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Research

Estimating the population health burden of Lyme disease in Ontario, Canada: a microsimulation modelling approach

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Abstract

Background: If untreated, Lyme disease can lead to long-term sequelae and post-treatment Lyme disease syndrome (PTLDS), resulting in reduced health-related quality of life. The objective of this study was to develop a microsimulation model to estimate the population-level health burden of Lyme disease in Ontario, Canada.

Methods: We developed a Lyme disease history model using microsimulation, simulating 100 000 people (mean age 37.6 yr, 51% female) from 2017 in Ontario over a lifetime risk of infection and time horizon. We extracted the sensitivity and specificity of the 2-tier testing recommended by the Canadian Public Health Laboratory Network, probabilities and health state utility values from the published literature and health administrative data. Our reported outcomes from our stochastic analysis include diagnosed cases of Lyme disease (stratified by stage), undiagnosed infections, sequelae, individuals with PTLDS and quality-adjusted life-years (QALYs) lost.

Results: Our model estimated 333 (95% confidence interval [CI] 329–337) infections over the lifetime of 100 000 simulated people (mean age 37.6 yr, 51% female), with 92% (95% CI 91%–93%) of infections diagnosed. Of those 308 people with Lyme Disease diagnoses, 67 (95% CI 65–69) developed sequelae (e.g., arthritic, cardiac, neurologic sequelae), and 34 (95% CI 33–35) developed PTLDS. Lyme disease resulted in a loss of 84.5 QALYs (95% CI 82.9–86.2) over the lifetime of the simulated cohort. Sensitivity and scenario analysis showed that increasing incidence rates of Lyme disease, potential underreporting, duration of PTLDS and quality of life (health state utility) associated with PTLDS had the greatest impact on health burden.

Interpretation: Lyme disease contributes considerable health burden in terms of QALYs lost. Our analysis provides evidence to understand the disease burden and lays the foundation to assess the cost-effectiveness of pharmaceutical and nonpharmaceutical interventions.

Lyme disease is the most commonly reported vector-borne disease in North America,[1–3] with annual incidence rates of up to 130 per 100 000 people in Maine, United States,[4] and 85 per 100 000 people in high-risk areas of Ontario, Canada.[5] If Lyme disease is untreated in its early stages, it can lead to Lyme meningitis, cranial nerve neuropathies (e.g., Bell palsy), Lyme carditis and Lyme arthritis.[6] Treated patients may be at risk of post-treatment Lyme disease syndrome (PTLDS), defined as persistent symptoms for at least 6 months after treatment of Lyme disease that was documented by a physician and treated with standard-of-care antibiotics.[7] A systematic review of long-term sequelae and health-related quality of life of patients with confirmed Lyme disease showed that PTLDS may result in impaired quality of life.[8]

Three Markov cohort models have been developed to assess the cost-effectiveness of vaccination for Lyme disease,[9-11] and a fourth model was developed to assess the cost-effectiveness of oral antibiotic therapy.[12] However, these models assumed a homogeneous population, did not incorporate the issue of Lyme disease diagnosis (e.g., clinical v. diagnostic tests, stage of Lyme disease and associated test sensitivity), individual-level characteristics or the entire disease progression of Lyme disease (i.e., PTLDS).

The individual- and population-level burdens of Lyme disease are not well understood for several reasons, including the relative novelty of the disease in certain regions of North America, low incidence rates and lack of follow-up on long-term outcomes. In these instances, microsimulation models can simulate the disease history of Lyme disease based on current evidence from the literature and surveillance programs to inform estimates of its impact on health outcomes. New models should include updated case definitions, diagnostic effectiveness, treatment and disease progression. The objective of

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this study was to estimate the health burden of Lyme disease, including cases, outcomes and quality-adjusted life-years (QALYs), in Ontario, Canada, using an individual-level, state-transition model.

Methods

Design, setting and population

We developed an individual-level, state-transition model to simulate a cohort representative of the population of Ontario in 2017.

We simulated a cross-sectional cohort of 100 000 people in Ontario in accordance with Ontario demographics (mean 37.6 yr, standard deviation [SD] 22.7 yr, 51% female), representing 63% of the total population (8.8 million of 14 million) residing in high-risk areas (Mark Nelder, Public Health Ontario, Toronto, Ont.: personal communication, 2021). The average life expectancy of Ontarians of our cohort was 81.0 years, simulating a lifetime risk of Lyme disease of about 43 years.

We sampled individual characteristics (i.e., age, sex, risk area of residence) from distributions informed by census data (details about sampling are described in Appendix 1, Section 1, available at www.cmajopen.ca/content/9/4/E1005/suppl/DC1).[13] We designated possible health states as healthy, undiagnosed infection, diagnosed Lyme disease at various stages of disease or recovery. The model used weekly cycle lengths (i.e., each timestep in the model represents a week).

Outcomes

We reported health outcomes per 100 000 people, including the number of cases of Lyme disease (diagnosed at the early localized, early disseminated and late disseminated stages), frequency of different types of sequelae (including PTLDS) and QALYs. Outcomes were accrued over the patient's lifetime and discounted at 1.5% to account for time preference of health outcomes.[14] We conducted all modelling and analyses using Treeage.

Model structure

Lyme disease incidence and exposure

We assumed that individuals enter the model in a healthy (susceptible) state (Figure 1), with a probability that these individuals can be bit by an infected tick and develop Lyme disease according to age- and sex-dependent incidence rates. Age-dependent incidence rates ranged between 2.9 and 10 per 100 000 females, and 5.0 and 13.9 per 100 000 males in 2017 (Appendix 1, Section 2).[5]

People who develop an erythema migrans rash may receive a clinical diagnosis and transition to the early localized health state. Those who present with erythema migrans can be misdiagnosed depending on clinician awareness of Lyme disease,[13] and remain undiagnosed in the undiagnosed infection state, where they may have decreased quality of life, eventually receive a diagnosis or remain undiagnosed. The likelihood of

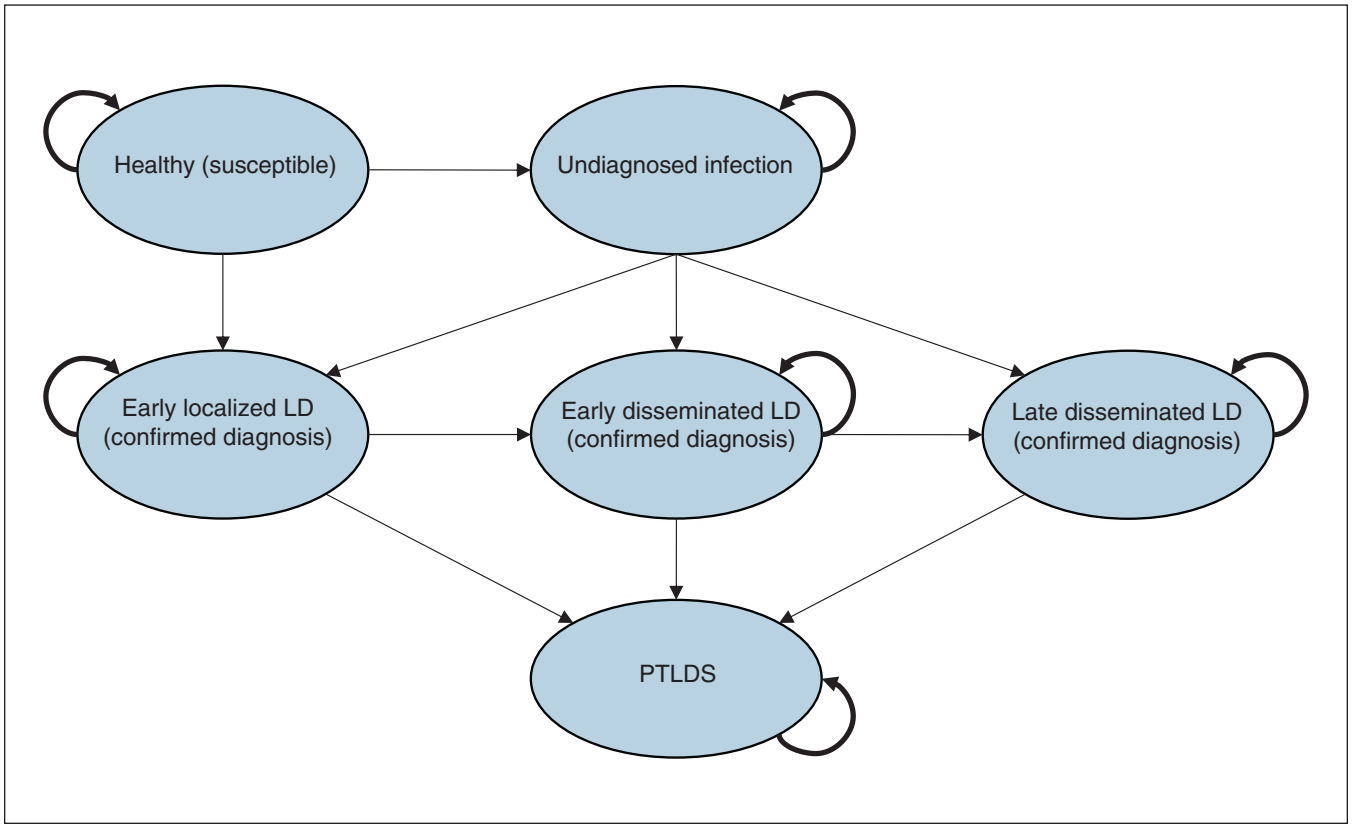

Figure 1: Model schematic of individual state-transition model. Note: LD = Lyme disease, PTLDS = post-treatment Lyme disease syndrome. Within the states of Lyme disease, individuals can develop sequelae. Individuals can recover to a healthy state from any state of Lyme disease.

clinical diagnosis after presenting with erythema migrans in high- and low-exposure areas was 58% and 26%, respectively.[15] Once a diagnostic test confirms Lyme disease, individuals transition to the early localized, early disseminated or late disseminated health states, depending on the time since initial infection, which is defined in this model as between 0 and 30 days, 31 and 90 days, and 91 days and onwards, respectively.[16]

Diagnostic testing

The model incorporated 2-tier tests (e.g., immunoglobulin [Ig] M/IgG ELISA, Western blot), recommended by the Canadian Public Health Laboratory Network.[17] Two-tier tests with negative or positive results are returned within 1 or 2 weeks, respectively.[17] Individuals in the undiagnosed infection state have a weekly probability of getting tested depending on whether or not they develop sequelae. An average of 80.4% (63% to 98%, depending on sequelae) of individuals would be tested if presenting with sequelae from the initial infection, and 40.2% if not.[15]

We extracted sensitivity and specificity from a meta-analysis, stratified by stage of Lyme disease. The sensitivity for early localized, early disseminated and late disseminated Lyme disease was 46.3%, 89.7% and 99.4%, respectively, and the specificity was between 99.3% and 99.7%.[18]

Sequelae and manifestations of Lyme disease

In the early disseminated stage, multiple erythema migrans, cardiac abnormalities, cranial nerve palsies and other neurologic sequelae (meningitis and polyneuropathy) can develop, whereas in the late disseminated stage, arthritic and cognitive sequelae can develop.[8] The 1-year, sex-dependent probability of developing early disseminated and late disseminated stage sequelae was 17%, and 10% to 11%, respectively, as informed by population-based health administrative data in Ontario (Table 1, details in Appendix 1, Section 3). Hospitalizations from disseminated stages of Lyme disease can result in lower quality of life for a short period.

Individuals with clinically diagnosed Lyme disease or with laboratory confirmation receive 2 to 3 weeks of oral antibiotics, which may be followed by subsequent courses of intravenous antibiotics, depending on sequelae.[27] We define treatment success as an absence of sequelae or manifestations of the respective stage of Lyme disease (i.e., no more persistent symptoms). On treatment, individuals have a 4% to 6% chance of having minor or major adverse events from antibiotic treatment,[12] and an 85% to 95% chance of recovery.[19–24] Unsuccessful treatment leads to possible development of PTLDS; we assumed, with expert guidance, that PTLDS persists for 5 years. After recovery from any stage of Lyme disease, individuals are assumed to be immune from reinfection for 6 months.

Utilities

Health state utility values are preference values for being in a health state, used to measure the quality of life (morbidity) in conjunction with life-years to output QALYs.[28] Mean utility values for the Ontario population ranged from 0.62 to 0.90, depending on age and sex.[13] We extracted utilities for the health states of Lyme disease from a systematic review,[8] corresponding to the experienced sequelae. For instance, an individual with cranial nerve palsy would have a utility of 0.61, whereas PTLDS is associated with a utility of 0.54.[10] All parameters are summarized in Table 1.

Statistical analysis

We ran 100 simulations of 100 000 individuals with a risk of Lyme disease infection throughout their lifetime, assuming that treatment starts after diagnosis (clinical or laboratory diagnosis). We calculated the mean (95% confidence intervals [CIs]) and median (interquartile range [IQR]) incidence for outcomes per 100 000 people.

Assessing uncertainty

For scenario and sensitivity analyses, we used a seeded deterministic simulation for computational efficiency and to illustrate the impact of the variable of interest, within its specified range, on the results, while keeping all other parameters and processes identical (Table 1). In the scenario of increasing incidence rates of Lyme disease, we increased the incidence annually by 1 per 100 000 people for each age group for the subsequent 10 years. All scenarios are described in Appendix 1, Section 4.

We also simulated the health burden for 1 million people (using a similar mean age, sex and proportion of endemic residence in Ontario in 2017), over a 1-year risk of Lyme disease to contextualize annual health burden. We conducted a deterministic 1-way sensitivity analysis to assess the robustness of model results to key parameters and associated uncertainty. We followed modelling best practices; 2 clinical experts (authors G.A.E. and S.N.P.) internally validated the model, which we also externally validated to observational data from the literature.[29]

Ethics approval

We did not require ethics approval for this type of modelling study.

Results

Using our cross-sectional cohort of 100 000 people in Ontario, we estimated a mean of 333 (95% CI 329–337) infections per 100 000 people, of which 4 (95% CI 3–4; 1.3%) were reinfections. From these 333 people with infections, an average of 308 (95% CI 304–311; 92%) had Lyme disease diagnosed, and 26 (95% CI 25–27; 8%) remained undiagnosed. All results are summarized in Table 2.

The mean age at the time of infection was 54.6 (SD 17.9) years, with most infections in the 50–55 and 60–65 year age groups (Appendix 1, Section 5). The median duration of Lyme disease infection was 7 (range 2–260) weeks (Appendix 1, Section 5). The median time from infection to diagnosis, and from infection to treatment was 5 (IQR 3–6), and 6 (IQR 4–7) weeks, respectively (Appendix 1, Section 5).

Of the people with diagnoses, an average of 107 (95% CI 105–109; 32%) were diagnosed at the early localized stage, of which 44 (95% CI 43–46; 13%) were clinically diagnosed, and 63 (95% CI 62–64; 19%) were diagnosed through laboratory confirmation. Laboratory-confirmed diagnosis of early disseminated and late disseminated cases occurred in an average of 137 (95% CI 134–140; 41%), and 63 (95% CI 61–65; 19%) infections, respectively.

Table 1 (part 1 of 2): Key parameters and data sources

Parameter	Base case value (range)*	Data sources
Key Lyme disease probability parameters and data sources		
Lyme disease		
Probability of high-risk exposure	0.628 (0.471–0.786)†	Personal communication, PHO
LD incidence rates, per 100 000 (varies by age and sex)	2.9–13.9 (0.000029–0.000139)‡	Nelder et al. 2018[5]
Probability of clinical diagnosis after EM rash, high-risk exposure area	0.583 (0.437–0.729)‡	Henry et al. 2012[15]
Probability of clinical diagnosis after EM rash, low-risk exposure area	0.261 (0.196–0.326)†	Henry et al. 2012[15]
Diagnostics		
Sensitivity, early localized	0.463 (0.391–0.537)§	Waddell et al. 2016[18]
Sensitivity, early disseminated	0.897 (0.783–0.954)§	Waddell et al. 2016[18]
Sensitivity, late disseminated	0.994 (0.957–0.999)§	Waddell et al. 2016[18]
Specificity, early localized	0.993 (0.983–0.997)§	Waddell et al. 2016[18]
Specificity, early disseminated	0.997 (0.984–0.999)§	Waddell et al. 2016[18]
Specificity, late disseminated	0.993 (0.985–0.997)§	Waddell et al. 2016[18]
Probability of testing (varies by presence or absence of sequelae)	0.402–0.805 (0.30–0.98)†	Henry et al. 2012[15]
Delay in results	1–2 wk	PHO 2017[17]
Treatment		
Treatment efficacy		
Erythema migrans	0.85 (0.80–1.00)‡	Magid et al. 1992[19]
Arthritic sequelae	0.85 (0.40–0.80)‡	Liu et al. 1989[20]
Cardiac sequelae	0.90 (0.80–1.00)‡	Steere et al. 1993[21]
Neurologic sequelae	0.90 (0.76–0.97)‡	Logigian and Steere 1992[22] Dattwyler et al. 1988[23] Karlsson et al. 1994[24]
Oral treatment completion	0.90 (0.68–1.00)†	Magid et al. 1992[19]
IV treatment completion	0.99 (0.75–1.00)†	Magid et al. 1992[19]
Probability of adverse event, oral	0.04 (0.03–0.05)†	Shadick et al. 2001[10]
Probability of adverse event, IV	0.06 (0.05–0.08)†	Shadick et al. 2001[10]
Outcomes		
Probability of hospitalization	0.05 (0.04–0.06)†	Shing et al. 2019[25]
Length of hospitalization, d	7.9 (3.8–12.1)§	Shing et al. 2019[25]
EM rash	0.80 (0.60–1.00)†	Shadick et al. 2001[10]
Probability of developing sequelae (varies by LD stage and sex)	0.10–0.17 (0.08–0.21)†	Unpublished data from cited study[26]**
Arthritic sequelae (M, F)	0.56–0.63 (0.41–0.76)†	Unpublished data from cited study[26]**
Cardiac sequelae (F, M)	0.43–0.48 (0.29–0.53)†	Unpublished data from cited study[26]**
Cognitive sequelae (F, M)	0.37–0.44 (0.29–0.58)†	Unpublished data from cited study[26]**
Cranial nerve palsy sequelae (F, M)	0.11–0.24 (0.08–0.26)†	Unpublished data from cited study[26]**
Multiple EM sequelae (M, F)	0.22–0.36 (0.16–0.40)†	Unpublished data from cited study[26]**
Meningitis or polyneuropathy sequelae (F, M)	0.06–0.11 (0.12–0.24)†	Unpublished data from cited study[26]**

Table 1 (part 2 of 2): Key parameters and data sources

Parameter	Base case value (range)*	Data sources
Key utility parameters and data sources		
Utilities		
Healthy, stratified by age and sex	0.62–0.90 (0.38–0.98)§	Guertin et al. 2018[13]
Arthritic sequelae	0.69 (0.51–0.86)¶	Shadick et al. 2001[10]
Cardiac sequelae	0.61 (0.38–0.78)¶	Shadick et al. 2001[10]
Cognitive sequelae	0.60 (0.37–0.73)¶	Shadick et al. 2001[10]
Erythema migrans	0.80 (0.70–0.93)¶	Shadick et al. 2001[10]
Cranial nerve palsy	0.61 (0.36–0.81)¶	Shadick et al. 2001[10]
Meningitis or polyneuropathy	0.52 (0.27–0.73)¶	Shadick et al. 2001[10]
PTLDS	0.54 (0.30–0.70)¶	Shadick et al. 2001[10]
Minor adverse events, disutility	0.05 (0.04–0.06)†	Eckman et al. 1997[12]
Major adverse events, disutility	0.10 (0.08–0.13)†	Eckman et al. 1997[12]
Oral treatment, disutility	0.01 (0.00–0.01)†	Eckman et al. 1997[12]
Intravenous treatment, disutility	0.03 (0.02–0.04)†	Eckman et al. 1997[12]

Note: CI = confidence interval, EM = erythema migrans, F = female, IQR = interquartile range, IV = intravenous, LD = Lyme disease, M = male, PHO = Public Health Ontario, PTLDS = post-treatment Lyme disease syndrome.
*Type of range varies by study, as indicated.
†Range represents plausible range.
‡Range represents full range.
§Range represents 95% CI.
¶Range represents IQR.
**Study authors provided these data.

Within the early disseminated stage, 12 (95% CI 12–13) people developed disseminated or multiple erythema migrans, 8 (95% CI 7–8) developed cranial nerve palsy, 20 (95% CI 19–20) developed cardiac abnormalities and 4 (95% CI 3–4) developed other neurologic sequelae (e.g., meningitis, polyneuropathy). Of those with late disseminated Lyme disease, 14 (95% CI 13–15) developed arthritis and 9 (95% CI 9–10) developed cognitive sequelae. Of all people with diagnoses, 34 (95% CI 33–35) developed PTLDS. Over the lifetime of 100 000 people, Lyme disease resulted in a mean loss of 84.5 (95% CI 82.9–86.1) QALYs, discounted at 1.5%, or 112.6 (109.6–115.4) QALYs undiscounted.

In the deterministic simulation of the cross-sectional cohort of 1 million people (Appendix, Section 6), there were 53 Lyme disease infections, mostly diagnosed at the early localized (40%) and early disseminated stages (38%). About 9% of people had a diagnosis of PTLDS, and no one was reinfected, which was as predicted, given the low probability of being reinfected within 1 year. In this scenario, 1 year of risk of Lyme disease infection resulted in 19.4 QALYs lost. For Ontario (with its population of about 14 million), this translates to 271 QALYs lost in 1 year.

Assessing uncertainty

The tornado diagram (Figure 2) summarizes multiple 1-way sensitivity analyses of the impact of all parameters on QALYs lost using a seeded simulation (i.e., 1 constant simulation), where 70.6 QALYs were lost because of Lyme disease. The following parameters (within their plausible range) have the most impact: duration of the PTLDS stage, utility value for PTLDS, probability of full recovery after treatment, probability of developing an erythema migrans rash and diagnostic test performance.

When the duration of PTLDS state was 1 year, 50.4 QALYs are lost, whereas being in the PTLDS health state for an average of 10 years resulted in 87.8 QALYs lost. At the higher estimate for PTLDS utility value of 0.70, 58.3 QALYs were lost. A lower utility value of 0.30 resulted in 89.1 QALYs lost. With the probability of recovery at its upper limit (e.g., close to 100% chance of recovery), there is a total of 68.5 QALYs lost, whereas the lower limit resulted in 86.0 QALYs lost.

The other major influential parameter was the incidence of Lyme disease (Appendix 2). In a scenario where incidence rates increased by 1 per 100 000 people annually over the subsequent 10 years, 165.5 QALYs were lost. Underreporting factors of 3 (Canadian estimate), and 10 (US estimate) resulted in 257.5 and 881.3 QALYs lost, respectively (Appendix 1, Section 4).

Interpretation

We developed an individual-level state-transition model to estimate the health burden of Lyme disease over the lifetime of 100 000 people in Ontario. Lyme disease resulted in 84 QALYs lost, with 22% of people developing sequelae and

Table 2: Base-case results of 100 simulations of 100 000 people in Ontario with lifetime risk of Lyme disease

Outcomes	Mean incidence per 100 000 (95% CI)	Proportion of mean incidence of total LD infections, %*	Median incidence per 100 000 (IQR)	Proportion of median incidence of total LD infections, %*
Total LD infections	333 (329–337)		334 (320–346)	
Diagnosed cases	308 (304–311)	92.5	308 (294–321)	92.2
Early localized	107 (105–109)	32.1	108 (100–116)	32.3
Clinically diagnosed	44 (43–46)	13.2	45 (38–49)	13.5
Laboratory-confirmed	63 (62–64)	18.9	63 (58–68)	18.9
Early disseminated (laboratory-confirmed)	137 (134–140)	41.1	137 (129–144)	41.0
Late disseminated (laboratory-confirmed)	63 (61–65)	18.9	63 (58–69)	18.9
Undiagnosed cases	26 (25–27)	7.8	26 (22–29)	7.8
Reinfections	4 (3–4)	1.2	4 (2–5)	1.2
Sequelae				
Early disseminated stage				
Cardiac	20 (19–20)	6.0	19 (17–22)	5.9
Cranial nerve palsy	8 (7–8)	2.4	9 (6–10)	2.7
Multiple erythema migrans	12 (12–13)	3.6	12 (10–15)	3.6
Neurological (meningitis, polyneuropathy)	4 (3–4)	1.2	3 (2–5)	0.9
Late disseminated stage				
Arthritic	14 (13–15)	4.2	14 (12–16)	4.2
Cognitive	9 (9–10)	2.7	9 (7–11)	2.7
All stages				
PTLDS	34 (33–35)	10.2	34 (31–37)	10.2
QALYS				
Undiscounted	112.6 (109.6–115.4)		113.0 (105.7–120.1)	
Discounted (1.5%)	84.5 (82.9–86.1)		84.6 (78.6–88.8)	

Note: CI = confidence interval, IQR = interquartile range, LD = Lyme disease, PTLDS = post-treatment Lyme disease syndrome, QALY = quality-adjusted life-year.
*Mean and median frequency may not sum up exactly because of rounding.

10% developing PTLDS. The duration and quality of life associated with PTLDS had a substantial effect on the overall burden. Our sensitivity analyses suggest that the disease progression toward PTLDS substantially contributes to the health burden associated with Lyme disease infections. Further research and understanding of PTLDS can aid in reducing the health burden of Lyme disease.

Our model was internally validated by clinical experts and was compared with the literature for external validation using health outcomes and estimated QALYs lost. We estimated that 10% of cases develop PTLDS, which is consistent with the lower range of what has been reported in the literature (10%–20%).[30] Since reinfection rates in Ontario, Canada are not accessibly reported, our 1.3% estimated probability of reinfection was similar to estimates of 1.2 to 1.7% for adults in the US,[31] and lower than 3.4% in hyperendemic areas in the US.[32]

We also compared our model to a descriptive study of cases of Lyme disease in Ontario from 2005 to 2014. The proportion of people notifying public health systems within 30 days, 1–3 months and > 3 months of symptom onset was 45.2%, 38% and 16.8%, respectively.[33] Our model similarly estimated that 32% of diagnosed (and reported) cases were diagnosed within 30 days, 41% were within 1–3 months, and 19% were after 3 months. The slight differences between our results can be attributed to how our model considers the stage of Lyme disease at diagnosis based on time from tick bite or infection, and sequelae developed after infection, which is difficult to identify using administrative data.

Estimates of QALYs lost from Lyme disease and other infectious diseases are limited. An Ontario Burden of Infectious Diseases study from 2012 estimated the annual burden of 51 infectious diseases in health-adjusted life-years (HALYs), a composite measure similar to the QALY that incorporates both mortality (years of life lost) and morbidity (year-equivalents of reduced functioning).[34] In an indirect comparison, the annual burden of Lyme disease (271 QALYs) is similar in magnitude to herpes simplex virus (256 HALYs)

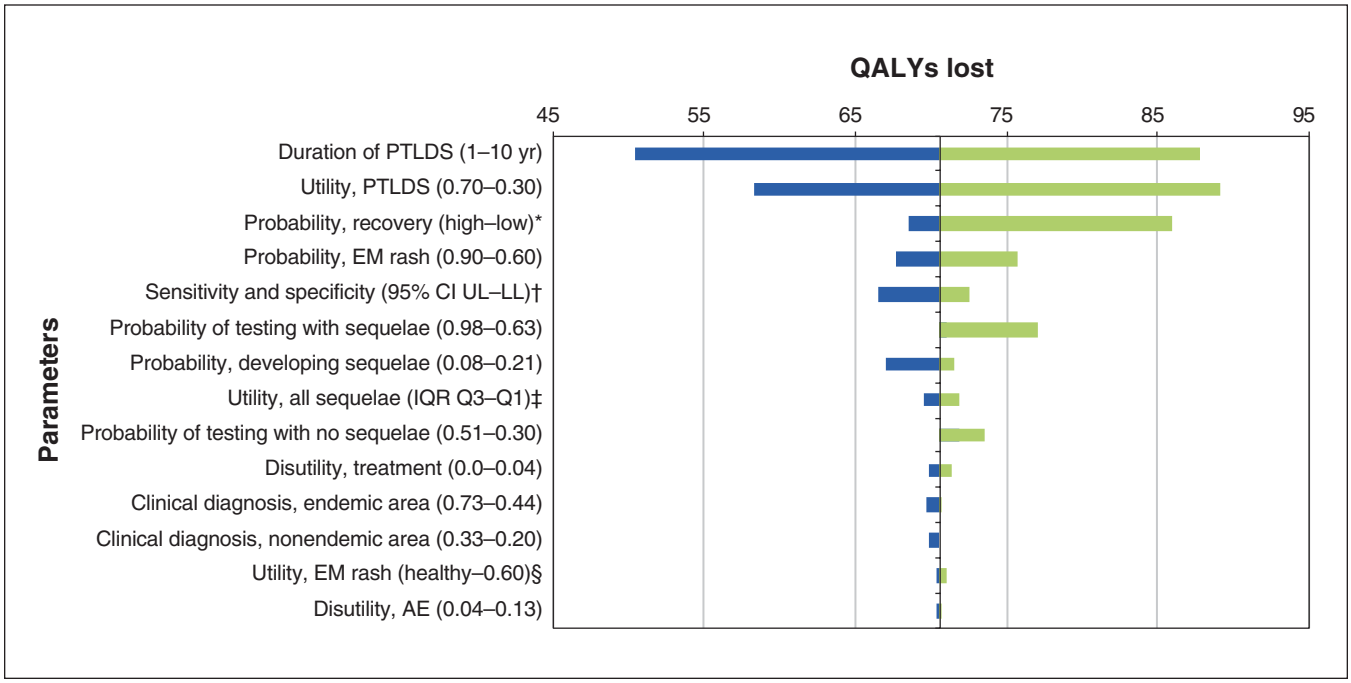

Figure 2: Sensitivity analysis of key parameters on quality-adjusted life-years (QALYs) lost over the lifetime of 100 000 people in Ontario in a seeded deterministic simulation, using a base-case reference of 70.6 QALYs lost because of Lyme disease. Note: AE = adverse event, CI = confidence interval, EM = erythema migrans, IQR = interquartile range, LL = lower limit, PTLDS = post-treatment Lyme disease syndrome, Q1 = quartile 1, Q3 = quartile 3, UL = upper limit. *Lower range is 75% of the recovery parameter (varies by sequelae). †Upper and lower limits of the 95% CI for diagnostic test characteristics (values in Table 1). ‡Q1 values for low values, Q3 values for high values, simultaneously for all sequelae utility values. §Equivalent to having a utility value of a healthy person (varies by age and sex).

and pertussis (220 HALYs), a pathogen that did not contribute any years of life lost, but many year-equivalents of reduced functioning.[34]

Modelled scenarios also suggest that the health burden resulting from Lyme disease can be reduced by introducing interventions to lower the ecological transmission of *Borrelia burgdorferi* in hosts to reduce incidence rates, or by reducing the number of people who may be susceptible to Lyme disease. Previous Markov models assessing the cost-effectiveness of a vaccine for Lyme disease concluded that the disease's incidence rate greatly influences the economic value of interventions.[9,10]

Limitations

We may have underestimated the probability of developing sequelae as we extracted it from an Ontario cohort with laboratory-confirmed Lyme disease from 2006 to 2013, when incidence rates of Lyme disease were lower. To date, there are limited observational studies reporting health outcomes of Lyme disease in Canada;[25,35] hence, we were unable to compare results of our study.

Much remains unclear about PTLDS, including its diagnosis, treatment and recovery.[36] As a result, we had to assume the average duration of the PTLDS health state. In our sensitivity analysis, we showed that PTLDS (duration and utility value) influenced QALYs lost, indicating that this is an area for future research. Our model does not consider seasonality because it affects the rate, but not the severity of disease; we assumed that the health burden of Lyme disease can be simplified to result from a uniform infection risk throughout the year.

This individual-level state-transition model simulated the disease history of Lyme disease from infection to the end of life, capturing individual differences (e.g., age, sex, probability of residing in high-risk areas) to estimate population-level health burden. A modelling approach allows for the estimation of the number of infections that may not be captured by the health care system (e.g., observational studies using administrative data) capturing their expected burden and converting it to QALYs. This approach is critical in understanding the overall burden of Lyme disease as it captures the reduction in quality of life, given that Lyme disease rarely results in death. Decision-makers can adapt this model to evaluate the effectiveness, costs and value of a potential vaccine, awareness and education campaigns, improved diagnostics, or interventions to reduce the probability of an infected individual developing PTLDS.

Conclusion

Based on our model, Lyme disease infection in Ontario, Canada, contributes considerable health burden as measured by QALYs, resulting from potential sequelae, undiagnosed cases and individuals with PTLDS. The incidence rate of Lyme disease, and the duration of PTLDS and associated quality of life, were most influential to model results and should be the focus of future research and interventions.

References

1. Why is CDC concerned about Lyme disease? Atlanta: Centers for Disease Control and Prevention; reviewed 2021 Jan. 13. Available: https://www.cdc.gov/lyme/why-is-cdc-concerned-about-lyme-disease.html (accessed 2020 Aug. 3).
2. Rochlin I, Ninivaggi DV, Benach JL. Malaria and Lyme disease: the largest vector-borne US epidemics in the last 100 years — success and failure of public health. *BMC Public Health* 2019;19:804.
3. Mead PS. Epidemiology of Lyme disease. *Infect Dis Clin North Am* 2015;29:187-210.
4. Lyme disease data tables: historical data. Atlanta: Centers for Disease Control and Prevention; reviewed 2021 May 5. Available: https://www.cdc.gov/lyme/stats/tables.html (accessed 2018 Feb. 5).
5. Nelder MP, Wijayasri S, Russell CB, et al. The continued rise of Lyme disease in Ontario, Canada: 2017. *Can Commun Dis Rep* 2018;44:231-6.
6. Kugeler KJ, Griffith KS, Gould LH, et al. A review of death certificates listing Lyme disease as a cause of death in the United States. *Clin Infect Dis* 2011;52:364-7.
7. Aucott JN. Posttreatment Lyme disease syndrome. *Infect Dis Clin North Am* 2015;29:309-23.
8. Mac S, Bahia S, Simbulan F, et al. Long-term sequelae and health-related quality of life associated with Lyme disease: a systematic review. *Clin Infect Dis* 2020;71:440-52.
9. Hsia EC, Chung JB, Schwartz JS, et al. Cost-effectiveness analysis of the Lyme disease vaccine. *Arthritis Rheum* 2002;46:1651-60.
10. Shadick NA, Liang MH, Phillips CB, et al. The cost-effectiveness of vaccination against Lyme disease. *Arch Intern Med* 2001;161:554-61.
11. Meltzer MI, Dennis DT, Orloski KA. The cost effectiveness of vaccinating against Lyme disease. *Emerg Infect Dis* 1999;5:321-8.
12. Eckman MH, Steere AC, Kalish RA, et al. Cost effectiveness of oral as compared with intravenous antibiotic therapy for patients with early Lyme disease or Lyme arthritis. *N Engl J Med* 1997;337:357-63.
13. Guertin JR, Feeny D, Tarride JE. Age- and sex-specific Canadian utility norms, based on the 2013–2014 Canadian Community Health Survey. *CMAJ* 2018;190:E155-61.
14. *Guidelines for the economic evaluation of health technologies: Canada*. 4th ed. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH); 2017:1-76.
14. Henry B, Crabtree A, Roth D, et al. Lyme disease: knowledge, beliefs, and practices of physicians in a low-endemic area. *Can Fam Physician* 2012;58:e289-95.
16. For health professionals: Lyme disease. Ottawa: Public Health Agency of Canada; modified 2021 Feb. 8. Available: https://www.canada.ca/en/public-health/services/diseases/lyme-disease/health-professionals-lyme-disease.html (accessed 2021 Apr. 19).
17. Lyme disease — Serology. Toronto: Public Health Ontario; updated July 2020. Available: https://www.publichealthontario.ca/en/laboratory-services/test-information-index/lyme-disease-serology (accessed 2020 Sept. 23).
18. Waddell LA, Greig J, Mascarenhas M, et al. The accuracy of diagnostic tests for Lyme disease in humans, a systematic review and meta-analysis of north American research. *PLoS One* 2016;11:e0168613.
19. Magid D, Schwartz B, Craft J, et al. Prevention of Lyme disease after tick bites. A cost-effectiveness analysis. *N Engl J Med* 1992;327:534-41.
20. Liu NY, Dinerman H, Levin RE, et al. Randomized trial of doxycycline vs. amoxicillin/probenecid for the treatment of Lyme arthritis: treatment of non-responders with intravenous penicillin or ceftriaxone. *Arthritis Rheum* 1989;32:S46.
21. Steere AC, Taylor E, McHugh GL, et al. The overdiagnosis of Lyme disease. *JAMA* 1993;269:1812-6.
22. Logigian EL, Steere AC. Clinical and electrophysiologic findings in chronic neuropathy of Lyme disease. *Neurology* 1992;42:303-11.
23. Dattwyler RJ, Volkman DJ, Halperin JJ, et al. Treatment of late Lyme borreliosis — randomised comparison of ceftriaxone and penicillin. *Lancet* 1988;1:1191-4.
24. Karlsson M, Hammers-Berggren S, Lindquist L, et al. Comparison of intravenous penicillin G and oral doxycycline for treatment of lyme neuroborreliosis. *Neurology* 1994;44:1203-7.
25. Shing E, Wang J, Khoo E, et al. Estimating direct healthcare costs attributable to laboratory-confirmed Lyme disease in Ontario, Canada: a population-based matched cohort study using health administrative data. *Zoonoses Public Health* 2019;66:428-35.
26. Mac S, Jung J, Kopp A, et al. Estimating health burden attributable to laboratory-confirmed Lyme disease in Ontario, Canada: a population-based matched cohort study using health administrative data. *Med Decis Making* 2020;40:E102-3.
27. Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2006;43:1089-134.
28. Gold MR, Stevenson D, Fryback DG. HALYs and QALYs and DALYs, Oh My: similarities and differences in summary measures of population health. *Annu Rev Public Health* 2002;23:115-34.
29. Caro JJ, Briggs AH, Siebert U, et al. Modeling good research practices — overview: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-1. *Med Decis Making* 2012;32:667-77.
30. Rebman AW, Bechtold KT, Yang T, et al. The clinical, symptom, and quality-of-life characterization of a well-defined group of patients with posttreatment Lyme disease syndrome. *Front Med (Lausanne)* 2017;4:224.
31. Nadelman RB, Wormser GP. Reinfection in patients with Lyme disease. *Clin Infect Dis* 2007;45:1032-8.
32. Jares TM, Mathiason MA, Kowalski TJ. Functional outcomes in patients with *Borrelia burgdorferi* reinfection. *Ticks Tick Borne Dis* 2014;5:58-62.
33. Johnson KO, Nelder MP, Russell C, et al. Clinical manifestations of reported Lyme disease cases in Ontario, Canada: 2005–2014. *PLoS One* 2018;13:e0198509.
34. Kwong JC, Ratnasingham S, Campitelli MA, et al. The impact of infection on population health: results of the Ontario burden of infectious diseases study. *PLoS One* 2012;7:e44103.
35. About the network. Canadian Lyme Disease Research Network. Available: https://www.clydrn.ca/about-the-network/# (accessed 2021 Apr. 19).
36. Rebman AW, Aucott JN. Post-treatment Lyme disease as a model for persistent symptoms in Lyme disease. *Front Med (Lausanne)* 2020;7:57.

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