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The cost of Lyme borreliosis

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Background: Lyme borreliosis (LB) is the most frequently reported tick-borne infection in Europe and North America. The aim of this study was to estimate the cost-of-illness of LB in the Netherlands. **Methods:** We used available incidence estimates from 2010 for tick bite consultations and three symptomatic LB outcomes: erythema migrans (EM), disseminated LB and Lyme-related persisting symptoms. The cost was estimated using these incidences and the average cost per patient as derived from a patient questionnaire. We estimated the cost from a societal perspective, including healthcare cost, patient cost and production loss, using the friction cost method and a 4% annual discount rate. **Results:** Tick bites and LB in 2010 led to a societal cost of €19.3 million (95% CI 15.6–23.4; 16.6 million population) for the Netherlands. Healthcare cost and production loss each constituted 48% of the total cost (€9.3 and €9.2 million/year), and patient cost 4% (€0.8 million/year). Of the total cost, 37% was related to disseminated LB, followed by 27% for persisting symptoms, 22% for tick bites and 14% for EM. Per outcome, for an individual case the mean cost of disseminated LB and Lyme-related persisting symptoms was both around €5700; for EM and GP consultations for tick bites this was €122 and €53. As an alternative to the friction cost method, the human capital method resulted in a total cost of €23.5 million/year. **Conclusion:** LB leads to a substantial societal cost. Further research should therefore focus on additional preventive interventions.

Introduction

Lyme borreliosis (LB) is the most common tick borne infection in Europe and North America. It is caused by *Borrelia burgdorferi sensu lato* that in Europe is transmitted by the tick *Ixodes ricinus*. The disease most commonly manifests as erythema migrans (EM), a slowly expanding skin lesion. If left untreated, disseminated LB can develop, such as Lyme neuroborreliosis or Lyme arthritis.[1,2] Diagnostic criteria and clinical case definitions for LB in the Netherlands and other European countries are largely based on the criteria published by Stanek et al.[1] LB generally responds well to antibiotic treatment, and thus most LB patients have a good prognosis.[3,4] A minority of patients report persisting symptoms after antibiotic treatment.[1,2,4–6]

In the United States the LB incidence is 329 000 cases per year (107/100 000 persons).[7] In the Netherlands and some other areas in Europe the LB incidence is increasing, and the geographic distribution of *I. ricinus* ticks in Europe is expanding.[8,9] European-wide incidence estimates are complicated by large heterogeneity in surveillance data, but available estimates range from 65 000 to more than 200 000 LB cases per year.[8,10] In the Netherlands, the total LB incidence is almost 25 000 cases per year (145/100 000).[6]

Insight in the burden of disease and the economic impact of LB is important to prioritize allocation of public resources. Recently, we reported the disease burden of LB in disability adjusted life years (DALYs): the annual disease burden for the Netherlands in 2010 was 1749 DALYs for the 16.6 million population.[11] Research on the economic impact of LB is scarce. Assessment of the cost-of-illness may be informative for economic evaluations of prevention and control interventions for LB. This study aimed to assess the cost-of-illness of LB taking healthcare cost, production loss and patient cost into account.

Methods

Outcomes

First we mapped out potential disease outcomes after a tick bite in a tree diagram (see figure 1). Similar as in our previous work,[11] we defined five possible health outcomes to which cost can be attributed. The first two outcomes ''no infection'' and ''asymptomatic infection'' go without any symptoms. Nevertheless, tick bites without (or before) occurrence of symptoms incidentally result in GP consultation. The third and fourth outcome EM and ''disseminated LB'' are manifestations of acute symptomatic LB,[1] both requiring medical services, see also figure 1. Both EM and disseminated LB patients might either fully recover, or develop the fifth outcome ''Lyme-related persisting symptoms'' that patients and their physicians attribute to LB.[1,2,5,12–14]

Cost-of-illness approach

We estimated the total cost of LB by first using incidence data from 2010 to derive the number of new *Borrelia* infections and tick bites, and then model the lifetime cost associated with LB for affected individuals. We followed the Dutch guidelines for health economic evaluations,[15] which prescribe cost calculation from a societal perspective—implying that all cost due to LB was included no matter who incurs the cost—and use of the friction cost method to attribute the cost of production loss to LB.[16,17] According to the friction cost method, production loss is only included for the so-called friction period, which is the time needed to replace a sick, physically disabled or deceased worker. A friction period of 12.1 weeks was used, following the Dutch guidelines for health economic evaluations.[15] All costs were expressed in Euro for the year 2014, where necessary

corrected using Dutch consumer price indexes. Costs in future years were discounted with an annual rate of 4%.[15]

Cost categories

We assessed (a) healthcare cost, (b) patient cost—or out-of-pocket cost—and (c) production loss. Healthcare cost for medical services included GP consultations, paramedic consultations, complementary medicine consultations, specialist consultations at the outpatient clinic, hospitalization, prescribed medications and formal home care, no matter who incurred the cost. The patient cost included informal care—such as self-paid household assistance or assistance by a relative or friend. Unfortunately data collection of other patient costs (e.g. over-the-counter medication, travel) seemed inadequate, and these were therefore excluded from the baseline estimate (see table 1 and Results section). Production loss included all cost due to work absenteeism of affected cases from paid work as a consequence of disease symptoms and/or visits to healthcare providers. Production loss due to impaired functioning during work hours was not included.

Incidence data

To extrapolate the mean cost per patient to national cost, the annual incidence per disease outcome was needed. We used incidence estimates for 2010 from a nationwide GP survey: 81 997 GP consultations for tick bites, 21 802 cases of EM, 1268 cases of disseminated LB and 905 new cases with Lyme-related persisting symptoms.[6] These estimates were based on likely and very likely diagnoses and were adjusted for reporting bias. The GP consultations for tick bites include tick bites that are not followed by any symptoms (outcomes 1 and 2, figure 1), as well as tick bites that are later followed by symptomatic LB outcomes (outcomes 3, 4 and 5). We assumed that no cost occurred for tick bites for which no GP was consulted (92% of all tick bites[9]).

Patient data

Data on disease duration, resource utilization (i.e. healthcare and other resources) and sick leave were derived from a patient survey that we earlier used to estimate the disease burden of LB.[11] The Medical Ethics Review Committee of the University Medical Centre Utrecht declared that the Medical Research Involving Human Subjects Act does not apply to this study (protocol number 14-283/C, letter number WAG/om/14/015644).[18] Patients were eligible for this survey if they suffered symptoms of LB in the 12 months preceding the questionnaire, and were enrolled through their physician, or on their own request (the latter were recruited through an announcement by the national Lyme patient association). A total of 949 patients responded, of whom 660 patients were included in the analysis: 88 EM patients [of which 87 (99%) enrolled through their physicians], 96 disseminated LB patients [88 (92%) enrolled through physicians] and 476 patients with Lyme-related persisting symptoms [189 (40%) enrolled through physicians]. See our previous work for details on the questionnaire response and classification of patients in LB manifestations.[11]

Lifetime cost for tick bite consultations and symptomatic LB outcomes

For GP consultations for tick bites, we included the cost of one GP consult plus 1 h of work-absenteeism per consult for the working population (table 1). In addition, we included cost for prophylactic antibiotic treatment after 10% of the GP consultations for a tick bite (table 1).[19] For the symptomatic LB outcomes, we derived disease duration and resource utilization from the patient survey.[11] Cost per LB patient was calculated *post hoc* by multiplying used resources with corresponding unit cost prices from Dutch guidelines for health economic evaluations[15] and http://www.medicijnkosten.nl. See table 1 for resources utilization and prices.

Estimation of the lifetime cost per outcome was complicated by the censored disease durations and cost histories in our patient data. To overcome this, the mean lifetime cost per patient was modelled for each symptomatic LB outcome in four steps: (a) estimate mean disease duration, (b) recreate cost histories over time, (c) estimate average cost per time interval during disease and (d) estimate the mean cost per disease episode. See Appendix 1.

Sensitivity analysis

Sensitivity analyses were conducted assuming different estimates for the incidence, severity and disease duration, or for possible mortality due to LB (scenario 1–6). In addition, in scenario 7 the cost was estimated without discounting, and in scenario 8 and 9 the human capital method was applied, with and without possible mortality due to LB. The human capital method values all absenteeism until the retirement age as production loss, other than the friction cost method that only values production loss for the time until replacement.[17] See legend of figure 2, and table A1.

Results

Cost per patient

Table 1 shows the cost per patient for all cost categories, including unit cost prices and the mean resource utilization. For all outcomes, both healthcare cost and production loss were the most important cost (table 1). The healthcare cost was highest for disseminated LB, followed by persisting symptoms, EM and tick bite consultations. As a proportion per outcome, the healthcare cost was highest for tick bite consultations (66%), followed by EM (55%), disseminated LB (47%) and persisting symptoms (32%) (figure A1). Production loss was—both absolute and as a proportion of the outcome—highest for persisting symptoms, followed by disseminated LB, EM and tick bites (figure A1).

Patient cost was only observed in patients with disseminated LB and persisting symptoms (table 1). Note that the patient cost only contained informal domestic support. Other types of patient cost—such as travel cost and other payments by patients—were excluded, although they had been included in the patient questionnaire; many patients misinterpreted the timeline and seemed to have administered the cost for their entire disease episode, whereas this should only have been 4 weeks preceding the questionnaire. Therefore, we restrained ourselves to exploring the possible range of this cost by calculating a lower and upper bound; the lower assuming that all cost was listed by participants since the onset of disease, and the upper bound assuming cost listed for the four preceding weeks (table 1). On the 16.6 million population level, the point estimates of these lower and upper bound for patient cost—other than informal domestic support—ranged from €12 thousands to €3.9 million.

National cost stratified by outcome and type of cost

Table 2 shows that the total cost due to LB was estimated at €19.3 million/year (95% CI 15.6–23.4) for the 16.6 million population. Stratified by outcome, the cost was €4.3 million/year (22% of the total cost) for tick bite consultations, €2.7 million/year (14%) for EM, €7.2 million/year (37%) for disseminated LB and €5.2 million/year (27%) for persisting symptoms. Stratified by cost category, the healthcare cost and production loss were €9.3 and €9.2 million/year, respectively (table 2), both 48% of the total cost. The patient cost was €0.8 million/year (4%).

Table 1 Cost-of-illness per patient for tick bites and LB outcomes in the Netherlands in 2010, stratified for healthcare cost, patient cost and production loss, including all subcategories of cost resources and utilization

	Unit cost price, €	Average resource unit utilization				Cost (95% CI*) per patient, in €			
		Tick bite	EM	Disseminated LB	Persisting symptoms	Tick bite	EM	Disseminated LB	Persisting symptoms
Healthcare cost									
-GP consultation	33	1	1.04 (0.60–1.53)	4.22 (3.30–5.27)	5.43 (4.42–6.49)	33	34.23 (19.9–50.5)	139 (109–174)	179 (146–214)
-Medical specialist consultation	91	–	0.07 (0.00–0.17)	5.20 (3.50–7.19)	5.73 (4.88–6.64)	–	6.06 (0–15.75)	473 (319–654)	521 (444–604)
-Paramedic consultation	33	–	0.02 (0.00–0.06)	5.42 (0.92–11.84)	8.79 (5.90–12.10)	–	0.64 (0–2.08)	179 (30–391)	290 (195–399)
-Complementary healthcare provider consultation	33	–	0.16 (0.00–0.49)	0.84 (0.31–1.51)	3.65 (2.79–4.53)	–	5.38 (0–16.12)	27.82 (10.29–49.67)	120 (92–150)
-Surgery	754	–	–	–	0.07 (0.03–0.12)	–	–	–	54.68 (24.99–91.14)
-Hospital care (per day)	476	–	–	2.76 (0.81–4.94)	0.90 (0.52–1.35)	–	–	1.315 (386–2.351)	429 (247–644)
-Intensive care (per day)	2015	–	–	–	0.06 (0.00–0.18)	–	–	–	126 (0–358)
-Home care (per hour)	20	–	–	–	0.21 (0.00–0.65)	–	–	–	4.19 (0.00–12.96)
-Medication	n/a**	0.1***	n/a**	n/a**	n/a**	1.46	20.83 (10.5–31.9)	526 (145–997)	106 (87–127)
Total						**34.46**	**67.14 (43.3–93.3)**	**2660 (1292–4184)**	**1832 (1481–2223)**
Patient cost									
*Other costs upper bound^*	n/a	n/a	n/a	n/a	n/a	–	*30.56 (0–106.19)*	*188 (69–336)*	*3302 (1920–5209)*
*Other costs lower bound^*	n/a	n/a	n/a	n/a	n/a	–	*0.44 (0–1.18)*	*2.07 (0.75–4.35)*	*0 (0–0)*
Informal domestic support	14	–	–	20.76 (0.48–57.42)	34.29 (22.87–48.3)	–	–	291 (7–804)	480 (319–676)
Total						**–**	**–**	**291 (7–804)**	**480 (319–676)**
Production loss (work-absenteeism)	34.75 (per hour)	0.52^^	1.57 (0–4.28)	78.12 (37.7–118.8)	97.41 (74.8–119.6)	18.07	54.63 (0–148.85)	2715 (1311–4128)	3385 (2598–4157)
Total societal cost per outcome						**52.53**	**121.78 (51.7–221.1)**	**5666 (3502–7991)**	**5697 (4723–6693)**

Cost is expressed in 2014 euros.

*: We estimated 95% confidence intervals (CI) using a bootstrap procedure with 1000 iterations while including missing values (see Appendix 1).

**: Several prescribed medications due to LB per symptomatic patient were listed in the 4 weeks preceding the questionnaire, of which 44% were antibacterial medications, 36% pain medications and 20% other medications; when in doubt whether medications were taken upon prescription or as over-the-counter drugs, we assumed they were taken upon prescription. Definite over-the-counter drugs listed by some patients in the questionnaire were excluded, since we failed to systematically collect them. All medication cost prices were derived from www.medicijnkosten.nl.

***: For 10% of tick bite consultations we assumed that prophylactic treatment was prescribed,[19] with a cost price of €15 per treatment.

^: In the patient questionnaire we also asked for ''other costs'' in the 4 weeks preceding the questionnaire, in order to extrapolate these costs to complete disease episodes. Unfortunately many participants appeared to have misinterpreted this question; they seemed to have listed costs since the date of onset of disease. This complicated an accurate estimate of ''other costs'', and we excluded these costs from our estimate for the patient cost and total cost. However, to explore the possible range of these costs we calculated a lower and an upper bound for ''other costs''; the lower assuming that all ''other costs'' were listed by participants since the onset of disease, and the upper bound assuming costs listed for the four preceding weeks.

^^: For the working population, we assumed one hour of work-absenteeism per tick bite GP consultation; we estimated the working population at 52%, based on the age distribution of tick bite cases and data from Statistics Netherlands.[9]

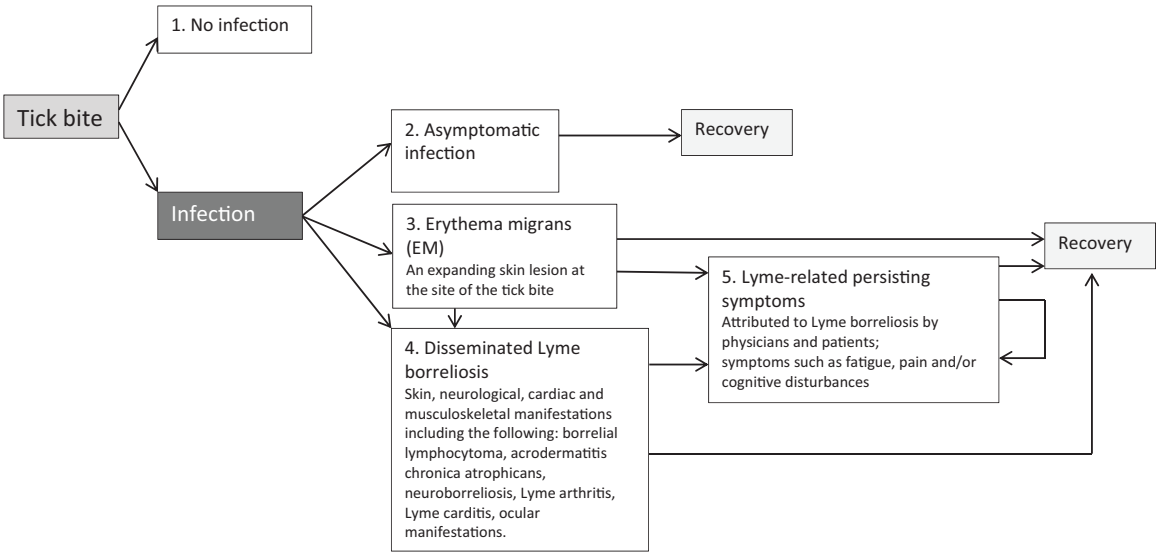

Figure 1 Outcome tree following a tick bite. Five possible health outcomes after a tick bite were defined: (1) ''no infection'' and (2) ''asymptomatic infection'' go without any symptoms; (3) EM and (4) ''disseminated LB'' are manifestations of acute symptomatic LB[1]; both EM and disseminated LB patients might either fully recover, or develop (5) ''Lyme-related persisting symptoms'' that patients and their physicians attribute to LB[1,2,5,12–14]

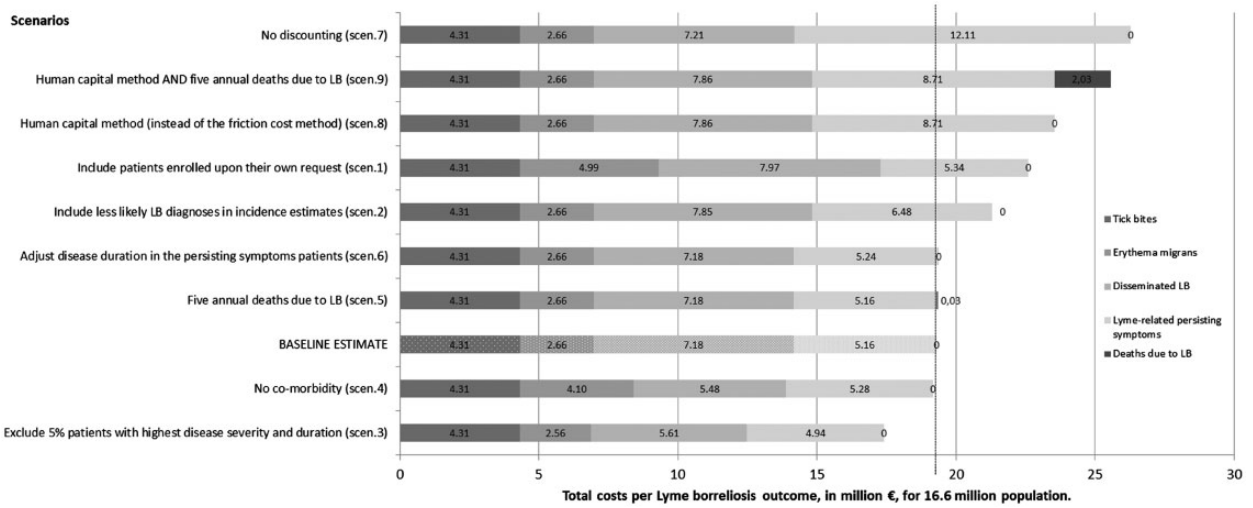

Figure 2 Sensitivity analysis of the cost-of-illness due to LB for nine scenarios compared with the baseline estimate. Cost is presented per outcome in million € for the Netherlands in 2010 (16.6 million population). Cost is expressed in 2014 euros. Scenario 1 evaluated the impact of including patients enrolled at their own request, that is mainly through the national patient association. Scenario 2 used higher incidence estimates per LB outcome from Hofhuis et al.,[6] by also including less likely LB diagnoses. Scenario 3 excluded the 5% patients with highest disease severity and duration, to assess the possible impact of including relatively more severely ill patients. In scenario 4, to explore whether our estimates could be biased by patients with co-morbidity that was not related to LB,[35] we excluded such patients. Although there is no definite evidence for substantial mortality due to LB,[36] several cases of LB-related deaths have been reported.[37–40] Scenario 5 therefore explored the possible impact of sporadic LB related deaths by assuming five annual deaths. For the patients with persisting symptoms, it was not possible to fit a survival curve to adjust for censored disease duration. Thus, in scenario 6 we increased the disease duration by 25% for censored patients with persisting symptoms. Scenario 7 presented the cost estimate without discounting, and scenario 8 presented the cost when applying the human capital method as an alternative for the friction cost method. Finally, in scenario 9 we again applied the human capital method, but now combined with the five annual deaths from scenario 5 whereby considering production loss up to age of retirement (i.e. 67 years). See also tables A1 and A2

Sensitivity analysis

Figure 2 and table A2 show the cost per LB outcome for the baseline and nine alternative scenarios. The human capital method[17] resulted in a 22% higher estimate (scenario 8: €23.5 million/year) than the friction cost method. In combination with possible mortality, the human capital method resulted in an even higher estimate (scenario 9: €25.6 million/year), whereas with the friction cost method mortality had hardly any influence (scenario 5). Not taking into account discounting (scenario 7) resulted in an estimate 36% above baseline. When including patients who enrolled in the survey on their own request (scenario 1), the cost was 17% higher. The total cost increased with 10%, when using higher incidence estimates (scenario 2), and decreased with 10%, when excluding the 5% most severely ill cases (scenario 3). Co-morbidity and

Table 2 Cost-of-illness of tick bites and Lyme borreliosis (LB) in the Netherlands in 2010, baseline scenario stratified for healthcare cost, patient cost, and production loss

	Cost-of-illness (95%CI*) per 16.6 million population, in million €				
	Tick bite	**EM**	**Disseminated LB**	**Lyme-related persisting symptoms**	**Total**
Healthcare cost	2.83 (2.73–2.92)	1.46 (0.93–2.05)	3.37 (1.63–5.30)	1.66 (1.34–2.02)	**9.32 (7.26–11.46)**
Patient cost	–	–	0.37 (0.01–1.03)	0.43 (0.29–0.61)	**0.80 (0.36–1.47)**
Production loss	1.48 (1.43–1.53)	1.19 (0–3.25)	3.44 (1.65–5.35)	3.06 (2.36–3.74)	**9.18 (6.64–12.01)**
Total cost	**4.31 (4.16–4.45)**	**2.66 (1.13–4.80)**	**7.18 (4.44–10.08)**	**5.16 (4.21–6.08)**	**19.30 (15.57–23.37)**

Cost is expressed in 2014 euros. The incidence per outcome was 81 997 GP consultations for tick bites, 21 802 cases of EM, 1268 cases of disseminated LB and 905 new cases with Lyme-related persisting symptoms.[6]
*: We estimated 95% confidence intervals (CI) using a bootstrap procedure with 1000 iterations while including missing values (see Appendix 1).

raising the disease duration of persisting symptoms hardly influenced the cost (scenario 4 and 6).

Discussion

We found a substantial cost-of-illness due to LB— the most frequent tick-borne infection in Europe and North America. Using incidence estimates from Hofhuis et al.[6] and a patient questionnaire on healthcare consumption and production loss, we estimated the total societal cost due to LB in the Netherlands in 2010 at €19.3 million (95% CI 15.6–23.4; 16.6 million population). Healthcare cost and production loss both constitute almost half (48%) of the total cost-of-illness, whereas patient cost were modest (4%). Of the total cost, 37% was related to disseminated LB, followed by 27% for persisting symptoms, 22% for tick bite consultations and 14% for EM. Per patient, the cost of both disseminated LB and Lyme-related persisting symptoms was very high and almost similar (€5666 and €5697 per patient); not surprisingly for the mild outcomes EM and tick bite consultations the cost per patient was much lower (€122 and €53), and their impact on the population level is thus mainly due to their high incidence.

The second highest societal cost was attributed to Lyme-related persisting symptoms (27% of the total cost), whereas it remains debated to what extent persisting symptoms attributed to LB are actually due to a current or preceding infection.[1,20,21] This implies that not all cost due to persisting symptoms may be mitigated through prevention and control of acute LB. Nevertheless, our results indicate the substantial cost due to persisting symptoms that are attributed to LB.

Our sensitivity analysis illustrated that long-term production loss has a much higher impact when using the human capital method as an alternative for the friction cost method (scenario 8 and 9, figure 2). The higher cost when including patients who enrolled in the survey on their own request (instead of through their physician), suggests that these patients are probably not representative for the cost of LB in the general population (scenario 1), which justifies their exclusion from the baseline estimate. The somewhat higher cost when using the alternative incidence estimates (scenario 2), shows that under-ascertainment may have led to some underestimation of the cost. The most severely ill cases had only a moderate impact on the total cost (scenario 3), which suggests at most a modest effect of selection bias on our baseline estimate.

To our knowledge, this is the first cost-of-illness estimate for LB that includes all possible health outcomes of LB, including tick bites and Lyme-related persisting symptoms, from a societal perspective. It adds to the few other studies that estimate the cost-of-illness of LB for countries in Europe and North America.[22–27] Most of these studies did not—or only partly—include production loss, which can be substantial as we showed in the current study. Comparing our results with these other studies is further complicated by differences in healthcare systems, the methods to attribute cost, and the disease outcomes to attribute cost to LB. An alternative for comparing the cost would be comparing the resource utilization per patient, but this is hardly reported.

For the US, Maes et al.[23] estimated an annual expenditure of 500 million USD on LB, but this estimate was based on a decision analysis model that was largely built upon assumptions and expert opinion. Also for the US, Zhang et al.[24] combined data from medical records and patient questionnaires to estimate the cost of LB, which resembles our patient data driven approach. Unfortunately, they did not report units of healthcare use, complicating direct comparison because of the differences in prices with the US. A recent study from the US by Adrion et al.[22] included Lyme-related persisting symptoms to estimate the healthcare cost due to LB. In line with our results they showed that Lyme-related persisting symptoms are associated with substantial healthcare cost.

In Europe, Joss et al.[25] reported in 2003 the cost of LB for Scotland—a country with a very low LB incidence—at £331 000. A more recent cost estimate comes from Germany, where the cost of LB was estimated around €80 million, by the combined estimations of two studies based on patient data from insurance company claims.[26,27] Comparison with our study was complicated since tick bites and persisting symptoms were not included in the German estimate, neither was production loss for outpatients. For Sweden, Henningsson et al.[28] estimated the healthcare cost of neuroborreliosis at €3300 per patient, which is quite similar to our estimate of €2660 for disseminated LB (table 1).

A limitation of our study was that we did not include the cost of long-term revalidation and nursery care, and the cost of LB serology, which were not included in the patient questionnaire. The cost of serology has been reported to be substantial in the US and Germany, with the majority of patients suspected of LB and not new incident LB cases.[26,29] The German study by Muller et al.[26] estimates a total cost of LB serology testing in Germany around €40 million per year for the 82 million population, of which only around €7 million/year was due to new LB incident cases. If we extrapolate this German data to the 16.6 million population of the Netherlands this would imply a cost of around 8 million per year for all LB serology, of which only around €1.5 million would be due to new LB incident cases. This calls for further research into the cost of LB serology in the Netherlands, not in the first place to complete the healthcare cost estimate for LB cases, but also to explore the probably much higher economic impact of serology for suspected cases. Another limitation was the exclusion of patient payments such as travel cost in our study due to misinterpretations during the data collection. Inclusion of such payments could possibly have led to up to €3.9 million higher annual costs.

Compared with other infectious diseases, our estimate of the cost of LB in the Netherlands is higher than the cost of 7 out of 14 food-borne pathogens, and comparable to the cost of *Toxoplasma gondii*

and *Salmonella* spp.[30] Restricting our estimate to the cost attributed to tick bites, EM and disseminated Lyme (together €14.1 million)—and thus ignoring the cost of persisting symptoms—does not change the ranking of LB.[30] The total cost due to LB and other infectious diseases is only marginal compared with the total Dutch healthcare expenses of 88 billion in 2010 (highest impact by mental disorders and cardiovascular disease, 20 and 9%, respectively).[31]

To reduce the cost due to LB, prevention of disseminated LB and persisting symptoms should have priority, since these go with the highest cost. In the Netherlands prevention and control has been focused on early removal of tick bites.[32] Education of physicians in the early diagnosis and treatment of EM and disseminated LB is also crucial, since this can prevent severe cases of disseminated LB and persisting symptoms. In the last decade, additional research has been launched into control measures to reduce tick abundance, into mechanisms that lead to persisting symptoms,[33] and into development of a vaccine against LB and tick bites.[34] The results of these studies will possibly lead to additional prevention and treatment strategies. The result of the current study can facilitate cost-effectiveness studies of such interventions.

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Conflicts of interest: None declared.

Key points

- We estimated the cost-of-illness of LB in the Netherlands from a societal perspective, including healthcare cost, patient cost and production loss.
- This is the first cost estimate of LB that includes all possible health outcomes of LB—including tick bites and Lyme-related persisting symptoms—which makes our results relevant for public-health prioritization in all countries where the disease is endemic.
- We found that the cost-of-illness is substantial compared with other infectious diseases: on the population level the cost are higher than for 7 out of 14 food-borne pathogens.
- The observed cost due to disseminated LB and Lyme-related persisting symptoms—both on population level and per case—calls for further research into additional prevention and treatment strategies.

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Appendix 1

Patient questionnaire

We used a patient questionnaire to estimate duration of disease and cost-of-illness per symptomatic LB outcome. The questionnaire contained questions about disease severity,[1] disease duration and questions about healthcare consumption and work absenteeism adapted from the Tic-P questionnaire.[2] More specifically the patients were asked to provide the following data:

- The start date of their episode-of-illness;
- The end date of their episode-of-illness, if the disease was no longer present; otherwise the date of patient questionnaire completion was noted;
- Number of LB related contacts with an health care provider in the past 12 months (GP, medical specialist, paramedic care provider, complementary healthcare provider, medical surgeons, hospital and intensive care unit);
- (Average) Number of weekly hours of contact with formal home care in the past 4 weeks;
- The types of drugs, the number of days these drugs were taken, and the daily dosage in the past 4 weeks;
- ''other'' costs: total costs incurred in the past 4 weeks (such as travel costs);
- Duration in time in which absenteeism from work had occurred, due to Lyme. Absenteeism was recorded in four degrees: 100%, >50%, 50% and <50%; in the calculations this was implemented as 100%, 75%, 50% and 25%, respectively.

The questions about onset and end of disease resulted in an estimate of disease duration for each respondent, which can be regarded as right-censored, because the survey is held at a specific point of time at which the episode-of-illness may not have yet ended; the response variables concerning healthcare providers and absenteeism are interval-censored, because these variables pertain to the last 12 months or 4 weeks only.

Estimation of duration of disease and mean lifetime cost per outcome

Estimation of the mean lifetime cost per outcome was complicated by the censored durations of symptoms and cost histories in our patient data. To overcome this, the mean lifetime cost per patient was estimated for each symptomatic LB outcome in four steps: (a) estimate mean duration of symptoms, (b) recreate cost histories over time, (c) estimate average cost per time interval during disease and (d) estimate the mean cost per disease episode. Below we elaborate on each of these four steps.

a) Estimate duration of symptoms
   As described in our earlier work[1], survival analysis was applied to obtain the mean duration of symptoms for EM (5 weeks) and disseminated LB (22.5 weeks). For the outcome ''persisting symptoms'' we used the censored estimate instead (4.6 years), since very few individuals with persisting symptoms have reported that their episode of illness has ended, and thus a survival model could not be fitted.
b) Recreate cost histories over time
   We asked patients at a specific moment in time about costs in a preceding period. Then, to obtain cost histories over time we 'recreated' the cost history process by means of Monte Carlo simulation (1000 simulations). We did so by assuming that the probability of a contact with a healthcare provider (or other cost category) in a given time interval is equal to the ratio of the interval length and the sum of all time interval in a disease episode. The moments of contact and costs can then be simulated using these probabilities. For the outcome Lyme-related persisting symptoms the disease episode was relatively long and not for every time interval cost data was available in our patient data. We therefore assumed that costs were evenly distributed over time and extrapolated the administered costs to the entire disease episode.
c) Estimate mean cost per time interval during disease
   We followed Lin's method here:[3] after recreating cost histories in (b), we split up the cost histories in intervals, and simply estimated the sample mean of the costs in each interval.
d) Estimate mean cost per outcome
   We can combine estimates from (a) and (c) to estimate the mean cost per outcome as follows:

$$C = \sum_{j=0}^{M} C_j = \sum_{j=0}^{M} S_{max\,(0,j\,-\,1)}\mu_j$$

   where μ_j is the average cost per individual incurred at interval j, and S_j the cumulative fraction of individuals that has survived interval j. Thus, the weighted average costs C_j is the fraction of individuals that have survived up until j, i.e. S_{j-1} (or S_0 is $j=0$), multiplied with the average cost μ_j. M is the total number of intervals. Incomplete intervals are left out of the analysis. See also Basu and Manning.[4]

To assess the uncertainty that comes with the four steps described above, we used the following bootstrap procedure. We first made a bootstrap replicate, applied steps a/b/c/d, and saved the results. Then this process was repeated for 1000 times while including missing values. Taking the mean of these 1000 iterations gave our point estimate of costs. We regarded the intervals between the 2.5 and 97.5% quantiles as confidence interval, although it also includes the model uncertainty from the cost history recreation step.

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Table A1 Sensitivity analysis scenarios to calculate cost-of-illness due to LB based upon disease duration and costs assessed in a patient questionnaire, and incidence estimates available from Hofhuis et al.[5]

Scenarios	Criteria for included patients and parameters
Baseline estimate	-Restrict to patients that were enrolled through their physicians to estimate the disease duration and cost -discounting the cost in coming years with a rate of 4% per year -friction cost method applied to production loss[13]
Scenario 1: Include patients enrolled upon their own request	-Same as baseline AND -include patients enrolled upon their own request—i.e. mainly through the national patient association)
Scenario 2: Include less likely LB diagnoses in incidence estimates	-Same as baseline AND -Use higher LB incidence estimates that also include less likely LB diagnoses; i.e. for disseminated LB 1386 cases per year and for Lyme-related persisting symptoms 1137 cases[5]
Scenario 3: Exclude 5% patients with highest disease severity and duration	-Same as baseline BUT -exclude per LB outcome patients with the 5% highest extreme values for disability weights and disease duration
Scenario 4: No co-morbidity	-Same as baseline BUT -exclude patients with any co-morbidity
Scenario 5: Five annual deaths due to LB	-Same as baseline AND -inclusion of five deaths attributable to LB per year, the mean age of death was assumed to be the same as the mean age of people acquiring a tick bite, i.e., 39 years of age,[9] and the corresponding residual life expectancy was derived from Dutch mortality data, i.e. 43 years
Scenario 6: Adjust for censored disease duration in the persisting symptoms patients.	-Same as baseline AND -raise the disease duration for persisting symptoms patients with 25%
Scenario 7: No discounting	-Same as baseline BUT -no discounting of the cost in coming years
Scenario 8: Human capital method (instead of the friction cost method)[13]	-Same as baseline BUT -apply human capital method to production loss
Scenario 9: Human capital method[13] AND five annual deaths due to LB (5 and 8 combined)	-Same as baseline BUT inclusion of five deaths attributable to LB per year, with mean age 39 years and considering productivity losses up to age of retirement (i.e. 65 years) -apply human capital method to production loss

Table A2 Estimation of cost-of-illness of LB in the Netherlands 2010: baseline estimate vs. sensitivity analysis

Scenario	LB outcome	Enrollment	Societal cost in €per patient (95% CI*)	Annual numbers (16.6 million pop.) cases[5] (95% CI*)	Societal cost in million € per 16.6 million population (95% CI*)
Baseline estimate	**Tick bite consults**	n/a	52.53 (52.53–52.53)	81 997 (79 253–84 827)	4.31 (4.16–4.45)
	EM	(*n* = 87)	121.78 (51.72–221.13)	21 802 (21 064–22 545)	2.66 (1.13–4.80)
	Disseminated LB	(*n* = 88)	5666 (3502–7991)	1268 (1186–1353)	7.18 (4.44–10.08)
	Persisting symptoms	(*n* = 189)	5697 (4723–6693)	905 (845–966)	5.16 (4.21–6.08)
	All LB including tick bite consults				**19.30 (15.57–23.37)**
1. Include patients enrolled upon their own request	**Tick bite consults**	n/a	52.53 (52.53–52.53)	81 997 (79 253–84 827)	4.31 (4.16–4.45)
	EM	(*n* = 88)	229 (60–488)	21 802 (21 064–22 545)	4.99 (1.30–10.62)
	Disseminated LB	(*n* = 96)	6289 (4044–8835)	1268 (1186–1353)	7.97 (5.18–11.22)
	Persisting symptoms	(*n* = 476)	5896 (5131–6635)	905 (845–966)	5.34 (4.58–6.09)
	All LB including tick bite consults				**22.61 (17.32–29.03)**
2. Include less likely LB diagnoses in incidence estimates	**Tick bite consults**	n/a	52.53 (52.53–52.53)	81 997 (79 253–84 827)	4.31 (4.16–4.45)
	EM	(*n* = 87)	121.78 (51.72–221.13)	21 802 (21 064–22 545)	2.66 (1.13–4.80)
	Disseminated LB	(*n* = 88)	5666 (3502–7991)	1386 (1296–1479)	7.85 (4.85–11.02)
	Persisting symptoms	(*n* = 189)	5697 (4723–6693)	1137 (1061–1214)	6.48 (5.29–7.64)
	All LB including tick bite consults				**21.29 (17.29–25.57)**
3. Exclude 5% patients with highest disease severity and duration	**Tick bite consults**	n/a	52.53 (52.53–52.53)	81 997 (79 253–84 827)	4.31 (4.16–4.45)
	EM	(*n* = 66)	117.39 (44.14–229.70)	21 802 (21 064–22 545)	2.56 (0.96–5.00)
	Disseminated LB	(*n* = 68)	4427 (2614–6390)	1268 (1186–1353)	5.61 (3.30–8.27)
	Persisting symptoms	(*n* = 158)	5452 (4436–6634)	905 (845–966)	4.94 (3.98–6.07)
	All LB including tick bite consults				**17.42 (14.39–21.32)**
4. No co-morbidity	**Tick bite consults**	n/a	52.53 (52.53–52.53)	81 997 (79 253–84 827)	4.31 (4.16–4.45)
	EM	(*n* = 39)	188.06 (30.04–403.30)	21 802 (21 064–22 545)	4.10 (0.65–8.77)
	Disseminated LB	(*n* = 40)	4320 (2261–6441)	1268 (1186–1353)	5.48 (2.82–8.13)
	Persisting symptoms	(*n* = 75)	5831 (4151–7525)	905 (845–966)	5.28 (3.74–6.96)
	All LB including tick bite consults				**19.16 (14.12–24.78)**
5. Five annual deaths due to LB	**Tick bite consults**	n/a	52.53 (52.53–52.53)	81 997 (79 253–84 827)	4.31 (4.16–4.45)
	EM	(*n* = 87)	121.78 (51.72–221.13)	21 802 (21 064–22 545)	2.66 (1.13–4.80)
	Disseminated LB	(*n* = 88)	5666 (3502–7991)	1268 (1186–1353)	7.18 (4.44–10.08)
	Persisting symptoms	(*n* = 189)	5697 (4723–6693)	905 (845–966)	5.16 (4.21-6.08)
	Assumed nr of 5 deaths	n/a	5445	5	0.03
	All LB including tick bite consults				**19.33 (15.60–23.40)**
6. Adjust for censored disease duration in the persisting symptoms patients	**Tick bite consults**	n/a	52.53 (52.53–52.53)	81 997 (79 253–84 827)	4.31 (4.16–4.45)
	EM	(*n* = 87)	121.78 (51.72–221.13)	21 802 (21 064–22 545)	2.66 (1.13–4.80)
	Disseminated LB	(*n* = 88)	5666 (3502–7991)	1268 (1186–1353)	7.18 (4.44–10.08)
	Persisting symptoms	(*n* = 189)	5792 (4822–6778)	905 (845–966)	5.24 (4.28–6.19)
	All LB including tick bite consults				**19.39 (15.66–23.42)**
7. No discounting	**Tick bite consults**		52.53 (52.53–52.53)	81 997 (79 253–84 827)	4.31 (4.16–4.45)
	EM		121.78 (51.72–221.13)	21 802 (21 064–22 545)	2.66 (1.13–4.80)
	Disseminated LB		5685 (3502–8008)	1386 (1296–1479)	7.21 (4.44–10.13)
	Persisting symptoms		13 373 (10 739–16 483)	1137 (1061–1214)	12.11 (9.49–15.07)
	All LB including tick bite consults				**26.28 (21.44–31.44)**
8. Human capital method (instead of the friction cost method[13])	**Tick bite consults**		52.53 (52.53–52.53)	81 997 (79 253–84 827)	4.31 (4.16–4.45)
	EM		121.78 (51.72–221.13)	21 802 (21 064–22 545)	2.66 (1.13–4.80)
	Disseminated LB		6198 (3845–8800)	1386 (1296–1479)	7.86 (4.89–11.13)
	Persisting symptoms		9620 (7752–11 483)	1137 (1061–1214)	8.71 (6.96–10.44)
	All LB including tick bite consults				**23.53 (19.09–28.08)**
9. Human capital method[13] AND five annual deaths due to LB	**Tick bite consults**	n/a	52.53 (52.53–52.53)	81 997 (79 253–84 827)	4.31 (4.16–4.45)
	EM	(*n* = 87)	121.78 (51.72–221.13)	21 802 (21 064–22 545)	2.66 (1.13–4.80)
	Disseminated LB	(*n* = 88)	6198 (3845–8800)	1386 (1296–1479)	7.86 (4.89–11.13)
	Persisting symptoms	(*n* = 189)	9620 (7752–11 483)	1137 (1061–1214)	8.71 (6.96–10.44)
	Assumed nr of 5 deaths	n/a	405 210	5	2.03
	All LB including tick bite consults				**25.55 (21.12–30.11)**

For each scenario in the sensitivity analysis the table shows the cost estimates per patient, and the costs per population based on the annual incidence per LB outcome. Cost is expressed in 2014 euros. See also figure 3.

*: We estimated 95% confidence intervals (CI) using a bootstrap procedure with 1000 iterations while including missing values.

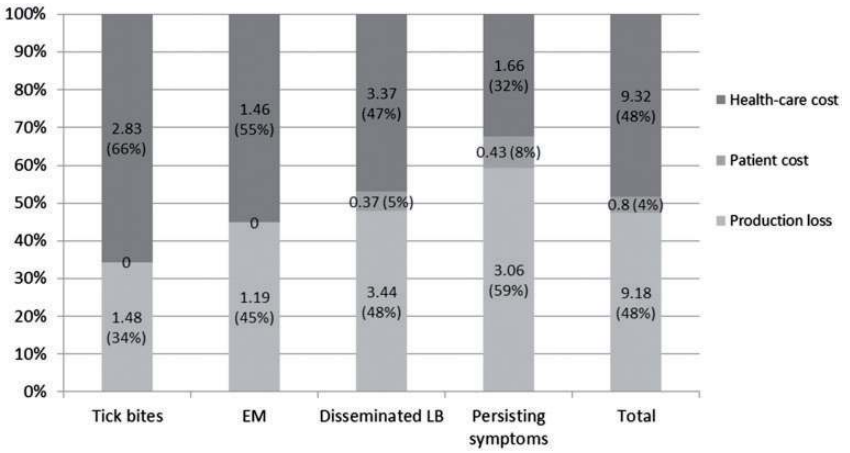

Figure A1 Cost-of-illness due to tick bites and LB, stratified for healthcare cost, patient cost and production loss. Cost is presented in million € and % per outcome for the Netherlands in 2010 for the baseline total cost estimate of €19.3 million (16.6 million population). Cost is expressed in 2014 euros