Cost of Illness and Disease Burden in The Netherlands Due to Infections with Shiga Toxin–Producing \textit{Escherichia coli} O157

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\textbf{ABSTRACT}

Infections with Shiga toxin–producing \textit{Escherichia coli} O157 (STEC O157) are associated with hemorrhagic colitis, hemolytic uremic syndrome (HUS), and end-stage renal disease (ESRD). In the present study, we extend previous estimates of the burden of disease associated with STEC O157 with estimates of the associated cost of illness in The Netherlands. A second-order stochastic simulation model was used to calculate disease burden as disability-adjusted life years (DALYs) and cost of illness (including direct health care costs and indirect non–health care costs). Future burden and costs are presented undiscounted and discounted at annual percentages of 1.5 and 4\%, respectively. Annually, approximately 2,100 persons per year experience symptoms of gastroenteritis, leading to 22 cases of HUS and 3 cases of ESRD. The disease burden at the population level was estimated at 133 DALYs (87 DALYs discounted) per year. Total annual undiscounted and discounted costs of illness due to STEC O157 infection for the Dutch society were estimated at €91.9 million and €4.5 million, respectively. Average lifetime undiscounted and discounted costs per case were both €126 for diarrheal illness, both €25,713 for HUS, and €2.76 million and €1.22 million, respectively, for ESRD. The undiscounted and discounted costs per case of diarrheal disease including sequelae were €4,132 and €2,131, respectively. Compared with other foodborne pathogens, STEC O157 infections result in relatively low burden and low annual costs at the societal level, but the burden and costs per case are high.

Infections with Shiga toxin–producing \textit{Escherichia coli} O157 (STEC O157) are an important cause of morbidity and mortality, with associated loss of life years and diminished health-related quality of life. STEC O157 induces a severe form of gastroenteritis characterized by bloody stools (hemorrhagic colitis) and may cause hemolytic uremic syndrome (HUS) in young children and sporadically in adults. HUS may result in end-stage renal disease (ESRD). Patients with ESRD are initially treated with peritoneal dialysis or hemodialysis and may later be eligible for kidney transplantation. Information on the disease consequences of STEC O157 was reviewed by Havelaar et al. (13).

As in other industrialized countries, the incidence of STEC O157–associated diarrheal illness in The Netherlands is low (approximately 2,000 cases per year), compared with that of illness associated with other enteric pathogens (e.g., 79,000 cases of campylobacteriosis per year) (11). Nevertheless, much effort is being made in The Netherlands and internationally to prevent diseases associated with STEC O157 because of the severity of the sequelae of this infection and the fact that it occurs more often in young children. Any outbreak or increase in incidence of STEC O157 infection will be significant for public health (13, 16).

Various approaches have been used to quantify the societal impact of (foodborne) disease, as discussed in depth by Buzby and Roberts (3) and Mangen et al. (15). Valuation of public health impact is typically done using some form of health-adjusted life years, combining the effects of premature mortality and morbidity and accounting for health-related quality of life. The two most prominent health-adjusted life year metrics are quality-adjusted life years and disability-adjusted life years (DALYs). The public health impact of foodborne and zoonotic disease also can be characterized in monetary terms. The human capital approach is largely restricted to impacts on labor productivity, and willingness to pay (WTP) methods are based on revealed or stated preferences on the tradeoffs that individuals must make between health and other goods. WTP is therefore consistent with the theoretical foundation of welfare economics. The most well-known WTP measure is the value of a statistical life, a practical estimation that is not intended to place a monetary value on life itself but that refers to what an average individual in a population is willing to pay to avoid the risk of premature death. However, WTP is a function of ability to pay, and therefore results may reflect wealth and benefit. The reported value of a statistical life differs widely between and within countries;

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one landmark study found a range of $0.7 million to $20.8 million (30). An alternative approach to monetary valuation is the cost of illness (COI) method, which traces the economic flow associated with an adverse health outcome through the quantification of measurable monetary costs. Mangen et al. (15) stated, “it seems a reasonable conclusion that prioritization efforts should consider using a combination of approaches, namely, the use of COI with either WTP or health-adjusted life years, both of which capture the intangible costs of adverse health states missing from COI.”

In this study, we evaluate the societal impact of STEC O157 infection in The Netherlands using a combination of DALYs and COI and compare this approach to that used commonly in the United States with the value of a statistical life.

Foodborne illnesses generate a considerable disease burden and major economic losses. According to Buzby and Roberts (3), foodborne illnesses generate costs that are borne by households whose members become ill, the food industry, and the regulatory and public health sectors. For example, the costs of human Campylobacter infections in The Netherlands were estimated at €21 million (90% credible interval [CI] of €11 million to €36 million) per year (16). Little is known about the economic costs imposed on the Dutch or other societies by disease associated with STEC O157. Frenzen et al. (8) estimated the COI due to STEC O157 in the United States at $405 million (in 2003 dollars). Buzby and Roberts (3) updated this estimate to $459 million (in 2007 dollars). Scharff et al. (23, 24) suggested that STEC O157 infections cost about $990 million (in 2009 dollars) to U.S. residents. In these studies, valuation of death was the largest component of total costs, which was estimated using the value of a statistical life for premature deaths. In contrast, The Netherlands uses the friction cost method to account for productivity loss due to disease because of temporary absence from work, disability, and/or premature mortality (14).

In the present study, we extended the previous estimates of the burden of disease associated with STEC O157 infection with estimates of the COI in The Netherlands, using a previously developed detailed epidemiological model (13). We also present the impact of discounting on these estimates.

MATERIALS AND METHODS

Disease model. The disease model for STEC O157 infections is provided in Figure 1. Infections may be asymptomatic or may lead to diarrheal illness, including hemorrhagic colitis. HUS occurs mainly in young children and may lead to death during the acute phase, to ESRD, or to other sequelae.

In this study, we attributed and calculated costs and disease burden estimates for each disease state. In contrast to the model presented by Havelaar et al. (13), we assumed that patients with ESRD can maximally receive two kidney transplantations and that patients older than 70 years are not eligible for the second kidney transplantation.

Simulation model. To estimate the updated disease burden and COI associated with STEC O157 infections, a second-order stochastic simulation model was built in Excel (Microsoft, Redmond, WA) and implemented with the add-in software @Risk (version 5.0, Palisade Corp., New York). As explained previously in detail (13), the model simulates the annual incidence of STEC O157–associated gastroenteritis and death and the incidences of HUS and ESRD. The model was run with 250 simulations and 1,500 iterations per simulation to account for uncertainty and variability, respectively. Each iteration within one simulation calculated a possible set of life histories of HUS and ESRD patients. All transitions from one health state to the next in the outcome tree are represented by conditional probabilities, resulting in different realizations of the system in each iteration. Together, the 1,500 iterations represent the variability of the system and consequently of the disease burden and COI, for a particular set of uncertain input parameters. Different simulations use different samples from the uncertainty distributions of the input parameters and hence quantified the uncertainty in the model results. As found in a previous study (13), in this model uncertainty dominates.

FIGURE 1. Disease model for infection with Shiga toxin–producing Escherichia coli O157. Reprinted from Havelaar et al. (13) with permission.
variability; in this article we present the results of only the uncertainty analysis.

Disease burden. Disease burden is expressed in DALYs. By using the DALY methodology, morbidity (expressed in years lived with disability) and mortality (expressed in years of life lost) are summed into one metric (18). The number of reported cases of STEC O157 infection in The Netherlands from 1999 through 2008 was on average 40 per year (0.25 cases per 100,000 person years), without a clear trend (9, 29). Hence, the epidemiological estimates made by Havelaar et al. (13) were still considered valid. Serotype O157 represents only 20% of all STEC isolates from clinical material in The Netherlands. However, until now non-O157 STEC strains have not been associated with HUS in The Netherlands (11). Hence, we estimated that the additional burden and costs of non-O157 STEC strains would be low, and we did not include these strains in our analysis.

COI. Following the Dutch Pharmacoeconomic guidelines from the Dutch Health Insurance Board (4), the following cost categories were included in the COI estimates:

(i) direct healthcare cost, including costs such as medical consultations, hospitalization, drugs, rehabilitation, and other medical services, and

(ii) indirect non–health care costs, including costs associated with productivity loss due to disease because of temporary absence from work, disability, and/or premature mortality.

Productivity losses were estimated according to the friction cost method. Mainly, two methods are used to value productivity: the human-capital method and the friction cost method. The human-capital method takes the patient’s perspective and counts any hour not worked as an hour lost. The friction cost method takes the employer’s perspective and counts as lost only those hours not worked until another employee takes over the patient’s work (28).

Indirect health care costs (costs of unrelated medical care in life years gained during the extended life expectancy (27)) were not included in this study, as recommended by the Dutch Pharmacoeconomic guidelines (4). Contrary to these guidelines, direct non–health care costs (including patients’ travel costs and patients’ copayments for costs such as informal care) were not included because they were relatively low in previous studies (16).

Derivation of the model input parameters. The epidemiological model and DALY calculations were based on parameters described by Havelaar et al. (13). To quantify the COI caused by STEC O157 infection, data were gathered from several sources. We used consumer price indices from Statistics Netherlands (25) taking the year 1995 as an index and an exchange rate of €0.68 to $1 to adjust foreign currency to a 2009 price level. According to the method of Oostenbrink et al. (19), productivity losses were considered only for patients 15 to 64 years of age, using the friction cost method. We defined a friction period of 154 days as proposed by Koopmanschap et al. (14). The assumed productivity losses per day per person were based on the salary of an average person in that age class (in 2009). We calculated productivity losses per day and per friction period in the year 2009 for both an average person and an average working person, depending on the age group of the patients. In the absence of Dutch data, we used the data published by Buzby and Roberts (3), who suggest that a patient who had HUS but not ESRD and survived had an average cost of $38,695 (2007 price). For the costs of hemodialysis and kidney transplantation, Dutch estimates from de Wit et al. (6) for 1996 were used. Hemodialysis costs about 152,000 Dutch guilders (€93,000 in 2009 currency) in the first year of treatment and about 145,000 Dutch guilders (€88,000 in 2009 currency) in later years. Peritoneal dialysis costs about 130,000 Dutch guilders (€79,000 in 2009 currency) in the first year of treatment and about 114,000 Dutch guilders (€70,000 in 2009 currency) in later years. Kidney transplantation costs about 90,000 Dutch guilders (€55,000 in 2009 currency) in the first year and about 18,000 Dutch guilders
### RESULTS

In Table 2, mean values per year of the burden of STEC O157–associated illness and the COI estimates in The Netherlands are shown. The average burden per case and average COI associated with STEC O157 in The Netherlands are shown in Table 3.

**Disease burden.** The estimated undiscounted (discounted) mean disease burden of STEC O157–associated illness in the Dutch population was 133 (87) DALYs per year (90% CI, 97 to 182 DALYs) compared with a previous estimate of 116 DALYs (13). Death in the clinical phase of HUS was the largest single contributing factor, with 58 (38) DALYs. Overall, fatal outcomes accounted for 105 (67) DALYs, and morbidity accounted for 28 (22) DALYs.

**COI.** The estimated undiscounted (discounted) COI per year associated with STEC O157 infection in The Netherlands were €9.1 million (€4.5 million) (90% CI, €5.1 million to €13.5 million). Direct health care costs accounted for €8.8 million (€4.3 million) (90% CI, €4.8 million to €13.3 million). Indirect non–health care costs were not discounted and accounted for €0.3 million (90% CI, €0.05 million to €0.60 million). The cost category with the highest numbers in the estimated COI were direct health care costs, specifically costs within the first dialysis period, at an estimated €1.9 million (€835,000), and costs of dialysis after the second graft rejection, at an estimated €4.0 million (€1.8 million). Reasons for these high costs include the number of years spent in these disease states and the high costs of dialysis. Indirect non–health care costs were minor (3%). Total costs in the HUS clinical phase were estimated at €560,000, whereas total costs of ESRD accounted for €8.8 million. Figure 2 shows the distribution of the estimated COI associated with STEC O157 infection in The Netherlands without and with discounting, respectively.

**Uncertainty analysis.** The undiscounted (discounted) 90% CI of the burden of disease estimate per year was 97 to 182 (64 to 125) DALYs (Table 4). Years of life lost ranged from 77 to 145 (50 to 96) per year. Life years lived with disability ranged from 17 to 41 (11 to 29) per year. Total cost estimates per year ranged from €5.1 million to 13.5 million (€2.8 million to 7.3 million). Direct health care costs per year ranged from €4.8 million to €13.3 million (€2.6 million to €6.5 million). Indirect non–health care costs were not discounted because these costs occur within 1 year and ranged from €54,293 to €606,766.

Detailed statistics for the output data are available upon request from the corresponding author.
DISCUSSION

This study was conducted to estimate annual COI in The Netherlands due to disease associated with STEC O157 infection and provided updated estimates of the disease burden associated with STEC O157 infection in the Dutch population, e.g., HUS and ESRD. COI was €9.1 million per year undiscounted and €4.5 million per year discounted. Mean disease burden was 133 DALYs per year undiscounted and 87 DALYs per year discounted.

STEC O157 infection has a relatively low burden of disease and COI on a population basis. For example, Mangen et al. (16) estimated the costs of human Campylobacter infections and sequelae in The Netherlands at €21 million with a burden of 1.200 DALYs per year. However, on a per case basis, STEC O157 infection has a 12-fold higher health impact (55 DALYs per 1,000 cases of diarrheal illness) than does Campylobacter infection (4.6 DALYs per 1,000 cases) and a 16-fold higher COI (€4,300 per case of diarrheal illness versus €262 per case of Campylobacter infection). Notably, most of the COI associated with STEC O157 infection occurs within the health care sector, whereas this is not the case for other pathogen infections where indirect non–health care costs dominate. The indirect non–health care costs are much lower for STEC O157 infections (€0.2 million per year) than for Campylobacter infection (€14 million per year). However, cost categories such as cost associated with productivity losses because of (temporary) absence from work by parents of sick children are not included in this estimate.

In previous studies performed in the United States, much higher COI estimates of STEC O157 infection were found. Frenzen et al. (8) estimated the COI due to STEC O157 infection in the United States at $405 million (in 2003 dollars), including $370 million for premature deaths. Buzby and Roberts (3) updated this estimate to $459 million (in 2007 dollars), including $265 million for premature deaths. Scharff et al. (23, 24) suggested that STEC O157 infections cost about $990 million (in 2009 dollars) to U.S. residents, including $627 million due to HUS. Taking into account differences in population sizes in 2009 (The Netherlands, 16 million; United States, 301 million) and the fact that the estimated incidence rate in the United States is twice that in The Netherlands (0.28 compared with 0.14 cases per 1,000 people, respectively) (see data provided by Mead et al. (17)), the U.S. costs estimates are up to twice those for The Netherlands. In the

<table>
<thead>
<tr>
<th>Illness type</th>
<th>No. of cases</th>
<th>Total nondiscounted (discounted) DALYs</th>
<th>Total nondiscounted (discounted) costs (euros)</th>
<th>Costs/case</th>
</tr>
</thead>
<tbody>
<tr>
<td>GE</td>
<td>2,114</td>
<td>14 (14)</td>
<td>267,416 (267,416)</td>
<td>0.006 (0.006)</td>
</tr>
<tr>
<td>HUS</td>
<td>22</td>
<td>60 (40)</td>
<td>565,688 (565,688)</td>
<td>2.7 (1.8)</td>
</tr>
<tr>
<td>ESRD</td>
<td>3</td>
<td>58 (37)</td>
<td>8,283,931 (3,671,994)</td>
<td>19.33 (12.33)</td>
</tr>
<tr>
<td>Total</td>
<td>2,114</td>
<td>132 (91)</td>
<td>9,117,035 (4,505,098)</td>
<td>0.06 (0.04)</td>
</tr>
</tbody>
</table>

Values are given at nondiscounted rate (0%) and discounted rates of 1.5% for DALYs and 4% for costs per case.

GE, gastroenteritis; HUS, hemolytic uremic syndrome; ESRD, end-stage renal disease.

DAILYs, disability adjusted life years.

### TABLE 3. Average burden of disease and cost of illness per case associated with STEC O157 infection in The Netherlands

<table>
<thead>
<tr>
<th>Illness type</th>
<th>No. of cases</th>
<th>Total nondiscounted (discounted) costs (euros)</th>
<th>Costs/case</th>
</tr>
</thead>
<tbody>
<tr>
<td>GE</td>
<td>2,114</td>
<td>132 (91)</td>
<td>9,117,035 (4,505,098)</td>
</tr>
<tr>
<td>HUS</td>
<td>22</td>
<td>19.33 (12.33)</td>
<td>2,761,310 (1,223,998)</td>
</tr>
<tr>
<td>ESRD</td>
<td>3</td>
<td>19.33 (12.33)</td>
<td>2,761,310 (1,223,998)</td>
</tr>
<tr>
<td>Total</td>
<td>2,114</td>
<td>132 (91)</td>
<td>9,117,035 (4,505,098)</td>
</tr>
</tbody>
</table>

Values are given at nondiscounted rate (0%) and discounted rates of 1.5% for DALYs and 4% for costs per case.

GE, gastroenteritis; HUS, hemolytic uremic syndrome; ESRD, end-stage renal disease.

DAILYs, disability adjusted life years.
U.S. studies, valuation of death was the largest component of total cost, which was estimated using the value of a statistical life for premature deaths. In contrast, we used the friction cost method to account for productivity loss due to temporary absence from work, disability, and/or premature mortality, all the result of disease. This approach was proposed by Koopmanschap et al. (14) and has been widely accepted and applied in many European countries. However, we also ran our model using an updated estimated value of a statistical life of €3.6 million (3). This resulted in a total COI of €23 million undiscounted and €19 million discounted. Direct health care costs account for €8 million undiscounted and €4 million discounted. Indirect health care costs rose to €15 million (see Table 5). These estimates are similar to the U.S. estimates provided by Frenzen et al. (8) and Buzby and Roberts (3). Clearly, the valuation of premature deaths is a very influential factor in COI estimates of foodborne and other diseases.

In this study, statistical uncertainty was quantified with the second-order stochastic simulation model run with 250 simulations and 1,500 iterations. However, uncertainty regarding other input parameters remains. Havelaar et al. (13) quantified uncertainty of disease burden estimates with scenario analyses. Regarding COI estimates, uncertainty exists around costs of HUS and dialysis periods. Costs of HUS were derived from a U.S. study (3), with uncertainty about the transferability of these costs to The Netherlands. For costs during dialysis periods, Dutch estimates based on valid data were used from 1996 (6). Because costs of HUS are relatively low and have little influence on the outcomes of this study and costs of dialysis have substantial influence because they are relatively high, we used the dialysis estimates. However, more recent estimates are desirable.

The strength of this study lies in the use of the DALY and the COI methods to quantify intangible and monetary costs associated with STEC O157 infection. As argued by Mangen et al. (15), this combined approach provides the most complete basis currently available for comparison of and prioritizing foodborne hazards. Results of this study can be used for any cost-benefit analysis of STEC O157 infection. Using a threshold on the costs to avert 1 DALY, the costs of implementing interventions to reduce exposure to STEC O157 can be evaluated in a cost-utility framework as presented previously for human Campylobacter infections (12, 31).

The present study was restricted to the physical consequences of STEC O157 infection. However, STEC O157–associated gastroenteritis and its sequelae, HUS and ESRD, also may have indirect (psychological) impact. Some children hospitalized at the pediatric intensive care unit experienced negative behavioral changes, elevated

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**FIGURE 2.** Undiscounted and discounted cost of illness associated with STEC O157 infection in The Netherlands.

**TABLE 4. Summary statistics of output distributions**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nondiscounted</th>
<th>Discounted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean of means</td>
<td>SD of means</td>
</tr>
<tr>
<td>DALYs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>YLD</td>
<td>28</td>
<td>11</td>
</tr>
<tr>
<td>YLL</td>
<td>105</td>
<td>23</td>
</tr>
<tr>
<td>Cost of illness (euros)</td>
<td>9,128,353</td>
<td>2,800,415</td>
</tr>
<tr>
<td>DHC (euros)</td>
<td>8,827,788</td>
<td>2,738,266</td>
</tr>
<tr>
<td>INHC (euros)</td>
<td>300,565</td>
<td>346,175</td>
</tr>
</tbody>
</table>

a Values are given at nondiscounted rate (0%) and discounted rates of 1.5% for DALYs and 4% for cost of illness.
b DALYs, disability adjusted life years; YLD, years lived with disability; YLL, years of life lost; DHC, direct health care costs; INHC, indirect non–health care costs.
anxiety, and increased symptoms of posttraumatic stress disorder (20, 21, 32). Research conducted with parents of these children revealed that as many as one in three parents met the Diagnostic and Statistical Manual of Mental Disorders IV criteria for acute stress disorder, and after discharge, one in five parents experienced symptoms indicative of posttraumatic stress disorder (1, 2, 10, 21). These findings suggest that the results reported in the present study may underestimate the actual burden of disease and COI of STEC O157 infection because patients with psychological syndromes often continue to have symptoms for more than 1 year and the impact on health-related quality of life and health care is substantial (5, 22, 33, 34).

In conclusion, the annual undiscounted (discounted) COI due to infections with STEC O157 in The Netherlands is €9.1 million (€4.5 million), with a mean disease burden of 132 DALYs (91 DALYs). The findings of this COI study suggest that additional efforts to control this pathogen will reduce health care costs and may be cost-effective from a societal point of view.

ACKNOWLEDGMENT

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REFERENCES


