacter* spp. and rotavirus were associated with the highest costs, for both discounted and undiscounted costs. Norovirus infection costs were estimated at € 105.8 million/year, both discounted and undiscounted. *Campylobacter* infection costs were estimated at € 81.5 million/year (undiscounted) and at € 76.1 million/year, if discounted at 4%. Rotavirus infection costs were estimated at € 73.3 million/year, both discounted and undiscounted. The cost-of-illness of hepatitis-E virus infections is the lowest among all fourteen pathogens at € 0.2 million/year, both discounted and undiscounted (see Table 2).

Discounting of costs has an impact on *T. gondii*, *L. monocytogenes*, STEC O157, *Campylobacter* spp. and *Salmonella* spp., and affects ranking. The discounted costs of *T. gondii*, *L. monocytogenes* and STEC O157 are equal to 36%, 49% and 52% of the undiscounted costs, respectively, whereas the discounted costs of *Campylobacter* spp. and *Salmonella* spp. are equal to 93% of the undiscounted costs. *T. gondii* causes the fourth highest costs at the population level with € 55 million undiscounted costs, but falls to the seventh rank when comparing discounted costs. *L. monocytogenes* causes the ninth highest costs at the population level with € 9.4 million undiscounted costs, but falls to the eleventh rank when comparing discounted costs (see Table 2).

Fig. 2 shows the average annual discounted COI at population level (on logarithmic scale) and average discounted COI per symptomatic infection (on logarithmic scale) for each pathogen, using a societal perspective.

Cost-of-illness per case varied between € 275,282 for perinatal listeriosis to € 150 for *C. perfringens* intoxication. Perinatal listeriosis, congenital toxoplasmosis, acquired listeriosis, acquired toxoplasmosis and

Table 2
Overall disease burden and costs, as well as mean disease burden per case of illness and mean cost per case of illness in the Netherlands, 2011. Results are presented undiscounted (0%) and discounted (1.5% for DALY and 4% for costs).

Pathogen	Disease burden				Cost-of-illness			
	DALY per year		DALY per 1000 cases		Costs per year (×1,000,000)		Costs per 1000 cases (×1000)	
	0%	1.5%	0%	1.5%	0%	4.0%	0%	4.0%
<i>Bacteria-infections</i>								
<i>Campylobacter</i> spp.	3,633	3,250	39	34	81.5	76.1	757	706
STEC O157	138	109	158	125	9.9	5.1	4,668	2,380
<i>Salmonella</i> spp.	1,294	1,109	46	38	23.7	22.0	640	593
<i>L. monocytogenes</i> (perinatal)	156	91	17,160	10,070	7.1	2.5	786,070	275,282
<i>L. monocytogenes</i> (acquired)	47	45	600	570	2.3	2.2	29,551	27,430
<i>L. monocytogenes</i> (total)	203	136	2,275	1,527	9.4	4.6	106,922	52,779
<i>Bacteria-toxin producing</i>								
<i>B. cereus</i> toxin	113	113	2.6	2.3	9.2	9.2	181	181
<i>C. perfringens</i> toxin	543	535	3.2	3.1	25.6	25.6	150	150
<i>S. aureus</i> toxin	766	760	2.6	2.6	54.0	54.0	185	185
<i>Viruses</i>								
Norovirus	1,754	1,547	2.5	2.3	105.8	105.8	152	152
Rotavirus	1,603	1,437	5.6	5.0	73.3	73.3	244	244
Hepatitis A virus	98	88	167	145	0.9	0.9	1,426	1,426
Hepatitis E virus	23	20	460	380	0.2	0.2	4,224	4,224
<i>Protozoa</i>								
<i>Cryptosporidium</i> spp.	72	72	3.1	3.1	8.1	8.1	289	289
<i>Giardia</i> spp.	127	125	2.1	2.1	11.3	11.3	176	176
<i>T. gondii</i> (congenital)	2,210	1,300	6,350	3,730	52.1	17.0	143,182	46,596
<i>T. gondii</i> (acquired)	1,350	1,020	3,170	2,400	2.8	2.8	6,567	6,559
<i>T. gondii</i> (total)	3,570	2,320	4,483	2,951	54.9	19.8	69,514	25,006

hepatitis-E virus, all systemic pathogens, have the highest cost per case, while protozoa and viruses triggering GE have the lowest cost per case (see Table 2 and Fig. 2).

Given that the majority of costs for gastroenteritis pathogens were indirect non-healthcare costs, the ranking of the gastroenteritis pathogens on the basis of INHC is similar to that for total costs, if ranked at population level (see Fig. 1 and Table D.3 in web-appendix D). The non-gastrointestinal pathogens *T. gondii* and *L. monocytogenes*, for which INHC account for less than 10% of the total costs, have the lowest

proportion of INHC costs and are therefore lower ranked (web-appendix D). At the population level, the INHC of norovirus, rotavirus and *Campylobacter* spp. at € 97 million, € 59.5 million and € 47.5 million respectively are the highest per year, while the INHC of STEC O157 and hepatitis-E-virus are the lowest at € 0.4 million and € 0.1 million respectively.

For bacteria triggering GE, such as STEC O157, *Campylobacter* spp. and *Salmonella* spp., GE-associated costs account for 8%, 49% and 58% of the total costs (see Table D.4 in web-appendix D). IBS is a major driver

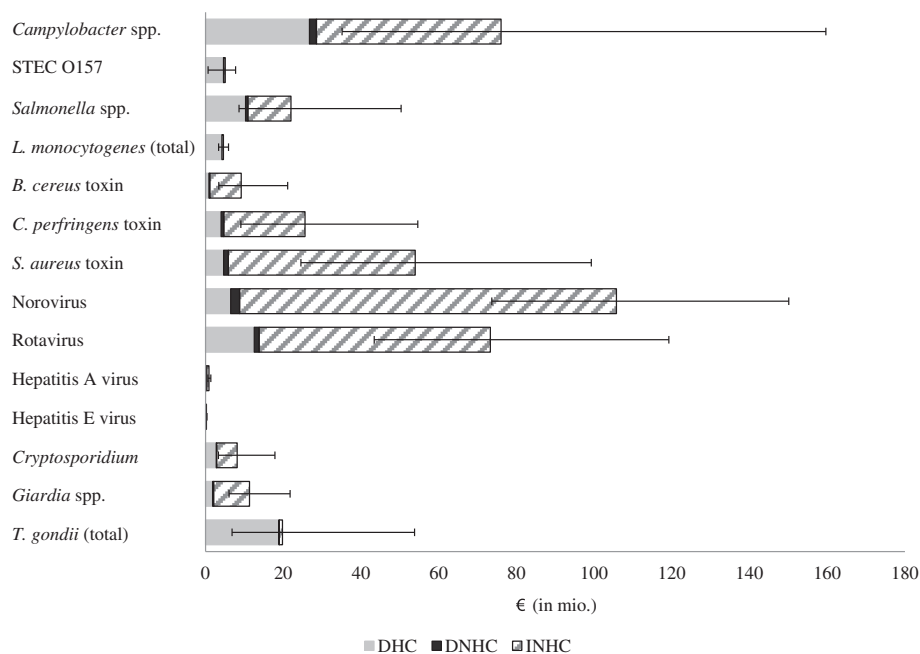


Fig. 1. Average discounted costs split into DHC, DNHC and INHC, and the attendant uncertainty for total costs (in million euros per year) for the different pathogens under study in 2011. Costs were discounted at 4% and expressed in 2011 euros.

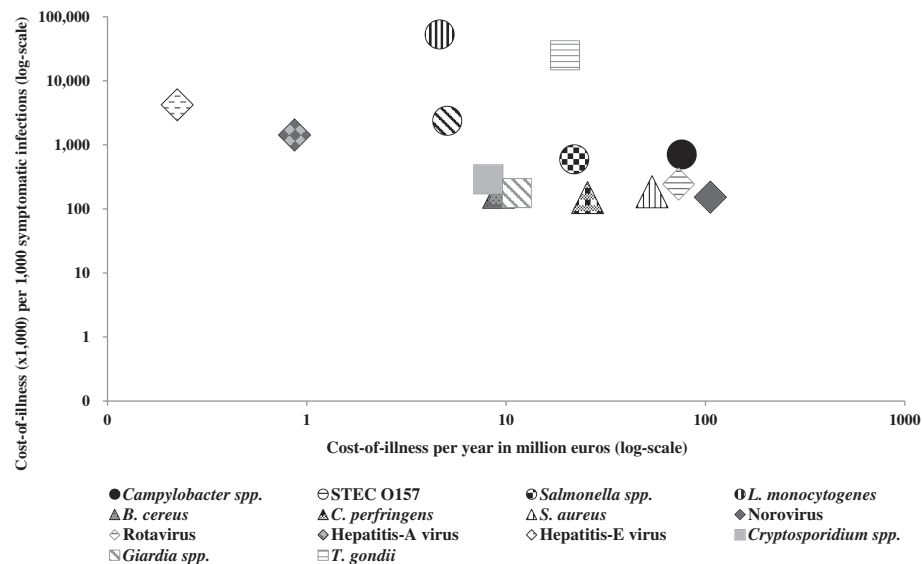


Fig. 2. Using the societal perspective, average cost-of-illness per 1000 symptomatic cases and average cost-of-illness (in million euros) per year at population-level for 14 foodborne pathogens in 2011. Costs were discounted at 4%. Note: We used the following symbols: ● for bacteria-infections; ▲ for toxin-producing bacteria; ◇ for viruses and ■ for protozoa.

of the costs for both *Campylobacter*-infections (38% of the total costs, and 76% of the costs associated with sequelae) and *Salmonella*-infections (37% of the total costs, and 89% of the costs associated with sequelae). HUS and ESRD are the major cost drivers in the case of STEC O157. For more details see web-appendix D.

For non-gastroenteric pathogens, it is the perinatal infection in particular that drives the cost for both *L. monocytogenes* (54% of the total costs) and *T. gondii* (86% of the total costs, see web-appendix D).

3.4. Scenario analysis

Only two of all scenario analyses conducted had a significant impact on the costs (see Table D.6 in web-appendix D). In particular the assumption that all CT cases with CNS abnormalities would require life-long institutional care and special education would increase the total costs of CT by almost 250% (Table D.6 in web-appendix D). Higher direct healthcare costs of IBS would more than double the total costs for both *Campylobacter* spp. (116% increase) and for *Salmonella* spp. (118% increase), whereas a longer or shorter temporary admission to a nursing home of elderly persons after hospital discharge has only a marginal impact on the costs, whether patients were admitted with GE or listeriosis.

3.5. Correlation

In Table 3 we have summarized Spearman's rho for incident cases, fatal cases, DALY/year (undiscounted and discounted), COI/year (undiscounted and discounted) and DHC/year (undiscounted and discounted). Both incident cases and fatal cases are more strongly correlated with COI/year than with DALY/year. DALY/year is slightly more strongly correlated with DHC/year (0.893, both discounted) than with COI/year (0.851, both discounted).

In Fig. 3 annual mean COI/year (log-scale) is plotted against the estimated mean DALY/year (log-scale), both discounted. Although they fit quite well – to be expected with a Spearman's rank correlation of 0.851 – the highest ranked is different depending on the use of DALYs (i.e. *Campylobacter* spp.) or COI (i.e. norovirus). However, three of the top four are the same when ranked on either COI or DALYs: *Campylobacter* spp., norovirus and rotavirus.

DALY/case and COI/case show a high and significant correlation (0.898 and higher, see Table D.7 in Appendix D).

There is no correlation or a negative correlation between population-level estimates and case-level estimates, for both DALY

and COI estimates (see Table D.7 in Appendix D). Consequently, the ranking of the fourteen pathogens on both DALY and COI is strongly influenced by the use of population-level estimates or case-level estimates (see Fig. 2 and Fig. D.2 in web-appendix D).

3.6. Attribution

The attribution of discounted costs/year to the main pathways is presented in Table 4. Table 5 shows the attribution of discounted costs to the main food groups. More than 40% of COI and of DALYs can be attributed to food, in total € 168 million per year and 5,150 DALYs (see Tables D.6 and D.7 in web-appendix D). The other costs can be attributed to exposure by human–human contact (28%), the environment (15%) and animal contact (7%), while 9% were travel-related. The remaining DALYs can be attributed to exposure by the environment (21%), human–human contact (17%), animal contact (8%) and traveling (9%).

S. aureus intoxications accounted for the highest share of costs attributed to food (€ 47.1 million/year), followed by *Campylobacter* spp. (€ 32.0 million/year) and norovirus (€ 17.7 million/year). Products of animal origin accounted for € 86 million/year (or 51% of the costs attributed to food) and 3,320 DALY/year (or 64% of the disease burden attributed to food). Fish, fruit and vegetables, beverages, grains and other foods account for 8%, 6%, 2%, 5% and 14% of the costs attributed to food, respectively, and for 7%, 6%, 2%, 3% and 8% of DALYs attributed to food, respectively. Human and animal contamination of foods accounts for 13.6% of the costs attributed to food, and for 10% of the DALYs attributed to food (for more details see web-appendix D).

4. Discussion

Both DALYs and COI are suitable integrated metrics enabling comprehensive comparisons of infectious pathogens having very different patterns of incidence and outcomes. However, the ranking of the pathogens at the population level only differs slightly, depending on the use of DALYs, COI or DHC. At the population level, the disease burdens of *Campylobacter* spp., *T. gondii* and norovirus are the highest among the 14 pathogens. For cost-of-illness, norovirus, *Campylobacter* spp. and rotavirus rank the highest, whereas for ranking based on DHC only, *Campylobacter* spp., *T. gondii* and rotavirus the rank highest. Pathogens ranking high for all three criteria, e.g. *Campylobacter* spp. and *T. gondii*, should also rank high on the agenda of policy makers. The DALY metric

Table 3

Spearman's rho correlations between ranking of various public health impact measures using estimates for the year 2011.

	Incidence	Fatal cases	DALY		COI		DHC		INHC	
			0%	1.5%	0%	4%	0%	4%	0%	4%
Incidence	–									
Fatal cases	.575*	–								
DALY (0%)	.547*	.852**	–							
DALY (1.5%)	.578*	.856**	.987**	–						
COI (0%)	.763**	.841**	.943**	.938**	–					
COI (4%)	.903**	.799**	.829**	.851**	.938**	–				
DHC (0%)	.257	.692**	.868**	.811**	.741**	.565*	–			
DHC (4%)	.436	.798**	.937**	.893**	.856**	.730**	.968**	–		
INHC (0%)	.946**	.752**	.675**	.724**	.823**	.955**	.374	.557*	–	
INHC (4%)	.964**	.726**	.642*	.686**	.805**	.946**	.334	.525	.992**	–

* Correlation is significant at the 0.05 level.

** Correlation is significant at the 0.01 level.

slightly favors prioritization of those pathogens resulting in severe illnesses and/or in acute infections followed by severe sequelae, as does the DHC criterion, hence DHC and DALY are highly correlated (Spearman's correlation of 0.893). In contrast the COI metric, using a societal perspective, emphasizes those pathogens frequently occurring in the population, but not necessarily leading to consumption of medical resources, and so COI is highly correlated with disease incidence (0.851).

4.1. DALYs and COI in 2011

The current study shows that food-related pathogens cause annual high costs to the Dutch society, in both economic and public health terms. The fourteen food-related pathogens studied resulted in a cost-of-illness for the Dutch society in 2011 of € 468 million/year if undiscounted, or € 416 million/year if discounted at 4%, and in a disease burden of 14,000 DALY/year if undiscounted, or 11,600 DALY/year if discounted at 1.5%. The calculated DALYs were similar to Havelaar et al. (2012) for the year 2009.

More than 40% of all cost-of-illness and disease burden can be attributed to food, in total € 168 million/year (discounted) and 5,150 DALY/year (discounted). Products of animal origin account for € 86 million (or 51% of the costs attributed to food) per year, and 3,320 DALY/year (or 64% of the disease burden attributed to food).

About 74% of the estimated cost-of-illness is due to indirect non-healthcare costs, in total € 309 million/year if discounted with 4% and € 312 million/year if undiscounted. DNHC was negligible at less than 2%, whereas direct healthcare costs – the only cost category considered when applying a third payer perspective – accounted for less than a quarter of the total costs. The fourteen food-related pathogens accounted for € 98 million/year DHC if discounted with 4%, or € 147 million/year if undiscounted. The impact is however only marginal when compared to the total Dutch healthcare expenditure of € 74,447 million in 2007 (and € 87,596 million in 2010) (Slobbe et al., 2011).

4.2. Assumptions and limitations

In particular productivity losses due to the absence from paid work are responsible for the majority of INHC and therefore also of the total costs. These costs would have been even higher if applying the human capital approach rather than the friction cost approach, as applied for example by Hoffmann et al. (2012) in their COI estimates. For pathogens where infections result in high numbers of deceased or disabled cases, COI estimates would have been far higher than those presented here, whereas for pathogens with mainly only short-term infections only, COI estimates would have been minimally affected.

Presenteeism is another form of production loss and describes the situation of patients being at work but working at a reduced capacity

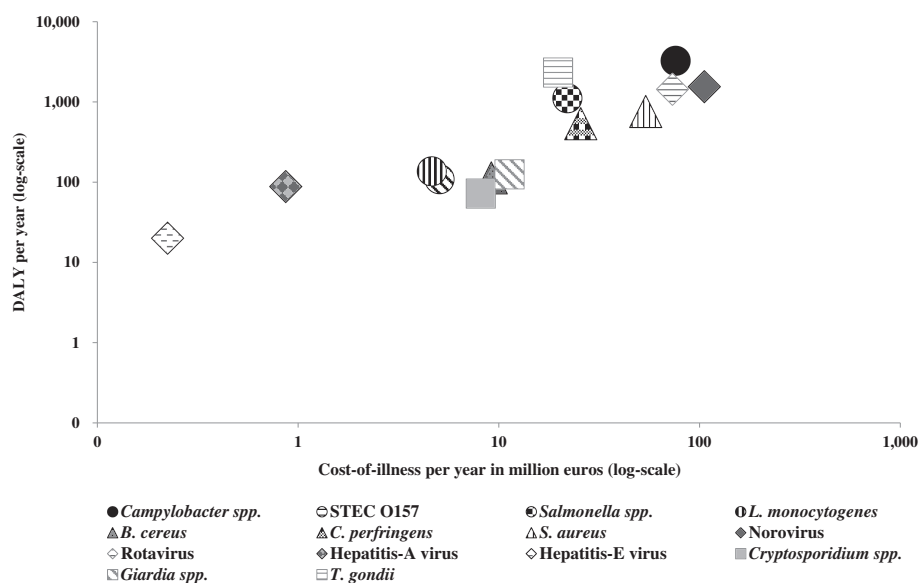


Fig. 3. Average DALY per year and average cost-of-illness per year (in million euros) for 14 foodborne pathogens in 2011. Costs and DALYs were discounted at 4% and 1.5%, respectively. Note: We used the following symbols: ● for bacteria-infections; ▲ for toxin-producing bacteria; ◇ for viruses and ■ for protozoa.

Table 4

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

Pathogens	Food	Environment	Human	Animal	Travel	Total
<i>Campylobacter</i> spp.	32.0	15.7	4.8	14.5	9.1	76.1
STEC O157	2.0	0.9	0.5	1.0	0.6	5.1
<i>Salmonella</i> spp.	12.0	2.8	2.0	2.0	3.1	22.0
<i>Listeria monocytogenes</i>	3.2	0.3	0.2	0.3	0.6	4.6
<i>B. cereus</i> toxin	8.2	0.1	0.1	0.1	0.7	9.2
<i>C. perfringens</i> toxin	23.2	0.6	0.5	0.5	0.8	25.6
<i>S. aureus</i> toxin	47.1	1.9	1.7	1.2	2.1	54.0
Norovirus	17.7	15.0	58.6	5.3	9.2	105.8
Rotavirus	9.5	12.5	42.6	2.2	6.5	73.3
Hepatitis-A virus	0.1	0.1	0.2	0.0	0.5	0.9
Hepatitis-E virus	0.0	0.1	0.0	0.0	0.1	0.2
<i>Cryptosporidium</i> spp.	1.0	2.3	2.2	1.1	1.6	8.1
<i>Giardia</i> spp.	1.5	2.7	3.9	1.2	2.0	11.3
<i>Toxoplasma gondii</i>	11.0	7.1	0.2	0.5	0.9	19.7
Total	168.4	62.1	117.7	30.0	37.8	416.0

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

For some of the considered health outcomes and/or pathogens good information on costs and/or used resources is available. However for other outcomes such as those associated with *T. gondii*, long-term consequences related to meningitis triggered by *L. monocytogenes*, and IBS, information is scarce and assumptions had to be made.

Although there were some recent studies reporting on sickness leave (e.g. Friesema et al., 2012c; Van der Valk et al., 2014), in general information was lacking and assumptions had to be made. We therefore strongly recommend data collection on sickness leave from paid and unpaid work for patients and their caregivers for all pathogens under study and in all kinds of epidemiological and clinical studies to get more accurate cost estimates in the future.

Information on resource use for toxoplasmosis patients is scarce, in particular for congenital toxoplasmosis. In our baseline we assumed that no infected baby born with congenital toxoplasmosis would require life-long institutional care and/or special education. However, this might be an underestimate. A scenario analysis assuming that all congenital toxoplasmosis with CNS abnormalities would require life-long institutional care and special education resulted in an increase of the total costs of congenital toxoplasmosis of almost 250%. This is

probably a worst case scenario, and the true costs are in between these two extremes.

Rotavirus rated high in both disease burden and cost-of-illness. It should be noted however that in other studies sometimes much lower foodborne transmission percentages are used, which would lower the impact. The available Dutch study on medical costs of IBS patients is probably an underestimate of the true IBS costs in the Dutch population. Cost studies conducted in neighboring countries mostly report values double the baseline values used here. When doubling the DHC of IBS, the total costs for *Campylobacter* spp. would increase by 116% and the total costs for *Salmonella* spp. by 118%.

As already mentioned by Havelaar et al. (2012), incidence estimates of bacterial intoxications and associated deaths are higher in the Netherlands than e.g. US-estimates (Scallan et al., 2011) or UK-estimates (Tam et al., 2012). Although, toxins of *B. cereus*, *C. perfringens* and *S. aureus* were frequently present in the stool samples of both patients and controls (de Wit et al., 2001a), the incidence estimates were not adjusted for asymptomatic carriage – similar to other pathogens. Hence, the incidence of GE due to specific causes may be overestimated. To what extent is currently unknown, but this may differ between toxins and infectious agents (Havelaar et al., 2012).

Uncertainty in attribution was not included in our study as this is the result of a lack of agreement between individual experts, and is therefore different from included sources of (statistical) uncertainty. We therefore used the mean of all experts as this was considered to be the most reliable estimate (Havelaar et al., 2012).

In the absence of evidence-based information allowing the attribution of DALYs and costs to different exposure pathways for all fourteen pathogens, our attribution was based on an expert elicitation study, and so is attended by the uncertainty associated with this study type. The expert elicitation was conducted in 2006 and might not fully reflect current practice.

4.3. Final conclusion

The current study shows that food-related pathogens cause high costs and burden to the Dutch society, in large part (more than 40%) attributed to transmission by food. Tackling this problem therefore remains a priority on policy decision makers' agendas, however, limited budgets force them to prioritize when allocating resources and in this regard integrated metrics such as DALYs and COI are both useful tools. Pathogens scoring high in rankings based on both criteria – in the current study *Campylobacter* spp. and *T. gondii* – should also receive priority when decision makers consider the most effective allocation of resources for policy implementation.

Table 5

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

Pathogen	Beef & lamb	Pork	Poultry	Eggs	Dairy	Fish & shellfish	Produce	Beverages	Grains	Other foods	Humans & animals	Total
<i>Campylobacter</i> spp.	1.3	1.6	17.2	1.0	2.8	2.2	1.7	0.5	0.7	1.1	1.7	32.0
STEC O157	0.9	0.1	0.1	0.0	0.2	0.1	0.1	0.1	0.1	0.1	0.3	2.0
<i>Salmonella</i> spp.	1.5	1.7	1.8	2.7	0.8	0.5	0.8	0.4	0.5	0.7	0.7	12.0
<i>L. monocytogenes</i>	0.4	0.3	0.2	0.1	0.8	0.6	0.2	0.1	0.2	0.2	0.2	3.2
<i>B. cereus</i> toxin	0.6	0.3	0.1	0.3	0.5	0.2	0.2	0.1	1.4	4.4	0.2	8.2
<i>C. perfringens</i> toxin	11.1	1.9	1.6	0.7	0.9	1.5	1.6	0.6	0.6	1.8	0.8	23.2
<i>S. aureus</i> toxin	3.5	3.8	3.7	1.6	6.9	2.7	0.9	0.8	3.5	13.9	5.6	47.1
Norovirus	0.6	0.5	0.5	0.3	0.4	2.7	1.3	0.5	0.9	0.9	9.0	17.7
Rotavirus	0.0	0.3	0.0	0.0	0.2	1.8	2.3	0.4	0.7	0.4	3.4	9.5
Hepatitis-A virus	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1
Hepatitis-E virus	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.03
<i>Cryptosporidium</i> spp.	0.3	0.0	0.0	0.0	0.1	0.2	0.2	0.0	0.0	0.0	0.1	1.0
<i>Giardia</i> spp.	0.3	0.1	0.1	0.0	0.1	0.2	0.5	0.1	0.0	0.0	0.2	1.5
<i>Toxoplasma gondii</i>	2.5	5.5	0.5	0.0	0.5	0.4	0.6	0.0	0.0	0.3	0.6	11.0
Total	22.9	16.3	25.9	6.7	14.2	13.2	10.4	3.7	8.7	23.8	22.8	168.4

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Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.ijfoodmicro.2014.11.022>.

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