Estimating Population Health Burden of Lyme disease in Ontario, Canada: A Microsimulation Modeling Approach

Stephen Mac[1,2], Gerald A. Evans[3,4], Samir N. Patel[5,6], Eleanor M. Pullenayegum[7,8], Beate Sander[1,2,4,5]

[1] Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Canada

[2] THETA Collaborative, University Health Network, Toronto, Canada

[3] Department of Medicine, Queen's University, Kingston, Canada

[4] ICES, Toronto, Canada

[5] Public Health Ontario, Toronto, Canada

[6] Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Canada

[7] The Hospital for Sick Children (SickKids), Toronto, Canada

[8] Dalla Lana School of Public Health, University of Toronto, Toronto, Canada

Corresponding author: Stephen Mac, Institute of Health Policy, Management and Evaluation, University of Toronto, 155 College Street, 4th floor, Toronto, ON M5T3M6, Canada. E: 416-634-8020, e: sm.mac@mail.utoronto.ca

Funding Statement: This work was supported by the Canadian Institutes of Health Research (CIHR) project grant PJT149087 held by BS. SM is supported by a CIHR Frederick Banting and Charles Best Canada Graduate Scholarship Doctoral Award GSD-159274. BS is supported by a Canada Research Chair in Economics of Infectious Diseases (CRC-950-232429). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: All authors have no potential conflicts of interest to declare.

Keywords: Lyme disease; Borrelia burgdorferi; Illness burden; decision modeling; quality-adjusted life years

ABSTRACT

Background: Lyme disease (LD), untreated, 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 LD in Ontario, Canada.

Methods: We developed a LD disease history model using microsimulation, simulating 100,000 individuals (mean age 37.6 years, 51% female) in Ontario over a lifetime risk of infection and time horizon. Sensitivity and specificity for CDC-recommended two-tier testing, probabilities, and health state utility values were extracted from the published literature and health administrative data. Our outcomes include diagnosed LD cases (stratified by stage), undiagnosed infections, sequelae, individuals experiencing PTLDS, and quality-adjusted life years (QALYs) lost.

Results: Our model estimated 309 infections over the lifetime of 100,000 simulated individuals with 94% of infections diagnosed (35% at early localized stage, 38% at early disseminated stage, 21% at late disseminated stage) and 6% of infections remaining undiagnosed. Of those diagnosed, 23% developed sequelae (arthritic, cardiac, neurologic), and 9% developed PTLDS. LD resulted in a loss of 70.59 QALYs over the lifetime of 100,000 individuals. Sensitivity and scenario analysis revealed that increasing LD incidence rates, 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 value of potential pharmaceutical and non-pharmaceutical interventions.

INTRODUCTION

Lyme disease (LD) is the most commonly reported vector-borne disease in North America, (1–3) with incidence rates of up to 130 per 100,000 in Maine, United States (US), (4) and 85 per 100,000 in high risk areas of Ontario, Canada.(5)

Untreated LD at early stages can lead to: Lyme meningitis, cranial nerve neuropathies like Bell's palsy, Lyme carditis, and Lyme arthritis. (6) A recent systematic review of long-term sequelae and health-related quality-of-life of patients with confirmed LD showed that post-treatment Lyme disease syndrome (PTLDS) may result in impaired quality-of-life.(7) PTLDS is defined as persistent symptoms for at least 6 months post-treatment of LD that was documented by a physician and treated with standard-of-care antibiotics. (8) There are risks for physical and neurologic sequelae associated with laboratory-confirmed LD, (9) and the economic burden is similar to other vector-borne diseases, such as West Nile virus and Zika virus.(10)

Three Markov cohort models have previously been developed for LD, two assessing the cost-effectiveness of LD vaccination versus no vaccination, (11,12) and one assessing oral therapy versus intravenous administration of antibiotics.(13) However, these cohort models assumed a homogeneous patient population, did not incorporate LD diagnostics, individual-level characteristics, or the entire disease progression of LD (i.e., PTLDS). Individual and population-level burden of LD are not well understood for several reasons including the relative novelty of the disease in certain regions of North America, lower incidence rates, and lack of follow-up on long-term outcomes. In these instances, microsimulation models can be helpful in simulating the disease history based on current evidence from the literature and surveillance programs to inform estimates of the impact of LD on health outcomes. There is a need for updated models to include updated case definitions, diagnostic effectiveness, treatment, and disease progression.

The objective of this study was to develop an individual-level state-transition model to estimate the health burden associated with Lyme disease in Ontario, Canada. This model will report health burden in terms of number of LD cases and quality-adjusted life years (QALYs). QALYs consider morbidity and mortality of patients, taking into account life years and the quality-of-life experienced by patients; they are a common measure in burden of disease studies to capture all effects of diseases and to allow for comparisons to other health conditions.(14)

METHODS

Target population and setting

We developed an individual-level, state-transition model to simulate persons representative of the population of Ontario in 2017 where approximately 14 million individuals reside. We simulated a cross-sectional cohort of 100,000 individuals in Ontario with a mean (SD) age of 37.62 (22.67) years, 51% female and 63% (8.8M/13.98M) residing in high-risk areas (personal communication, Public Health Ontario). The life expectancy was 81.02 years, simulating a "lifetime" LD infection risk over approximately 43 years. Individual characteristics (age, sex, risk area of residence) were sampled from distributions informed by census data. (15) Figure 1 shows a model schematic with possible trajectories for individuals: infected with LD, diagnosed, progression to various LD stages, or recovery, in weekly time step. We reported health outcomes per 100,000 including: the number of LD cases (early localized, early disseminated, and late disseminated), sequelae including PTLDS, and QALYs. Outcomes are accrued over the patient's lifetime and discounted at 1.5%.(16) All modelling and analyses were conducted using Treeage Pro (Treeage Software, Inc., Williamstown, MA).

Model structure

Lyme disease incidence and exposure

We assumed that individuals enter the model in a "Healthy (susceptible)" state. There is a probability that these individuals can be bit by an infected tick and develop LD using age- and sex-dependent 2017 incidence rates reported from Public Health Ontario. Age-dependent incidence rates ranged between 2.9 and 10 per 100,000 for females, and 5.0 and 13.9 per 100,000 for males (Appendix 1). We assumed LD infections are caused by the dominant strain in Ontario, *Borrelia burgdorferi (sensu stricto)*.

Those developing an erythema migrans (EM) rash may be clinically diagnosed and transition to the "Early localized" health state. Individuals presenting with EM can be misdiagnosed depending on LD awareness,(15) and remain undiagnosed in the "Infected" state. Once a diagnostic test confirms LD diagnosis, individuals transition to: "early localized", early disseminated", or "late disseminated" health states depending on the time since initial infection, which is defined as between 0 and 30, 31 and 90, and 90 days and onwards, respectively.

Diagnostic testing

Diagnostic two-tier tests with negative, and positive results are typically returned within 1, and 2 weeks, respectively.(18) Undiagnosed individuals in the "Infected" 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 receive a test if presenting with sequelae from the initial infection, and 40.2% if not. (19) Sensitivity and specificity were extracted from a meta-analysis, stratified by LD stage. Sensitivity for early localized, early disseminated, and late disseminated LD was 46.3%, 89.7% and 99.4%, respectively, while specificity was between 99.3% and 99.7%.(20)

LD sequelae and manifestations

. In the early disseminated stage, multiple EM, 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.(7) The one-year, sex-dependent probability of developing

early disseminated and late disseminated stage sequelae was informed by population-based health administrative data in Ontario to be 17%, and 10-11%, respectively.

Individuals diagnosed clinically or with laboratory-confirmation receive 2-3 weeks of oral antibiotics, which may be followed by subsequent courses of intravenous antibiotics depending on the sequelae experienced.(22) We define treatment success as absence of sequelae or manifestations of the respective LD stage (i.e., no more persistent symptoms). On treatment, individuals have a 4-6% chance of experiencing minor or major adverse events from antibiotic treatment, (13) and 85-95% of recovery. (23–28) Unsuccessful treatment led to possible PTLDS development; we assumed with expert guidance that PTLDS persists for five years. After recovery (from any LD stage), individuals are assumed to be immune from re-infection for six 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 quality-adjusted life years (QALYs). Mean utility values for the Ontario population ranged from 0.616 to 0.902, depending on age and sex.(15) Utilities for LD health states were extracted from a systematic review, (7) and corresponded to the experienced sequelae. For example, an individual with cranial nerve palsy would have a utility of 0.61individuals with PTLDS have a utility of 0.54.(12) All parameters are summarized in Table 1.

Analysis

Base-case analysis

We simulated 100,000 individuals with a risk of LD infection throughout their lifetime, assuming that treatment starts after clinical diagnosis, or laboratory confirmation. The likelihood of clinical diagnosis after presenting with EM in high, and low exposure areas was 58%, and 26%, respectively.(19) We also simulated the health burden for 1 million individuals in Ontario over a 1-year risk of LD infection to contextualize annual health burden.

Assessing uncertainty

We conducted various scenario analyses to examine the impact of assumptions made, and influential parameters in plausible LD scenarios including increasing LD incidence rates over time. In this scenario, we increased the incidence annually by 1 per 100,000 for each age group for the next 10 years. All scenarios are described in Appendix 2.

We conducted deterministic one-way sensitivity analysis to assess the robustness of model results to key parameters. We followed modeling best practices.(31)

RESULTS

Base-case

In total, there were 309 infections per 100,000, of which 4 (1.3%) were re-infections. From the 309 infections, 289 (94%) were diagnosed, and 20 (6%) remained undiagnosed. All results are summarized in Table 2. The mean (SD) age at the time of infection was 54.6 (17.9) years, with most infections in the 50-55, and 60-65 age groups (Appendix 3). The median (range) duration of LD infection was 7 (2 – 260) weeks (Appendix 4). Median (IQR) time from infection to diagnosis, and from infection to treatment was 5 (3-6), and 6 (4-7) weeks, respectively (Appendix 5-6).

Of the 309 diagnosed cases, 107 (35%) cases were diagnosed at the early localized stage with 45 (42%) of those clinically diagnosed, and 62 (58%) diagnosed through laboratory confirmation. Laboratory-confirmed diagnosis of early disseminated and late disseminated stage cases were 118 (38%), and 64 (21%), respectively.

Individuals progressing into the early disseminated stage of LD developed disseminated/multiple EM (n=10), cranial nerve palsy (n=4), cardiac abnormalities (n=19), and other neurological sequelae (meningitis, polyneuropathy) (n=9). Individuals who were diagnosed with, or progressed to, late disseminated LD developed arthritis (n=16) and cognitive sequelae (n=8). Of those diagnosed, 25 (9%)

developed PTLDS. Over the lifetime of 100,000 individuals, LD resulted in a loss of 70.59 QALYs, discounted at 1.5%, or 102.90 QALYs undiscounted.

In the cross-sectional cohort of 1 million individuals in Ontario at risk of LD infection for one year (Appendix 7), there were 53 LD infections, with most infections diagnosed at the early localized (40%) and early disseminated stages (38%). Approximately 17% of individuals developed sequelae, 9% were diagnosed with PTLDS, and no one was re-infected. Given the low probability of being re-infected within one year, no re-infections were expected. In this scenario, one year of LD risk resulted in a loss of 19.38 QALYs. For Ontario (population of approximately 14M) this translates to 271 QALYs lost resulting from LD infections in one-year.

Assessing uncertainty

The tornado diagram (Figure 2) summarizes multiple one-way sensitivity analyses of all parameters' impact on QALYs lost. The following parameters have the most impact: duration of the PTLDS stage, utility value for PTLDS, probability of full recovery post-treatment, probability of developing an EM rash, and diagnostic test performance.

When the duration of PTLDS state was one-year, fewer QALYs are lost at 50.36, whereas being in the PTLDS health state for an average of 10 years resulted in 87.74 QALYs lost. At the higher estimate for PTLDS utility value of 0.70, 58.25 QALYs were lost. A lower utility value of 0.30 resulted in 89.11 QALYs lost. With the probability of recovery at its upper limit (e.g., close to 100% chance of recovery), there is a total of 68.52 QALYs lost, whereas the lower limit resulted in 85.97 QALYs lost. These sensitivity analyses suggest that the disease progression towards PTLDS, and this stage of LD substantially contribute to the health burden associated with LD infections.

The other major influential parameter was LD incidence (Appendix 2). In a scenario where LD incidence rates increased by 1 per 100,000 annually over the next 10 years, 165.51 QALYs were lost. Underreporting factors of 3 (Canadian estimate), and 10 (US estimate) resulted in 257.48 and 881.30

QALYs lost, respectively. Increased awareness of LD, translated as increased probability of clinical diagnosis of EM, resulted in fewer QALYs lost (i.e., lesser health burden).

INTERPRETATION

We developed an individual-level state transition model to estimate LD health burden over the lifetime of 100,000 individuals in Ontario. LD resulted in 71 QALYs lost, with 23% of individuals developing sequelae and 9% developing PTLDS. The number of individuals developing PTLDS was similar to the 10% reported in the literature,(29) and may be slightly underestimated since 6% of individuals remained undiagnosed. The duration of PTLDS, and the quality-of-life associated with the health state had a significant effect on the overall burden as shown in the sensitivity analyses. While it is uncommon in most cases of LD, given appropriate diagnosis and treatment, further research and understanding of this PTLDS can aid in reducing LD health burden.

Scenarios modeled also suggest that the health burden resulting from LD can be reduced by introducing interventions to lower the ecological transmission of *Borrelia burgdorferi* in hosts to reduce LD incidence rates, or reduce the number of individuals who may be susceptible to LD. Previous Markov models assessing the cost-effectiveness of a LD vaccine concluded that LD incidence rate was highly influential towards the economic value of interventions. (11,12)

In a descriptive study of 2005-2014 LD cases in Ontario, the proportion of individuals notifying public health systems within 30 days, 1-3 months, and >3 months of symptom onset was 45.2%, 38%, and 16.8%, respectively.(17) Our model similarly reports that 35% of cases are diagnosed (and reported) within 30 days, 38% within 1-3 months, and 21% after 3 months. The differences between our results can be attributed to how our model considers LD stage at diagnosis based on time from tick bite/infection and sequelae developed post-infection, which is difficult to identify using administrative data. Instead, Johnson and colleagues classify LD stage by manifestations and patient-reported symptoms.(17) Our

results suggest that while some individuals may have and report symptoms of acute LD, they may be diagnosed in the later stages.

Despite our best efforts to compare to other literature estimates of infectious diseases' burden in terms of QALYs, to our knowledge, there are none that report this in similar overall context. An Ontario Burden of Infectious Diseases Study from 2012 estimated the annual burden of 51 infectious diseases in terms of health-adjusted life years (HALYs), which similarly to the QALY, is a composite measure that incorporates both mortality (years of life lost) and morbidity (year-equivalents of reduced functioning). (32) In an indirect comparison, LD's annual burden (271 QALYs) is similar in magnitude to herpes simplex virus (256 HALYs), and pertussis (220 HALYs), a pathogen which contributed zero years of life lost but many year-equivalents of reduced functioning. (32)

Limitations

Our study has several limitations. The overall health burden estimated by our model is likely to be conservative given we only considered the *Borrelia burgdorferi* strain, and assumed that sequelae are mutually exclusive. The probability of developing sequelae may be underestimated as it was extracted from an Ontario laboratory-confirmed LD cohort with accrual between 2006-2013, when incidence rates of LD were lower.

Much remains unclear surrounding PTLDS: diagnosis, treatment and recovery. (34) 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) was influential towards QALYs lost, indicating that this is an area for future research. Our model does not consider seasonality; we assumed that health burden resulting from LD can be simplified to result from a uniform infection risk throughout the year.

This individual-level state transition model simulated the disease history of LD from infection and to end-of-life, capturing individual differences (e.g., age, sex, probability of residing in high-risk areas) to estimate population-level health burden. Reporting QALYs lost is critical in understanding the overall

burden of LD, a disease which 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, LD infection in Ontario, Canada, contributes considerable health burden in terms of quality-adjusted life years, resulting from potential sequelae, undiagnosed cases, and individuals with PTLDS. The incidence rate of LD, and PTLDS (duration and quality-of-life) were most influential to model results and should be the focus of future research and interventions.

REFERENCES

1. Centers for Disease Control and Prevention. Why is CDC concerned about Lyme disease? [Internet]. 2017 [cited 2020 Aug 3]. Available from: https://www.cdc.gov/lyme/why-is-cdc-concerned-about-lyme-disease.html

2. Rochlin I, Ninivaggi D V., 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(1):1–11.

3. Mead PS. Epidemiology of Lyme Disease. Infect Dis Clin North Am. 2015;29(2):187–210.

4. Centers for Disease Control and Prevention. Lyme disease data tables [Internet]. 2017 [cited 2018 Feb 5]. Available from: https://www.cdc.gov/lyme/stats/tables.html

5. Nelder MP, Wijayasri S, Russell CB, Johnson KO, Cronin K, Johnson S. 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, Kochanek K, Delorey MJ, Biggerstaff BJ, et al. A Review of Death Certificates Listing Lyme Disease as a Cause of Death in the United States. Clin Infect Dis [Internet]. 2011 Feb 1 [cited 2017 Dec 22];52(3):364–7. Available from: https://academic.oup.com/cid/article-lookup/doi/10.1093/cid/ciq157

7. Mac S, Bahia S, Simbulan F, Pullenayegum EM, Evans GA, Patel SN, et al. Long-Term Sequelae and Health-Related Quality of Life Associated With Lyme Disease: A Systematic Review. Clin Infect Dis. 2020;71(2):440–52.

8. Aucott JN. Posttreatment Lyme Disease Syndrome. Infect Dis Clin N Am. 2015;29:309–23.

9. Mac S, Jung J, Kopp A, Evans G, Pullenayegum E, Patel SN, 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 Mak. 2019;40(1):E102–3.

10. Mac S, da Silva SR, Sander B. The economic burden of lyme disease and the cost-effectiveness of lyme disease interventions: A scoping review. PLoS One. 2019;14(1):e0210280.

11. Hsia EC, Chung JB, Schwartz JS, Albert DA, E.C. H, J.B. C, et al. Cost-effectiveness analysis of the Lyme disease vaccine. Arthritis Rheum. 2002;46(6):1651–60.

12. Shadick NA, Liang MH, Phillips CB, Fossel K, Kuntz KM, N.A. S, et al. The cost-effectiveness of vaccination against Lyme disease. Arch Intern Med. 2001;161(4):554–61.

13. Eckman MH, Steere AC, Kalish RA, Pauker SG, M.H. E, A.C. S, 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(5):357.

14. 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.

15. 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(6):E155–61.

16. Canadian Agency for Drugs and Technologies in Health (CADTH). Guidelines for the Economic Evaluation of Health Technologies: Canada. 4th ed. 2017. 1–76 p.

17. Johnson KO, Nelder MP, Russell C, Li Y, Badiani T, Sander B, et al. Clinical manifestations of reported Lyme disease cases in Ontario, Canada: 2005–2014. PLoS One. 2018;13(6).

18. Public Health Ontario. Lyme Disease – Serology [Internet]. 2020 [cited 2020 Sep 23]. Available from: https://www.publichealthontario.ca/en/laboratory-services/test-information-index/lyme-disease-serology

19. Henry B, Crabtree A, Roth D, Blackman D, Morshed M. Lyme disease: Knowledge, beliefs, and practices of physicians in a low-endemic area. Can Fam Physician. 2012;58(5):289–95.

20. Waddell LA, Greig J, Mascarenhas M, Harding S, Lindsay R, Ogden N. The accuracy of

diagnostic tests for lyme disease in humans, a systematic review and meta-analysis of north American research. PLoS One. 2016;11(12):1–23.

21. Health Quality Ontario. Clinical Guidance Document: Management of Tick Bites and Investigation of Early Localized Lyme Disease [Internet]. 2018 [cited 2020 Sep 25]. Available from: https://www.hqontario.ca/Portals/0/documents/evidence/qs-clinical-guidance-lyme-disease-en.pdf

22. Wormser GP, Dattwyler RJ, Shapiro ED, Halperin JJ, Steere AC, Klempner MS, 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(9):1089–134.

23. Magid D, Schwartz B, Craft J, Schwartz S. Prevention of Lyme Disease After Tick Bites. A Cost-Effectiveness Analysis. N Engl J Med. 1992;327(23):534–41.

24. Liu NY, Dinerman H, Levin RE, Massarotti E, Molloy PJ, Schoen RT, et al. Randomized trial of doxycycline vs. amoxicillin/probenecid for the treatment of Lyme arthritis: treatment of non-responders with intravenous penicillin or ceftriaxone . In: Arthritis Rheum [Internet]. 1989 [cited 2020 Sep 23]. p. 32-S46. Available from: https://connects.catalyst.harvard.edu/Profiles/display/1010621

25. Steere AC, Taylor E, McHugh GL, Logigian EL. The Overdiagnosis of Lyme Disease. JAMA J Am Med Assoc [Internet]. 1993 Apr 14 [cited 2020 Sep 23];269(14):1812–6. Available from: https://jamanetwork.com/journals/jama/fullarticle/405293

26. Logigian EL, Steere AC. Clinical and electrophysiologic findings in chronic neuropathy of Lyme disease. Neurology [Internet]. 1992 [cited 2020 Sep 23];42(2):303–11. Available from: https://pubmed.ncbi.nlm.nih.gov/1310529/

27. Dattwyler RJ, Volkman DJ, Halperin JJ, Luft BJ. TREATMENT OF LATE LYME

BORRELIOSIS-RANDOMISED COMPARISON OF CEFTRIAXONE AND PENICILLIN. Lancet [Internet]. 1988 May 28 [cited 2020 Sep 23];331(8596):1191–4. Available from: https://pubmed.ncbi.nlm.nih.gov/2897008/

28. Karlsson M, Hammers-Berggren S, Lindquist L, Stiernstedt G, Svenungsson B. Comparison of intravenous penicillin G and oral doxycycline for treatment of lyme neuroborreliosis. Neurology [Internet]. 1994 [cited 2020 Sep 23];44(7):1203–7. Available from: https://pubmed.ncbi.nlm.nih.gov/8035916/

29. Rebman AW, Bechtold KT, Yang T, Mihm EA, Soloski MJ, Novak CB, et al. The Clinical, Symptom, and Quality-of-Life Characterization of a Well-Defined Group of Patients with Posttreatment Lyme Disease Syndrome. Front Med. 2017;4(224):1–10.

30. Aucott JN, Rebman AW, Crowder LA, Kortte KB. Post-treatment Lyme disease syndrome symptomatology and the impact on life functioning: Is there something here? Qual Life Res. 2013;22(1):75–84.

31. Caro JJ, Briggs AH, Siebert U, Kuntz KM. Modeling good research practices--overview: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-1. Med Decis Mak. 2012;32(5):667–77.

32. Kwong JC, Ratnasingham S, Campitelli MA, Daneman N, Deeks SL, Manuel DG, et al. The Impact of Infection on Population Health: Results of the Ontario Burden of Infectious Diseases Study. PLoS One. 2012;7(9).

33. Semproni M, Rusk R, Wuerz T. Fatal Lyme carditis presenting as fluctuating high-grade atrioventricular block. CMAJ. 2020;192(21):E574–7.

34. Rebman AW, Aucott JN. Post-treatment Lyme Disease as a Model for Persistent Symptoms in Lyme Disease. Front Med. 2020;7(February):1–16.

35. Shing E, Wang J, Khoo E, Evans GA, Moore S, Nelder MP, 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 Jan;

LIST OF TABLES

Table 1. Key parameters and data sources

Parameter	Base-case value	Type of Range	Range	Data Sources
Probabilities				
Lyme disease				
Probability of high-risk exposure	0.628	P, Range	(0.471, 0.786)	Personal communication, Public Health Ontario
LD incidence rates [varies by age and sex]	2.9 – 13.9 per 100,000	Full, Range	(0.000029, 0.000139)	Nelder 2018 (5)
Probability of clinical diagnosis after EM rash, high-risk exposure area	0.583	Full, Range	(0.437, 0.729)	Henry 2012 (19)
Probability of clinical diagnosis after EM rash, low-risk area	0.261	P, Range	(0.196, 0.326)	Henry 2012 (19)
Diagnostics				
Sensitivity, early localized	0.463	Full, 95%CI	(0.391, 0.537)	Waddell 2016 (20)
Sensitivity, early disseminated	0.897	Full, 95%CI	(0.783, 0.954)	Waddell 2016 (20)
Sensitivity, late disseminated	0.994	Full, 95%CI	(0.957, 0.999)	Waddell 2016 (20)
Specificity, early localized	0.993	Full, 95%CI	(0.983, 0.997)	Waddell 2016 (20)
Specificity, early disseminated	0.997	Full, 95%CI	(0.984, 0.999)	Waddell 2016 (20)
Specificity, late disseminated	0.993	Full, 95%CI	(0.985, 0.997)	Waddell 2016 (20)
Probability of testing [varies by (no) presence of sequelae]	0.402 – 0.805	P, Range	(0.30 – 0.98)	Henry 2012 (19)
Delay in results	1 – 2 weeks			PHO 2017 (18)
Treatment				
Treat efficacy, erythema migrans	0.85	Full, Range	(0.80, 1.00)	Magid 1992 (23)
Treat efficacy, arthritic sequelae	0.85	Full, Range	(0.40, 0.80)	Liu 1989 (24)
Treat efficacy, cardiac sequelae	0.90	Full, Range	(0.80, 1.00)	Steere 1993 (25)
Treat efficacy, neurologic sequelae	0.90	Full, Range	(0.76, 0.97)	Logigian 1992 (26) Dattwyler 1988 (27) Karlsson 1994 (28)
Oral treatment completion	0.90	P, Range	(0.68, 1.00)	Magid 1992 (23)
IV treatment completion	0.99	P, Range	(0.75, 1.00)	Magid 1992 (23)
Probability of adverse event, oral	0.04	P, Range	(0.03, 0.05)	Shadick 2001 (12)

Probability of adverse event, IV	0.06	P, Range	(0.05, 0.08)	Shadick 2001 (12)
Outcomes				
Probability of hospitalization	0.047	P, Range	(0.035, 0.059)	Shing 2019 (35)
Length of hospitalization (days)	7.9	Full, 95%CI	(3.75, 12.05)	Shing 2019 (35)
EM rash	0.80	P, Range	(0.60, 1.00)	Shadick 2001 (12)
Probability of developing sequelae [varies by LD stage and sex]	0.10 – 0.17	P, Range	(0.08, 0.21)	Unpublished data from cited study (9)
Arthritic | sequelae (M - F)	0.56 – 0.63	P, Range	(0.41, 0.76)	Unpublished data from cited study (9)
Cardiac | sequelae (F - M)	0.43 – 0.48	P, Range	(0.29, 0.53)	Unpublished data from cited study (9)
Cognitive | sequelae (F - M)	0.37 – 0.44	P, Range	(0.29, 0.58)	Unpublished data from cited study (9)
Cranial nerve palsy | sequelae (F-M)	0.11 – 0.24	P, Range	(0.08, 0.26)	Unpublished data from cited study (9)
Multiple EM | sequelae (M - F)	0.22 – 0.36	P, Range	(0.16, 0.40)	Unpublished data from cited study (9)
Meningitis or polyneuropathy | sequelae (F - M)	0.06 - 0.11	P, Range	(0.12, 0.24)	Unpublished data from cited study (9)
Utilities				
Healthy, stratified by age and sex	0.616 - 0.902	Full, 95%CI	(0.375, 0.983)	Guertin 2018 (15)
Arthritic sequelae	0.69	Full, IQR	(0.51, 0.86)	Shadick 2001 (12)
Cardiac sequelae	0.61	Full, IQR	(0.38, 0.78)	Shadick 2001 (12)
Cognitive sequelae	0.60	Full, IQR	(0.37, 0.73)	Shadick 2001 (12)
Erythema migrans	0.80	Full, IQR	(0.70, 0.93)	Shadick 2001 (12)
Cranial nerve palsy	0.61	Full, IQR	(0.36, 0.81)	Shadick 2001 (12)
Meningitis or polyneuropathy	0.52	Full, IQR	(0.27, 0.73)	Shadick 2001 (12)
PTLDS	0.54	Full, IQR	(0.30, 0.70)	Shadick 2001 (12)
Minor adverse events (disutility)	0.05	P, Range	(0.038, 0.063)	Eckman 1997 (13)
Major adverse events (disutility)	0.10	P, Range	(0.075, 0.125)	Eckman 1997 (13)
Oral treatment (disutility)	0.01	P, Range	(0.00, 0.01)	Eckman 1997 (13)
Intravenous treatment (disutility)	0.03	P, Range	(0.02, 0.04)	Eckman 1997 (13)

CI, confidence interval; EM, erythema migrans; F, female; IQR, interquartile range; IV, intravenous; M, male; P, plausible; PHO, Public Health Ontario; PTLDS, post-treatment Lyme disease syndrome; RR, relative risk

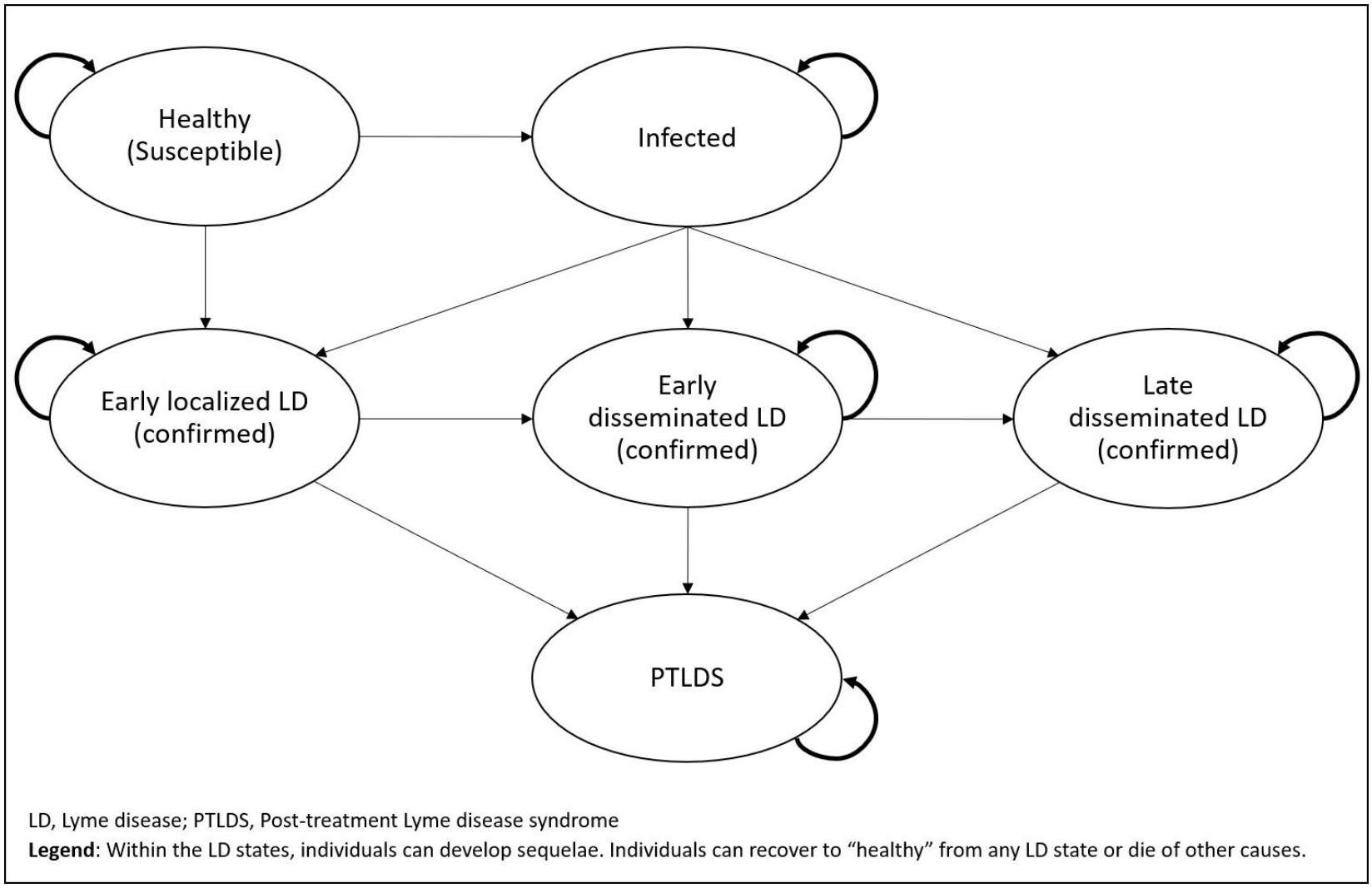
Table 2. Base-case results per 100,000 in Ontario with lifetime risk of Lyme disease

Outcomes	Incidence per 100,000, n (%)
Total LD infections	309
Diagnosed cases	289 (0.94)
Early localized	107 (0.35)
Clinically diagnosed	45 (0.42)
Lab-confirmed	62 (0.58)
Early disseminated (Lab-confirmed)	118 (0.38)
Late disseminated (Lab-confirmed)	64 (0.21)
Undiagnosed cases	20 (0.06)
Re-infections	4 (0.01)
Sequelae	
Arthritic	16 (0.06)
Cardiac	19 (0.07)
Cognitive	8 (0.03)
Cranial nerve palsy	4 (0.01)
Multiple erythema migrans	10 (0.03)
Neurological (meningitis, polyneuropathy)	9 (0.03)
PTLDS	25 (0.09)
QALYS	
Undiscounted	102.90
Discounted (1.5%)	70.59

Abbreviations: LD, Lyme disease; LY, Life years; PTLDS, post-treatment Lyme disease syndrome; QALY, quality-adjusted life year

LIST OF FIGURES

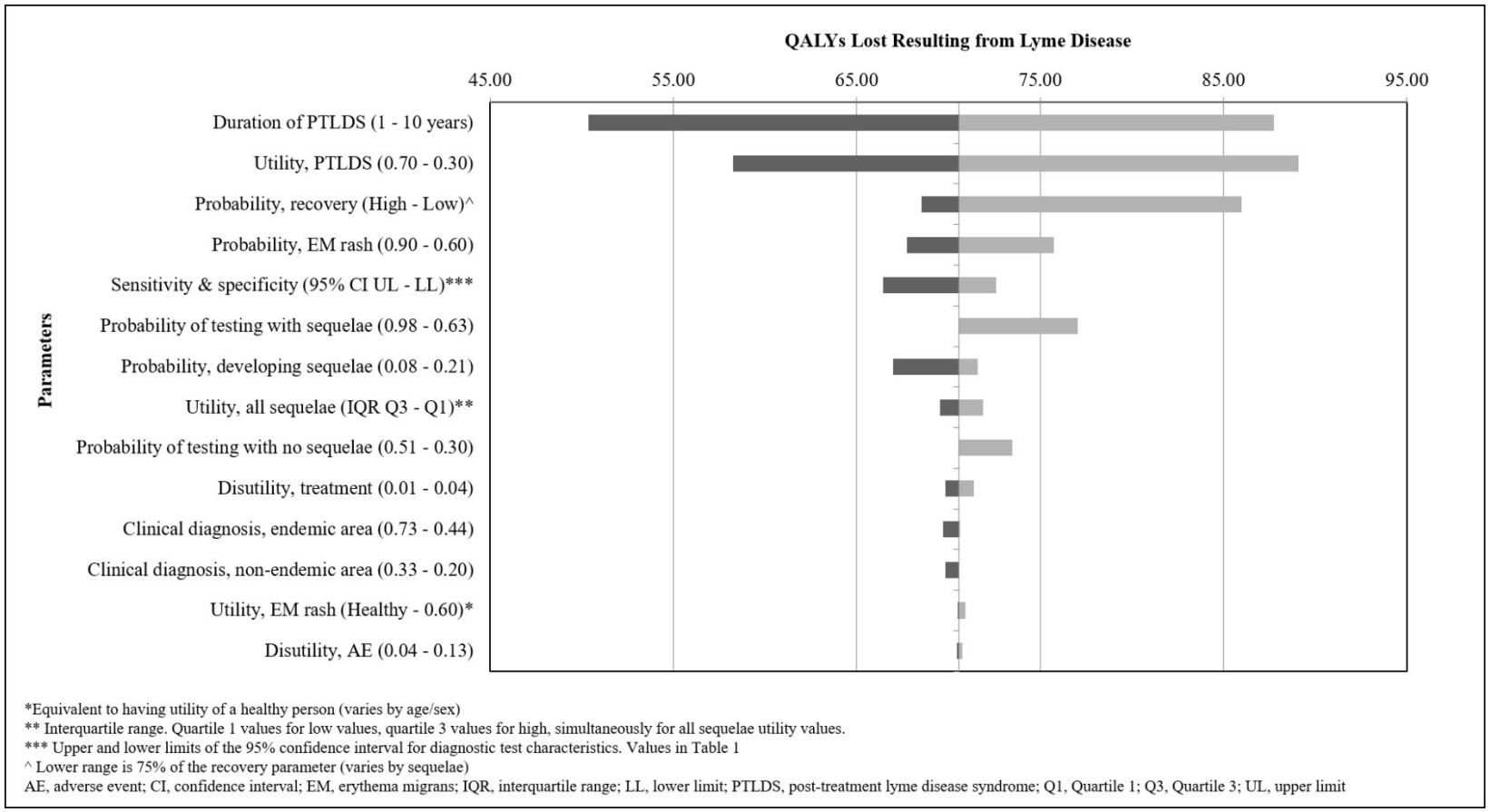
Figure 1. Model schematic of individual state-transition model



LD, Lyme disease; PTLDS, Post-treatment Lyme disease syndrome

Legend: Within the LD states, individuals can develop sequelae. Individuals can recover to "healthy" from any LD state or die of other causes.

Figure 2. Sensitivity analysis of key parameters on health burden



*Equivalent to having utility of a healthy person (varies by age/sex)
** Interquartile range. Quartile 1 values for low values, quartile 3 values for high, simultaneously for all sequelae utility values.
*** Upper and lower limits of the 95% confidence interval for diagnostic test characteristics. Values in Table 1
^ Lower range is 75% of the recovery parameter (varies by sequelae)
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

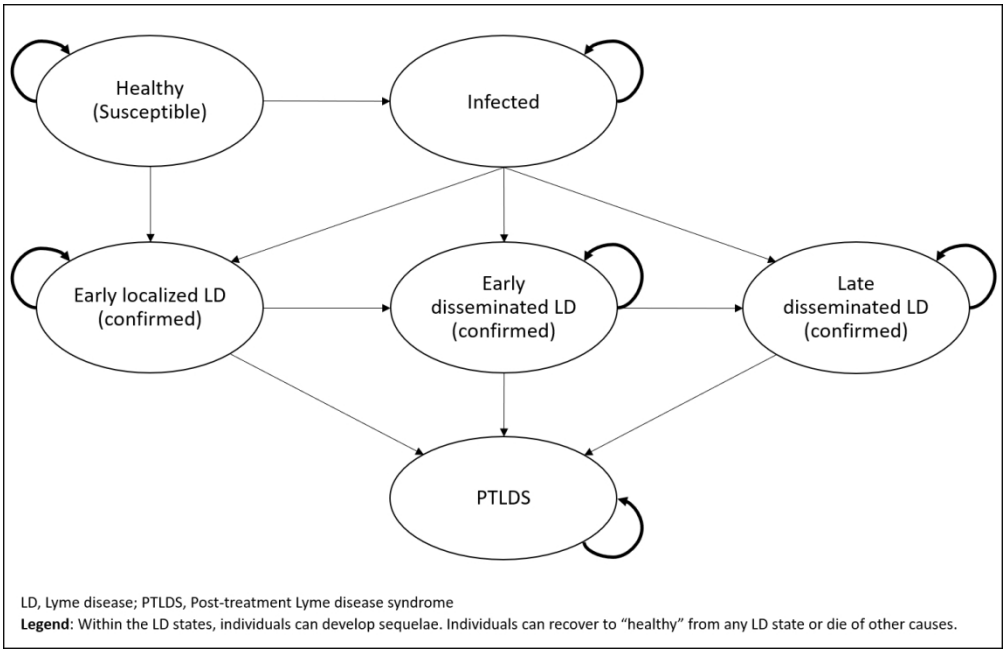


Figure 1. Model schematic of individual state-transition model

257x166mm (150 x 150 DPI)

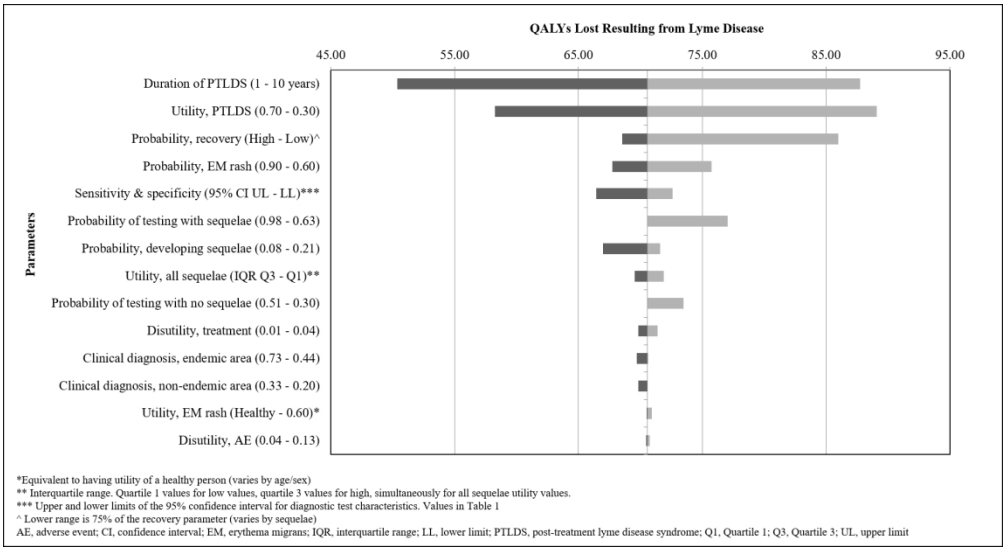


Figure 2. Sensitivity analysis of key parameters on health burden

325x176mm (150 x 150 DPI)

APPENDIX

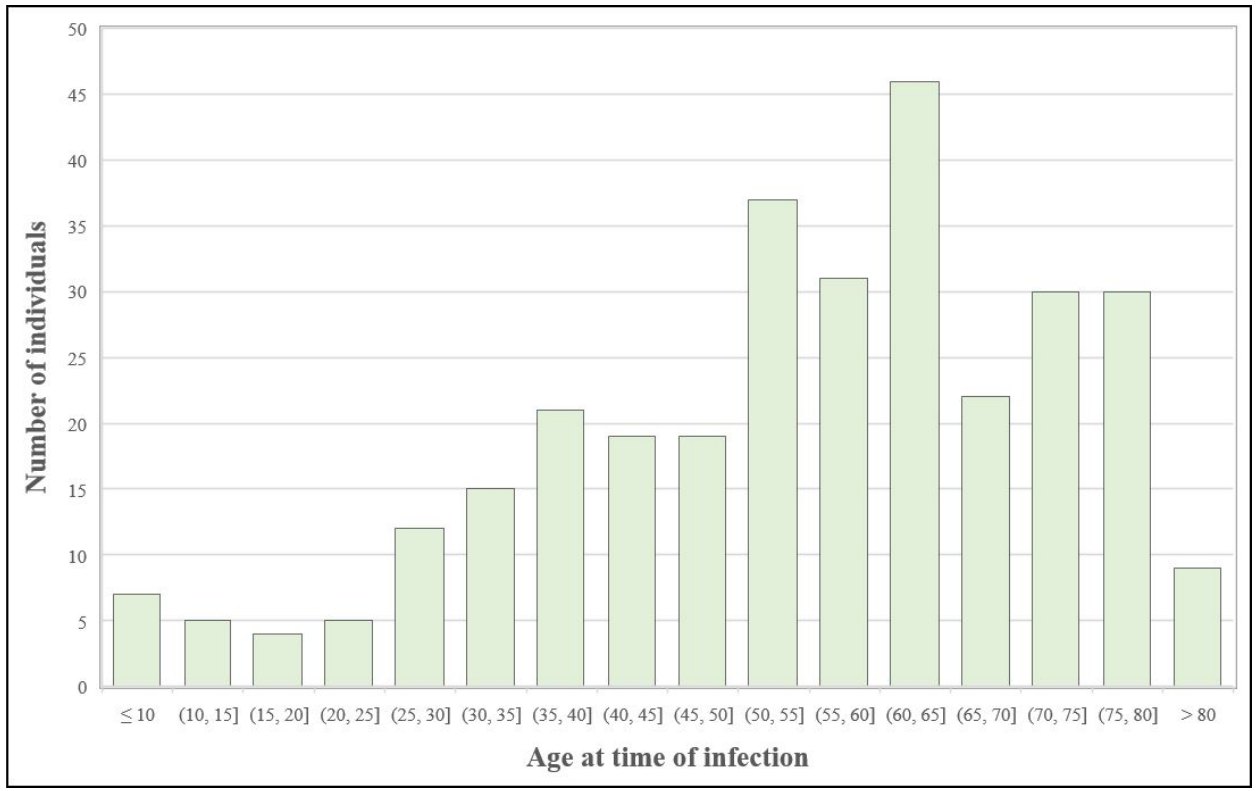
Appendix 1. Lyme disease incidence by age and sex in Ontario in 2017

	Female		Male	
AGE GROUPS	**Reported cases**	**Incidence rate**	**Reported cases**	**Incidence rate**
≤ 14	41	0.000029	71	0.000050
15 to 49	108	0.000075	199	0.000139
50 to 65	143	0.000100	181	0.000126
≥ 65	94	0.000066	121	0.000085

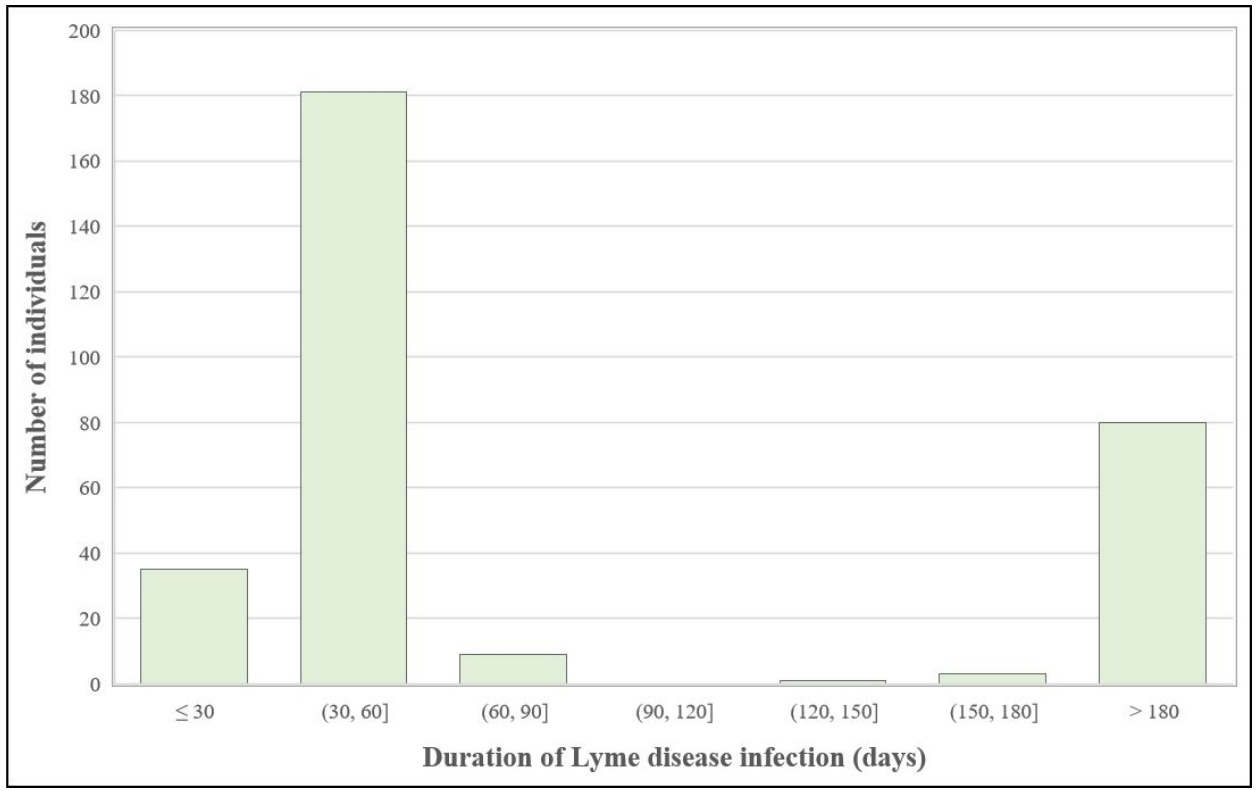
Appendix 2. Scenario analysis descriptions and results by descending health burden

Scenario	Description and Rationale	QALYs Lost
A. Underreporting (factor of 10)	Estimate of possible underreporting in United States. Rationale: To explore true burden if underreporting factor is as concluded by Kuehn 2013 (46)	881.30
B. Underreporting (factor of 3)	Rough estimate of possible underreporting in Canada. Rationale: To explore true burden if underreporting factor is as concluded by Ogden 2019 (47)	257.48
C. LD incidence Increasing for 10 years	Increase by 1 per 100,000 for each age group (by sex), in each of the next 10 years before becoming stable over the lifetime of all individuals. Rationale: To explore increasing risk areas	165.51
D. Assuming persistent symptoms for those undiagnosed for LD	This scenario assumes that undiagnosed individuals may experience persistent symptoms similar to PTLDS, but are not captured since they cannot be diagnosed with PTLDS without an appropriate diagnosis and treatment for LD. Rationale: To explore possible burden when including those who are undiagnosed.	85.29
E. Increased awareness for EM being diagnostic	Probability of clinical diagnosis in the presence of EM rash of 90% in all areas (high and low-risk). Rationale: To explore increase in early clinical diagnosis in high risk and low risk exposure areas.	68.64
F. Ontario: 1 M individuals, 1 year risk of LD infection	Burden for 1 million Ontarians over 1 year of risk of LD infection, discounted at 1.5%	19.38

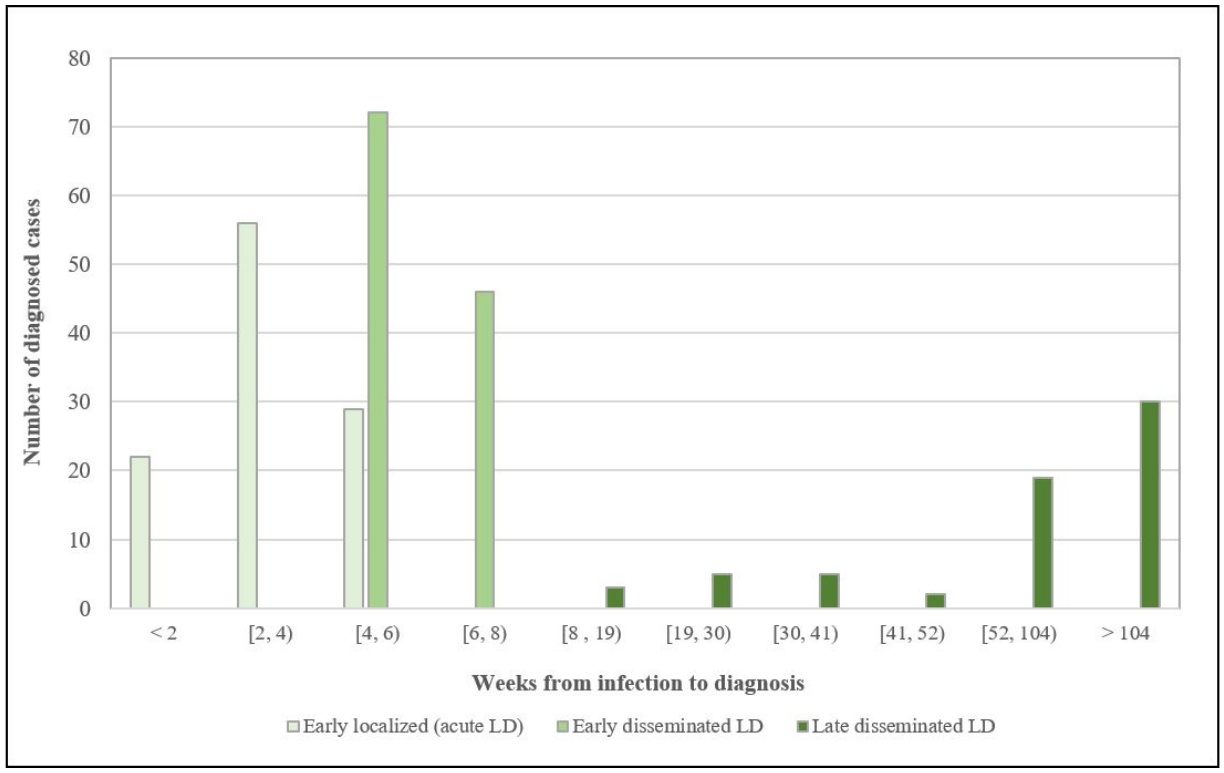
Appendix 3. Age distribution of Lyme disease cases



Appendix 4. Distribution of duration of active Lyme disease infection

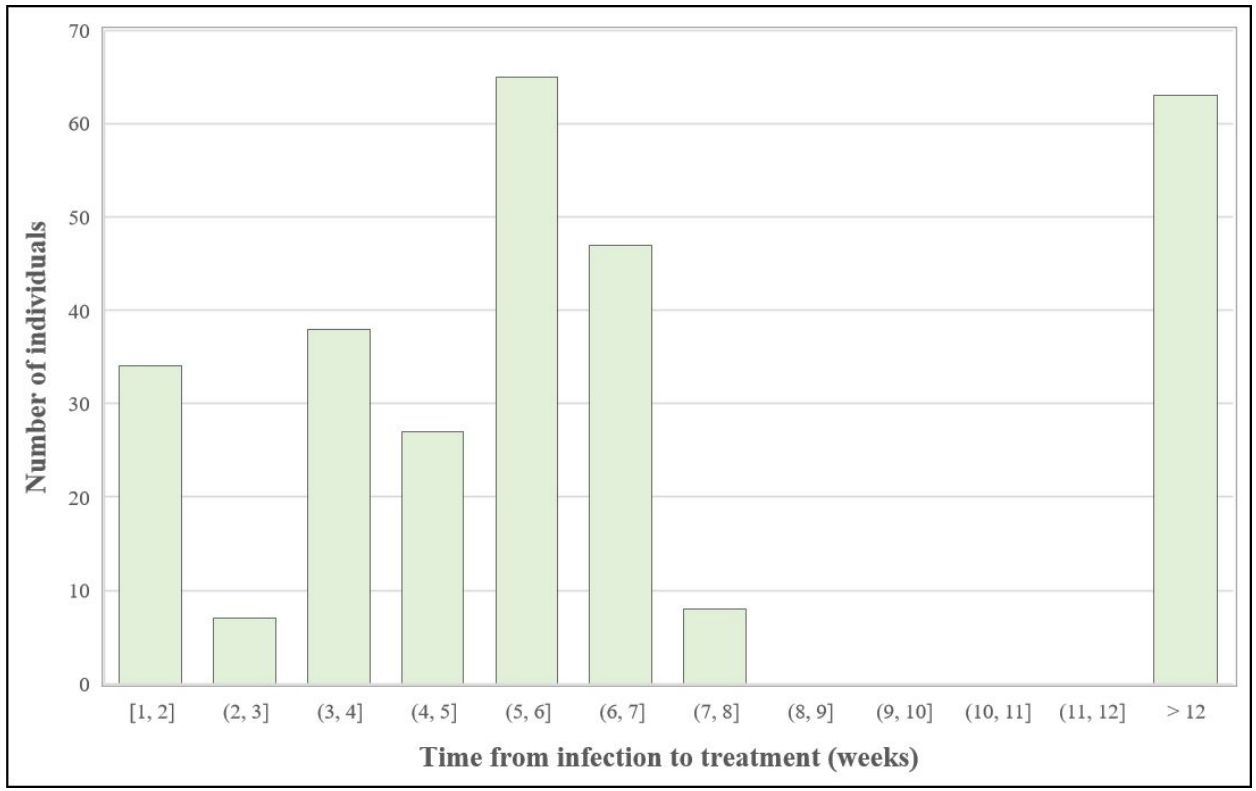


Appendix 5. Distribution of time from infection to diagnosis



Note: The horizontal axis time intervals (weeks) are not uniform.

Appendix 6. Distribution of time from infection to treatment



Appendix 7. Health outcomes for scenario F (1 million people with 1-year risk of LD infection)

Outcomes	Incidence per 100,000, n (%)
Total LD infections	53
Diagnosed cases	47 (0.89)
Early localized	21 (0.4)
Clinically diagnosed	7 (0.33)
Lab-confirmed	14 (0.67)
Early disseminated	20 (0.38)
Late disseminated	6 (0.11)
Undiagnosed cases	6 (0.11)
Re-infections	0 (0)
Sequelae	
Arthritic	4 (0.09)
Cardiac	0 (0)
Cognitive	0 (0)
Cranial nerve palsy	0 (0)
Multiple erythema migrans	2 (0.04)
Neurological (meningitis, polyneuropathy)	2 (0.04)
PTLDS	4 (0.09)
QALYS	
Discounted (1.5%)	19.38

LD, Lyme disease; LY, Life years; PTLDS, post-treatment Lyme disease syndrome; QALY, quality-adjusted life years