LIMITING LYME DISEASE: USING SYSTEM DYNAMICS SIMULATION TO TARGET HEALTH INTERVENTIONS

by

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DEDICATION PAGE

For my family.

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ABSTRACT

Lyme disease is the most common vector-borne infection in North America. While much is known about the biology and ecology of Lyme disease, little is known about the impact of public and physician awareness and behaviour on health outcomes, with respect to prevention, diagnosis, and treatment. Such studies are uncommon and poorly integrated, and they have not taken into account how these factors influence each other and change over time with increasing disease prevalence. This information is needed to clarify how health systems can best manage Lyme disease and identify where public health interventions directed to the public and clinical community should be targeted.

In order to address these limitations, the objectives of this study were: to model how public and physician awareness and behaviour surrounding Lyme disease evolves with increasing disease prevalence, and how this affects incidence, diagnosis, progression to treatment, and patient outcomes; and to apply the model to determine the best intervention strategies for targeting the public and physicians to minimize negative Lyme disease health outcomes. System dynamics modelling is an appropriate method for capturing such dynamic relationships at the population level that evolve over time and are environment dependent. Additionally, it allows all the best evidence on a topic with little data currently available to be synthesized.

The study results suggested that in situations similar to the scenarios modelled, public-based interventions have a greater chance of success than physician-based interventions. This was demonstrated by a greater reduction in negative outcomes such as Lyme disease incidence and late stage disease. However, the results indicated that until more research is conducted to assess the effectiveness of such interventions in practice, multifaceted interventions with a focus on the public are the best approach. Other gaps in knowledge around Lyme disease that were determined to be important to model behaviour, such as how disease stages progress, were also identified as priorities for future research. The model's value as a communication tool could facilitate different constituents of the health community, such as patients, researchers, physicians, and public health authorities, being brought together through knowledge translation to convert health research into public health policy.

LIST OF ABBREVIATIONS USED

Bb	*Borrelia burgdorferi*
EM	erythema migrans
PTLDS	post-treatment Lyme disease syndrome
DNA	deoxyribonucleic acid
PCR	polymerase chain reaction
ELISA	enzyme-linked immunosorbent assay
IgM	immunoglobulin M
IgG	immunoglobulin G
HIV	human immunodeficiency virus
AIDS	acquired immune deficiency syndrome
EL	early localized Lyme disease stage
ED	early disseminated Lyme disease stage
LD	late disseminated Lyme disease stage
PE	persisting effects Lyme disease stage

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CHAPTER 1: INTRODUCTION

Lyme disease, a bacterial infection caused by *Borrelia burgdorferi*, has been on the rise globally since its discovery in the mid-1970s in Lyme, Connecticut (1). This is evident in the United States, where only 9903 human cases were reported in 1992 compared to 19,931 by 2006 (2). It is currently the most common vector-borne infection in North America, although it is also found in Asia and Europe, and is within the top ten most frequently reported nationally notifiable diseases in the United States (1, 3). Approximately 20,000-30,000 confirmed cases occur annually in the US, but a 2008 study estimated the true frequency of cases to be between 240,000 and 444,000 (1, 3). While Canada only reported 707 human cases for 2015, it is increasing there as well with only 128 cases reported for 2009 (4). Surveillance efforts tend to only detect a portion of cases, meaning that the actual number of infected humans is likely higher (3, 4). *B. burgdorferi* is carried by ticks from the genus *Ixodes*, and transmitted to humans through a tick bite, which allows the bacteria to reach the blood stream of the tick's host and disseminate (1, 5). Typical symptoms of early Lyme disease include nonspecific flu-like symptoms, fever, and rashes, but if left untreated, the infection can develop into early and late disseminated forms that can cause severe joint, heart, and neurological conditions (1, 5). While the cost of Lyme disease to patients is high through its potential for considerable morbidity, it also is very costly for society as a whole; in 2002, a study found that the estimated annual nationwide economic impact of Lyme disease in the United States was 203 million US$, but this is considered to be a low approximation due to the suspected underreporting of Lyme disease cases (6). This is supported by a study conducted in 2008, which found the cost for only testing Lyme disease was approximately 492 million US$, which does not include other costs such as treatment (3).

It is believed that the rise in cases of Lyme disease worldwide, especially in regions previously unaffected, is due to a combination of factors including climate change, suburbanization, and larger deer populations, a primary final host for ticks (1, 7, 8). Canada is one region where Lyme disease has relatively recently emerged to become a public health issue of increasing concern (9). Lyme disease has been on the rise in Canada since 1997,

as endemic areas, which are defined as locations where *B. burgdorferi* has been shown to be transmitted by an established population of ticks, are becoming more common along with the risk of human exposure (10); by 2012, cases had been reported in all provinces, although these were not necessarily all locally acquired (9, 10). Consequently, Lyme disease is considered a significant public health concern for Canada, which is evident through being named a nationally reportable disease in 2009 to assist with surveillance efforts across the country (10).

However, despite surveillance efforts, only a fraction of the actual number of human cases in Canada has been captured (12). The number of cases reported is suspected to be an underrepresentation, and so uncertainty persists around the actual incidence and prevalence of Lyme disease in Canada, specifically in regard to early clinical Lyme disease (9, 11). To additionally complicate the situation, Lyme disease is accompanied by a fair amount of controversy in the United States, some of which appears to have crossed the border into Canada (12-15). Most of the controversy surrounds the accuracy of testing procedures for Lyme disease and the management of "chronic Lyme disease" or "post-treatment Lyme disease syndrome", about which there is considerable confusion even among its terminology and existence (12-15). The misconceptions around certain characteristics of Lyme disease have created divides within and between different sectors of society including the scientific, political, medical, and public (14). The controversy is particularly troublesome when it occurs between physicians and patients, and a number of Lyme disease advocacy groups have been formed as a consequence (15). While the controversy in Canada does not appear to have reached the extent of that in the US, that which does occur only serves to worsen the public health issue that Lyme disease has become, and has the potential to grow along with the number of cases if persisting misconceptions are not resolved.

While much is known about the biology, ecology, and epidemiology of Lyme disease, studies on behavioural risk factors and prevention measures are somewhat rare and poorly integrated (16). In an attempt to resolve the controversy caused by this health issue, a handful of studies have been done to assess public and physician awareness and behaviours

surrounding Lyme disease in different regions (16-22). Evidence on these factors was primarily obtained through similarly structured questionnaires, and overall it was concluded that study participants were fairly knowledgeable in terms of Lyme disease, but this varied based on the question asked (17-22). Topics included demographics, general Lyme disease knowledge, attitudes towards Lyme disease, preventive practices, and diagnosing and treating guidelines (17-22). Physicians in particular were weak in the areas of diagnostics, testing, and reporting (17-19). Higher levels of knowledge typically result in the practice of evidence-based behaviours, as displayed by one study that provided a targeted Lyme disease educational program to the public, although the direct effects of these interventions are not always predictable (7). Consequently, more research needs to be conducted in order to understand how physician and public awareness and behaviours are affecting Lyme disease outcomes. Not only does this have the potential to assist in resolving some of the controversy and division that surrounds Lyme disease, but it also may increase case reporting, preventive behaviours, and other best practices. To efficiently direct public health resources it would particularly be useful to determine the best strategies, within specific contexts, with which to target the public and physicians in order to achieve the greatest effects in reducing negative Lyme disease outcomes.

In order to address the gap in the current literature on Lyme disease, the objectives for this study are:

1. To model how public and physician awareness and behaviour surrounding Lyme disease evolves with increasing disease prevalence, and how this affects incidence, diagnosis, progression to treatment, and patient outcomes.
2. To apply the model to determine the best intervention strategies for targeting the public and physicians to minimize negative Lyme disease health outcomes.

Previous studies that have evaluated physician and public behaviours and awareness are largely descriptive, and have not taken into account how these behaviours and awareness inter-relate and change over time according to different societal perceptions of Lyme disease. These factors are likely susceptible to varying levels of disease prevalence, but little consideration has been given to how the relative effects of physician- or public-based

interventions may change depending on the endemicity of the infection in the environment. Furthermore, Lyme disease behaviours and awareness have been primarily studied through questionnaires or surveys to date, which are subject to limitations including non-response and recall bias. Using a questionnaire also allows for results to only be gathered from a single moment of time, like a snapshot, instead of displaying how an issue progresses. In order to address such limitations, system dynamics simulation was used to fully explore models of awareness and behaviours, and how these behaviours and awareness interact to result in different Lyme disease outcomes. System dynamics improves understanding of how a system functions by assisting in building a model of the system, its variables, and relationships. After development the model can be used to explore behaviour by running experiments where certain variables are held constant and others changed. To test the impact of public and physician awareness and behaviours on health outcomes, the model was used to run experiments targeting the public and physician populations separately with educational interventions to determine which was more successful at reducing negative Lyme disease outcomes such as cumulative incidence. System dynamics modelling is an appropriate method for analysing such dynamic population level relationships that evolve over time and are environment dependent. Additionally, on a topic with little data currently available, building a model permitted the inclusion and synthesis of all of the existing best evidence.

The results from this study demonstrated that in scenarios similar to those modelled, public-based interventions have a greater chance of success than physician-based interventions for reducing negative Lyme disease outcomes. This was evident through lower disease incidence and fewer late stage cases, while diagnosis rates stayed similar. However, the results indicated that until more research is conducted to assess the effectiveness of such interventions in practice, multifaceted interventions with a focus on the public are the best approach. Other gaps in knowledge around Lyme disease that were determined to be important to model behaviour, such as how disease stages progress and the initial level of population awareness, were also identified as priorities for future research. As a strong communication tool, the completed model provides an ideal opportunity to bring together different facets of the health community such as public health

authorities, patients, physicians, and researchers. As a result, knowledge translation and dissemination were key components of this project, as well as learning how to translate health research into public health policy.

CHAPTER 2: BACKGROUND AND LITERATURE REVIEW

2.1 History of Lyme Disease

Lyme disease, a bacterial infection caused by *Borrelia burgdorferi* (*Bb*), is currently on the rise worldwide (1). It was discovered in 1975 in Old Lyme and East Haddam, Connecticut, when an epidemic of arthritis arose, primarily among children (1, 23). The first period of symptoms was noted to typically last a week, bringing sudden pain and swelling in a large joint (23). Other symptoms included nonspecific flu-like symptoms such as a headache, fever, chills, and general malaise, and subsequent episodes of illness were common (23). A specific lesion, called erythema migrans (EM), was frequently present in patients as well; it had previously been linked to bites from sheep ticks, *Ixodes ricinus*, in Europe (23). Lyme disease is currently the most common vector-borne infection in North America, although it is also found in Asia and Europe, and is within the top ten most frequently reported nationally notifiable diseases in the United States (1, 3). Approximately 20,000-30,000 confirmed cases occur annually in the US, but a 2008 study estimated the true frequency of cases to be between 240,000 and 444,000 (1, 3). This number has grown considerably, as only 9903 cases were recorded in the United States in 1992 (2).

2.2 Borrelia burgdorferi: The Infectious Agent

Although the first recorded cases of Lyme disease occurred in the 1970s, the causative bacterium was not identified until 1982 (1, 2, 23). The gram-negative, helical, motile, spirochetal bacterium was named *Borrelia burgdorferi* after its discoverer Willy Burgdorfer, a medical entomologist (1, 23). Tick-borne *Borrelia* species are classified into three main phylogenetic groups (2). These include: the Lyme borreliosis group, which was formerly named *Borrelia burgdorferi* sensu lato; the relapsing fever group which contains species such as *B. miyamotoi* and *B. lonestari*; and the recently created group of reptile-associated borreliae, an example of which is *B. turcica* (2). Nineteen genospecies of the Lyme borreliosis group are currently recognized, of which at least eight can cause human disease (2, 23). However, *B. burgdorferi* sensu stricto, *B. afzelii*, and *B. garinii* are responsible for most human Lyme disease infections (2, 23). The genotypic and phenotypic

heterogeneity of these genospecies are apparent in that each has its own reservoir host(s) and clinical signs of infection (2, 23).

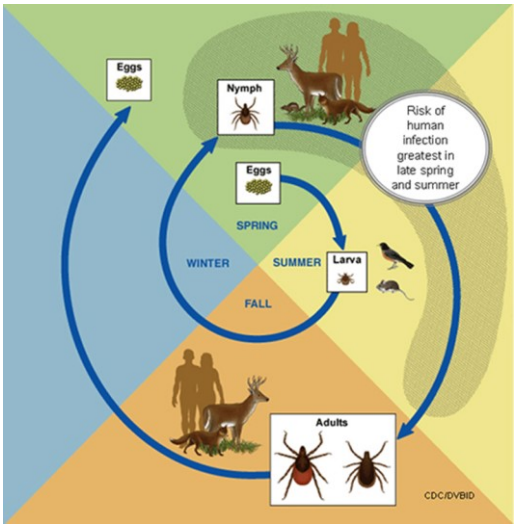
Bb persists through enzootic cycles, using a variety of mammals, reptiles, and birds as reservoirs (23). Griffin defines reservoir species as "hosts that are commonly infected with an organism and remain infectious for the vector for prolonged periods of time" (23). In the case of *Bb* specifically, the use of a species as a reservoir mainly depends on how well the host complement system can deactivate the bacterium; the key reservoir species of *Bb* is considered to be the white-footed mouse, *Peromyscus leucopus* (23). *Odocoileus virginianus*, white-tailed deer, is also an important reproductive host species in regards to *Bb* as a common final host for its tick vectors, thus enabling larger tick populations. However, deer blood can inactivate *Bb*, which means that deer cannot transmit the infection and are dead-end hosts for the bacterium (23).

2.3 Ixodes: The Vector

Lyme disease is transmitted to humans by ticks from the genus *Ixodes* (1). *Ixodes scapularis*, which was previously called *Ixodes dammini* and is commonly referred to as the deer tick or blacklegged tick, acts as the main vector in North America (1, 10, 23). Related species of ticks, which provide a significant risk for directly transmitting *Bb* to humans through feedings, include: *I. pacificus*, which is found on the Pacific coast of North America; *I. persulcatus*, which occurs in Asia and Eastern Europe; and *I. ricinus*, which exists in Europe, West Asia, and North Africa (2, 23). The distribution of *I. scapularis* mainly depends on the availability of hosts, especially white-tailed deer, and if the requirement of high humidity is met in a region (23). As a result, there are significant populations of this tick in Southern Canada (23). *I. scapularis* is a hard tick, and it undergoes a complex life cycle that takes two years to complete (Figure 2.1) (23). Ticks transition from an egg to a six-legged larvae to an eight-legged immature nymph, before finally developing into an eight-legged mature adult (23). Adult ticks deposit eggs in early spring, which reach the nymphal stage by the following spring or summer, which is the first stage associated with Lyme disease (23). This causes Lyme disease to be considered a seasonal infection as cases mainly arise in the summer months due to the high number of

infection transmitting ticks during this time of year (23). At each stage, *I. scapularis* must obtain a blood meal for morphogenesis before it can advance to the next level of maturity (23). To do so, ticks walk to the tips of plants to "quest", which means they wave their front legs around until a suitable host comes close enough for attachment (23).

Figure 2.1 Life Cycle of Blacklegged Ticks (CDC, 2011)



*Available from: http://www.cdc.gov/lyme/transmission/blacklegged.html

While many different mammals, reptiles, and birds function as a host for *I. scapularis*, and by default for *Bb*, the white-footed mouse is the main host for immature *I. scapularis* (23). The white-footed mouse is prone to having ongoing *Bb* infections, which means that ticks often acquire *Bb* during their larval stage when they feed on these mice (23). In return, nymphal ticks typically infect the next generation of mice with *Bb* (23). Adult ticks tend to feed on larger animals, including deer, humans, or pets such as cats and dogs, but both nymphal and adult ticks can transmit *Bb* to humans during feedings (23). Transovarial transmission of *Bb* is rare (less than 0.1% of the time), so eggs are not commonly infected; however, larvae may pick up *Bb* at a tick's first feeding (23). Consequently, if nymphs feed before the next generation of larvae in a tick population, which is common in the Northern United States and Canada, host populations have an elevated prevalence of *Bb* compared to locations where the opposite situation occurs (23). Ticks can only clear a *Bb* infection from their system by feeding on an incompetent host, such as deer (23).

Ticks that have been infected with *Bb* have hundreds of spirochetes in their gut lumen (23). When these ticks feed on a host, the *Bb* organisms multiply in excess of a hundred-fold and then enter the tick salivary glands; it takes, on average, approximately 60 hours after a tick has begun feeding on a host of any kind for enough spirochetes to reach the salivary glands to pass infection (23). Humans acquire the infection when they are bitten by an infected tick, which allows the bacteria to enter and disseminate through the human blood stream and lymphatic system (5). The risk of transmission is affected by how long the tick is attached and if it is engorged from feeding (5); it takes 24-48 hours for an attached tick to transmit *Bb* infection specifically to a human host (24). *I. scapularis* ticks pose a greater risk of transmitting *B. burgdorferi*, as there are higher rates of bacteria-carrying ticks within their populations compared to other species of *Ixodes* (10).

2.4 Lyme Disease Surveillance

Lyme disease surveillance requires the analysis of at least two different species: ticks and humans. Tick surveillance assists provincial and territorial public health organizations in finding regions of Lyme disease risk prior to the development of autochthonous human cases (12). In Canada, tick surveillance involves both passive and active surveillance techniques. In terms of passive surveillance, the Public Health Agency of Canada's National Microbiology Laboratory, as well as other labs, accept tick specimens from medical and veterinary clinics and the public (12). The labs identify these ticks, test them for infections, and then study the results to identify emerging Lyme disease risk in the environment (12). For active tick surveillance in Canada, ticks are collected directly from the environment or host species in emerging at-risk areas, which are identified through the efforts of passive surveillance (12). These tick samples then undergo the same process in the lab as those received through passive surveillance, to better determine the actual risk of contracting Lyme disease in these areas.

Endemic areas for Lyme disease are generally defined as "locations where *B. burgdorferi* has been demonstrated to be transmitted by an established population of vector ticks" (3). More specifically, endemic areas are subdivided into confirmed endemic areas, suspected endemic areas, and risk areas (23). Confirmed endemic areas are regions where active

surveillance has detected a) reproducing vector tick populations, which are confirmed by finding larval, nymph, and adult ticks on local animals or in the environment for more than two years and b) *Bb* in ticks or wild animal hosts through culture, PCR, or immunofluorescent antibody staining (23). Suspected endemic areas are where active surveillance has found multiple ticks during one or more visits, which demonstrates that the tick vector is becoming established, and where *Bb* has been found in ticks or animals from the site (23). Risk areas are those where tick vectors have been found by sampling ticks from the environment or local animals, whether or not *Bb* has been detected in any samples (23).

Human surveillance helps to determine the incidence of Lyme disease, which human populations or subpopulations are at risk, where and when Lyme disease occurs, and what the clinical appearance of Lyme disease looks like (12). Currently Canada uses both a confirmed and probable case definition in the national surveillance of human cases. Confirmed cases are defined as:

> An individual with clinical evidence of illness with laboratory confirmation by isolation of *Bb* from an appropriate clinical specimen, or by detection of *Bb* DNA by PCR
>
> Or
>
> Clinical evidence of illness with a history of residence in, or visit to, an endemic area and with laboratory evidence of infection by approved serological methods and test interpretations (25).

Probable cases are defined as individuals with:

> Clinical evidence of illness without a history of residence in, or visit to, an endemic area and with laboratory evidence of infection (*i.e.*, positive or unequivocal ELISA and positive IgM and IgG Western-blots
>
> Or
>
> Clinician-observed erythema migrans without lab evidence but with a history of residence in, or visit to, an endemic area (25).

Consequently, while cases from all diagnostic methods (clinical and laboratory) are supposed to be reported for surveillance, usually only cases diagnosed through laboratory tests are (5). In Canada, more than 700 human cases were reported in 2015. However, surveillance is noted to only detect a portion of cases, meaning the actual number is likely to be higher. The Public Health Agency of Canada asks provincial and territorial agencies to report their number of human cases each year, which is based on what health care providers and laboratories report to these regional authorities; if Lyme disease is a reportable disease in a province, reporting to public health is legally required.

2.5 Clinical Progression of Lyme Disease

It is rare for cases of Lyme disease to result in death, with only seven cases reported in the US and Europe by the end of 2013 and five additional Lyme disease associated deaths documented in a 2016 article (12, 26, 27). However, Lyme disease commonly causes morbidity (12). Typical symptoms of early localized Lyme disease include rashes, fevers, chills, malaise, a stiff neck, a headache, myalgia, arthralgia, or other nonspecific viral symptoms (1, 23). The most indicative and earliest symptom of infection is erythema migrans (EM), an expanding round to oval lesion with sharp borders that is red to bluish in colour and present in approximately 80% of cases (5, 23, 28). Developing from days to weeks at the site of a tick bite, EM causes no pain but is warm, with 50% of patients reporting mild symptoms such as itching or burning (23, 28). While the size can range from very small to up to 80 cm in diameter, with an average diameter of 16 cm, EM must be at least five cm in diameter for diagnosis (5, 28). It tends to be found in or around the bends of large joints, such as the armpit or groin, and while it can be found almost anywhere else on the body, it never occurs on the palms or soles (28). The two main forms of EM are: solitary, the most typically reported type, where the lesion can be uniform in colour or have a central clearing, causing it to look like the distinctive “bulls-eye”; and multiple, with patients having a range of two to 70 lesions, with a mean of three to five (5, 28). Lesions are most often homogenous, with only 19% presenting as bulls-eyes (5). In the case of multiple lesions, which occurs in 10-25% of EM patients and is more common in the US than Europe, it is thought that *Bb* either disseminates from the original source to cause the additional lesions or that the cause is multiple bites (5, 28, 29). While EM comes in several

different forms, they are generally distinct enough from other similar conditions to allow for recognition and diagnosis (28). There are rare cases of incomplete annular lesions that do not resemble classic EM which are harder to diagnose, but based on the time course of development and distinctive EM features identification is possible (28). EM, compared to most other similar conditions, grows, rather than shrinks, with time (28). Additionally, EM tends to have less severe symptoms than those of confounding conditions (28). Even with no treatment, these cases of early Lyme disease regularly resolve by themselves within three to four weeks (23).

If early Lyme disease goes untreated, it can potentially progress into early, or secondary, disseminated Lyme disease one to six months after exposure (10, 23). This phase typically results in more generalized, or multiple, EM accompanied by symptoms similar to those experienced during early Lyme disease with the addition of neurological or cardiac symptoms (10, 23). Multiple secondary circular lesions can develop that are accompanied by symptoms such as encephalopathy, conjunctivitis, severe lethargy, generalized lymphadenopathy, or splenomegaly (23). Another type of skin lesion called lymphocytoma may also occur at this stage, but for the most part this only occurs in Europe (23). Carditis is present in 5-16% of untreated individuals with secondary disseminated Lyme disease, which may necessitate temporary pacing if severe palpitations are present; if not, it usually resolves within six weeks (23). Neurological symptoms occur in 10-15% of untreated individuals, as *Bb* has a propensity for invading the central nervous system (23). These manifestations include: meningitis, meningoencephalitis, central nervous palsies, and radiculitis (23). Patients who experience meningitis regularly present with signs of encephalitis, including seizures, behavioural abnormalities, ataxia, and depressed concentration (23). The most characteristic neurological conditions associated with Lyme disease are cranial or peripheral neuropathies, and in particular Bell's palsy (23).

If an infection remains untreated, it can further develop into late disseminated Lyme disease weeks to months after the initial exposure (10, 23). Further neurological manifestations can occur in this stage, but they are rare; the most common symptom of late disease is arthritis, which is sometimes referred to as Lyme arthritis (10, 23). Lyme arthritis

is present in 60% of untreated patients and usually affects large joints, such as the knee (23). Arthritis attacks can continue for weeks or months, and have the potential to become relapsing and reoccur over the years (23). Chronic arthritis which is resistant to treatment can also develop, which is thought to be attributable to an autoimmune response in certain individuals (23). A characteristic skin lesion, referred to as acrodermatitis chronica atrophicans, sometimes presents as well in the late stage of disease, but again typically only in Europe (23). This lesion ultimately progresses to finger or toe loss, and regularly results in joint deformities and polyneuropathy (23). The neurological effects of late Lyme disease are less recognized, but they include: chronic progressive leukoencephalitis, which can resemble MS and primarily occurs in Europe, encephalopathy, and generalized polyneuropathy (23).

2.6 Chronic Lyme Disease and Post-Treatment Lyme Disease Syndrome

Although controversial in its definition, when individuals have ongoing long-term effects or conditions associated with Lyme disease it can be referred to as "chronic Lyme disease" or "post-treatment Lyme disease syndrome" (PTLDS) (2, 9, 23). Although sometimes used interchangeably, in the medical community these terms typically have distinct meaning, particularly in regions with a long history of Lyme disease. Chronic Lyme disease is usually used to describe nonspecific symptoms caused by a lasting bacterial infection, even in many cases with little or no evidence of past or current *Bb* infection, and its advocates support long-term antibiotic treatment (2, 9). PTLDS is used to reference previously infected and treated individuals who have continuous or reoccurring symptoms with no evidence of an ongoing infection; PTLDS is regularly misdiagnosed as a type of chronic Lyme disease (2). The controversy around PTLDS occurs when some affected individuals request additional antibiotic treatment for their symptoms. Many members of the medical community argue that a lack of lab or clinical evidence disproves an active infection, meaning no further antibiotic treatment is required (2, 9, 12). Furthermore, long-term antibiotic use is considered to be an unreasonable option, as its effectiveness has not been proven, it may cause adverse reactions, and it may allow bacterial resistance to develop (2). This issue is quite contentious within the health world, with physicians on both sides; some labs have even gone so far as to perform unvalidated tests, such as a urine antigen

test, in support of providing additional treatment for those with chronic Lyme disease and PTLDS (2).

Persistent conditions that have been linked to Lyme disease include: chronic fatigue syndrome, palpitations, dyslexia, and other degenerative, inflammatory, and neuropsychiatric conditions (2, 23). While many argue that no scientific evidence exist to support these claims, no satisfactory explanations currently account for these phenomena (2, 23). Suggestions of other reasons for the symptoms have been made which include undiagnosed co-infections, autoimmune reactions, or other syndromes such as fibromyalgia (2). The characteristics of Lyme disease serve to fuel further speculation on this issue: it is an emerging disease, symptoms can occur a long time after initial infection, definitive diagnostic tests are lacking, and high prevalence in endemic areas means some patients will unavoidably have another potentially confounding condition at the same time (23). Although it is clear that Lyme disease can cause lasting detrimental effects on the health of infected individuals, further investigations are needed to determine the exact mechanisms of this phenomenon and what can be done about it (23).

2.7 Tick-Borne Co-Infections

Many studies have recently been undertaken to detect other infections carried by *Ixodes* ticks that might be transmitted to humans during feedings (2). They were found to include: *Babesia* spp., *Anaplasma* spp., *Rickettsia* spp., *Francisella* spp., Q-fever agents, and tick-borne encephalitis virus (2). These co-infections regularly cause more severe or unusual Lyme disease outcomes, while at the same time complicating diagnosis and treatment (2). Furthermore, individuals can be infected with more than one *Borrelia* species at one time, a situation which also creates atypical and likely more severe Lyme disease symptoms (2). In nature, *Ixodes* commonly carry many different pathogens at the same time, which means that humans have a relatively high risk of experiencing co-infections if bitten by a tick (2). A northeastern US study found that after testing 845 nymphal ticks, 23 (2.7%) had both *Bb* and either the causative agent for human anaplasmosis or babesiosis (8). Due to the complicated characteristics of co-infections, they are frequently underdiagnosed although they regularly arise; this creates a problematic health issue (2). Prospective studies have

been conducted to attempt to determine the incidence of these co-infections in Lyme disease patients (30). Using molecular evidence, it was found that babesiosis and human anaplasmosis co-infections, two common types, occurred in 4-45% of Lyme disease patients from endemic areas (30). Lyme disease co-infections require current and accurate medical knowledge about Lyme disease to assist with the diagnosis and treatment of these cases in order to avoid more severe outcomes (2). It was concluded that more research is needed in this area, while a re-evaluation of diagnostic and treatment guidelines should also occur with co-infections in mind (2).

2.8 Diagnosis and Treatment Guidelines for Lyme Disease

Different stages of Lyme disease require different methods of diagnoses and treatment. Furthermore, as previously mentioned, tick transmitted co-infections can further contribute to diagnostic difficulties (2, 9). The presence of EM in an individual who visited an endemic area during Lyme disease season is considered diagnostic (2, 5, 23). In these cases, treatment is promptly initiated, and serological testing is not needed to confirm the diagnosis (31). If an infection has progressed to late dissemination, clinical evidence of secondary disease such as meningitis accompanied by peripheral or cranial neuropathy is indicative of a Lyme disease diagnosis, which can be confirmed by a laboratory test (23). Serology is the preferred initial laboratory method, although cultures are still the confirmatory diagnostic standard; cultures require isolating *Bb* from EM biopsies and are typically not available (2, 5, 23). Furthermore, *Bb* cultures are primarily positive only early in the disease (23). *Bb* DNA can also be detected by PCR in synovial fluid collected from joints affected by arthritis, as well as from cerebrospinal fluid and blood, but with varying levels of success (2, 23).

Serological guidelines recommend that a two-tier testing protocol be used, which employs an enzyme-linked immunosorbent assay (ELISA) test followed by a Western-blot test to confirm ELISA if it is positive (2, 5, 23). However, this testing protocol does not always give accurate results, even with its two-tiered approach, especially when a patient is in the early stages of Lyme disease (5). Serological tests, and IgM assays in particular, have been found to often have low specificity (2). Furthermore, a case-control study has demonstrated

that the two-tier protocol has only a 35% sensitivity and 98% specificity for early Lyme disease cases, and it is believed that these values may be even lower (5). Hence, the reason that diagnosis of early Lyme is a clinical diagnosis is because it is known that serology has poor sensitivity in the first four weeks of infection. Sensitivity does improve for later stages of Lyme disease (5), but this is not helpful for providing patients with an early diagnosis and treatment to lower the risk of persisting symptoms. It has been found that using enzyme immunoassays with recombinant or peptide antigens results in a more specific test than those that use whole-cell sonicates of *Bb* (23).

Consequently, it has been noted that physicians should have a good comprehension of why false negative or positive results may occur, and what limitations accompany these tests, to avoid misdiagnosis or inappropriate treatment (5). False results, and particularly false negatives, are usually attributable to when in the course of the disease a patient is tested, as antibodies develop slowly after the initial exposure (2, 12, 23). *Bb*-specific IgM antibodies form first, but may not be present early in disease (2, 12, 23). IgG antibodies usually become present in the blood only after an individual is ill for one or two months, during the secondary phase of infection; at this time these antibodies may also be present in the cerebrospinal fluid if there is a neurological aspect to the disease (12, 23). As a result, if IgG is tested for shortly after symptoms begin, instead of IgM, a false negative result will occur. Repeated testing is not recommended, even to determine if treatment has been effective, as IgG and IgM antibodies may persist for months to years after initial infection because of an incomplete or failed regression of the adaptive immune response (2, 12). Therefore, the long-term presence of antibodies does not necessarily mean an ongoing infection is occurring, but includes the possibility that the individual had a previous infection that resolved, so further treatment is rarely necessary (12).

The recommended treatment for Lyme disease depends on the symptoms of the patient, but oral doxycycline is typically the preferred medication, as it is effective in treating Lyme disease as well as other tick-borne illnesses (2, 5). However, doxycycline is not recommended for children or pregnant women, so other forms of oral antibiotics including amoxicillin and cefuroxime axetil are used as well (23). Early disease typically requires

treatment for 10-21 days, which has been found to shorten the duration of EM, decrease the levels of antibodies that form, and reduce secondary sequelae including arthritis, carditis, and neurological disease (23). Occasionally, intravenous antibiotics such as ceftriaxone and cefuroxime are used for 14 days if patients experience severe neurological, cardiac, or arthritis symptoms (2, 5, 23). Antibiotic treatment for Lyme disease is considered to be highly effective, with excellent long-term patient outcomes (32, 33). Persistence or recurrence of symptoms is often thought to be attributable to reinfection (32, 33). However, more severe illness at time of treatment was found to lower effectiveness, and antibiotics did not resolve persisting disease (32, 33). As a result, there is currently no evidence to indicate that long-term or repeated antibiotic treatment is beneficial for any stage of Lyme disease, particularly in regard to persistent symptoms, although this issue is still debated (5, 23). Additionally, no regimen of Lyme disease treatment has been found to be effective against co-infections caused by *Babesia* spp. (2).

2.9 Risk Factors and Control Measures for Lyme Disease

The risk of becoming infected with Lyme disease is based on the density of infected nymphal ticks in a region (23). Consequently, greater tick exposure, which can be approximated by time spent in wooded, rural locations (prime tick habitat), further increases an individual's risk (23). The probability of developing Lyme disease in an endemic area after being bitten by a tick has been found to be 0.012-0.05 (1.2-5%) (23). However, this likelihood varies based on how long an infected tick is attached to an individual once they are exposed; if the duration of feeding is greater than 72 hours, the incidence of Lyme disease becomes significantly higher at 20% versus 1.1% (23). To reduce the level of Lyme disease risk in populations, a number of control measures have been or continue to be explored with varying levels of success (23). These measures can be divided into environmental and human prevention practices, and include: controlling reservoir host species, such as the white-footed mouse; controlling vectors that maintain the host species, for example white-tailed deer; controlling the vector itself, tick populations; preventing human exposure by adopting certain behaviours and practices; and employing prophylaxis or immunization (23). Referring to the lifecycle of the blacklegged

tick (Figure 2.1), these measures attempt to intervene at each stage where the tick could become infected or transmit infection.

Environmental prevention strategies target the ecological system that ticks, and *B. burgdorferi* spirochetes, reside in. One stream of environmental prevention strategies simply seeks to reduce tick populations, so that infected ticks come into contact with humans less often. For example, area-wide acaricides (pesticides that kill ticks) can be used to reduce tick populations, but they are very expensive to use over large amounts of land and must be reapplied each season over the whole region of tick habitat to be effective (24, 34). Additionally, while residential acaricides were shown reduce tick populations, they were not found to reduce the incidence of tick-borne disease (35). In general, members of the public tend to be reluctant to accept this strategy because of its potential for toxicity, environmental contamination, and harm to other organisms, including pets (34). Host-target acaricides have the advantage of reducing the amount of acaricide needed compared to area-wide methods, as hosts that ticks need to feed on for survival, such as deer or mice, are directly treated with an acaricide, but their effectiveness is not clear (34). Vegetation management, such as brush and leaf clearing and burning, and least toxic pesticides are also used as strategies for reducing tick populations, but they have been found to only have a temporary effect (34). Finally, biological control has been proposed as a strategy for reducing tick populations (34). It involves introducing certain species of key tick predators or infectious agents, such as birds or specific types of fungi, into tick habitat (34). However, this approach needs further evaluation on its effectiveness and potential detrimental effects before it can be used (34).

Another stream of environmental prevention strategies targets the hosts that ticks utilize for their feedings. For example, tick host removal involves exterminating the different wild hosts ticks feed on for survival (34). This reduces both the overall tick population and the number of infected hosts that ticks come into contact with during their feedings. However, large numbers of hosts must be eradicated to measurably reduce the number of ticks and Lyme disease, which is not feasible in most situations. Removing deer has had the greatest effect, as smaller hosts, such as mice, are almost impossible to eradicate due to their

numbers and the variety of species they include (34). Another prevention method that targets tick hosts is administering wildlife vaccines; hosts are vaccinated against Lyme disease through various methods (34). However, more research needs to be done to determine if this is an effective approach. Despite generally enjoying popularity with the public, environmental prevention strategies have certain limitations. These measures require having an element of control over the environment that has been found to be very difficult to maintain, for example in eliminating all the hosts that could potentially affect Lyme disease rates (34). Furthermore, they are extremely costly for the most part, and may cause irreversible damage to both the environment and untargeted organisms, including people. Intervention strategies must strive to do no harm, arguably in an even greater capacity then other aspects of medicine, so appropriate measures should not have the potential for such negative consequences.

Conversely, human behavioural modifications have been found to be inexpensive, effective, reasonable, and universally applicable (23). These measures can be generally divided into two main groups: practices to avoid tick bites, and strategies to prevent infection after being bitten. The first measure for preventing tick bites is to simply avoid areas where ticks exist and Lyme disease is known to be endemic (36). If this is not possible, such as for those who live in endemic areas, tactics to prevent tick bites include: wearing light clothing so ticks are visible on it, avoiding areas of high grass and shrubbery, employing insecticides, and limiting tick access to skin by covering up with clothing (24, 36). However, these sorts of prevention efforts become less reasonable when exposure risk is not controllable, such as for residents of endemic areas who risk exposure to ticks whenever they venture outside (23). During the summer months, it is especially difficult to constantly cover up due to the hot ambient temperatures (23). Landscaping is a mixture of personal and environmental measures, as it involves nature but can be done on an individual level. Using fencing to separate high risk areas, such as woods, from yards has been shown to be protective (37). Other landscaping approaches include: using gravel or woodchips to form a barrier, which slows tick dispersal and serves as a visual reminder of risk; keeping grass short; and removing brush and leaves, as sun exposure dehydrates ticks (24, 34).

If unsuccessful at avoiding a tick bite, it is necessary to proceed to measures that prevent infection after being bitten. As previously mentioned, it takes approximately 24-48 hours for a tick to transmit *Bb* to a human during feeding, so if a tick is found and removed before that period of time, a person will not contract the infection (24). One study found that checking for ticks within 36 hours of being outside protected against Lyme disease (37). If a tick is found during a tick check, the proper method for removal is to use tweezers or fingers to gently grasp the tick as close to the skin as possible, then pull the tick straight out without jerking, twisting, or squeezing it (38). It is important to remove a tick in this way so that the tick's mid-gut section, which contains the *Bb* spirochetes, is not permitted to transmit infection (24). After removing the tick, clean and disinfect the bite (38). Bathing within two hours of being outside has been demonstrated to be protective against Lyme disease as well, as it also decreases the likelihood of a tick transmitting the infection (36, 37). One limitation of tick checks is that nymphal ticks are almost impossible to find and remove because of their small size (23). However, with all things considered, human behavioural prevention efforts appear to pose the best chance of success in reducing the risk of Lyme disease within populations, and the more often these practices are followed, the lower the risk of infection.

The final human measure for preventing infection is antibiotic prophylaxis. Antibiotic prophylaxis after tick exposure has been found to be effective, but is typically not recommended due to its expense; to be cost-effective in a human population, the probability of infection must be higher than 0.036 or 3.6%, with a prevalence of infected ticks above 10%, a situation which occurs in few regions (23). Furthermore, even in endemic areas the adverse reactions associated with such a treatment are greater than the risk of infection (23). While a vaccine for Lyme disease currently does not exist, in 1998 the United States released a transmission-blocking Lyme disease vaccine that had 76-100% efficacy after three doses with only moderate side effects (23). It was taken off the market in 2002 due to low acceptance from physicians and the public for reasons that included: concern about it causing autoimmune disease; its high cost compared to antibiotic treatment for infection; the need for regular boosters; and the low risk of Lyme disease in

many areas (23). However, new Lyme disease vaccines are currently being developed, with plans to improve on the previous design by using multiple immunogens (23).

2.10 Lyme Disease in Canada

Lyme disease is on the rise globally, both in terms of increasing rates and emerging in previously unaffected regions (2, 7). The incidence of Lyme disease and its prevalence, which is measured by the seropositivity in human populations, has been found to differ among regions due to: the prevalence of *Ixodes* ticks that feed on humans, the proportion of these ticks that are infected with *Bb*, the virulence of *Bb*, and the opportunity for human exposure (23). Consequently, factors for a higher number of cases of Lyme disease include suburbanization, larger deer populations, and climate change (1, 7, 8). Suburbanization provides more opportunities for individuals to be exposed to ticks, and Lyme disease, as suburban areas began to expand into habitats more suitable for ticks and their typical wildlife hosts. Larger deer populations, as important hosts for ticks, have also been linked to growing tick populations (1). Climate change in particular has been affecting Lyme disease rates in more northern climates, as warmer temperatures have enabled a northward migration of tick populations as well as reduced the typical tick mortality that occurs during cooler months (1, 7). However, others argue that there is little evidence that the increasing temperatures due to climate change are an important factor in the emergence of Lyme disease in previously unaffected regions, but rather that the key meteorological element related to climate change is having a moist environment in the spring (23). In either case, changing environmental conditions impact the incidence and prevalence of Lyme disease from one region to the next.

Canada has globally been one of the regions most affected by these environmental changes, with tick populations and endemic areas increasing across the country since 1997 (10). Human cases have now been reported in all provinces, making Lyme disease a great concern to public health (9). Canada reported 128 human cases of Lyme disease in 2009, which increased to 707 cases in 2015 (4). However, despite surveillance efforts, only a fraction of the actual number of human cases has been able to be captured (4). This is partly attributable to the passive nature of national human Lyme disease case surveillance in

Canada, as the Public Health Agency of Canada depends on each province and territory to independently submit their number of cases each year, which is based on reports that health care professionals and laboratories send to regional authorities (4). As a result, the number of cases reported is often an underrepresentation and uncertainty persists around the correct statistics for cases, specifically in regard to early clinical Lyme disease (9). In 2009, to assist with Lyme disease surveillance, Lyme disease became a nationally notifiable disease, which also emphasizes its importance as a public health issue (10). However, due to the relatively new endemicity of Lyme disease in Canada, some physicians may be inexperienced in detecting and recognizing this infection (9). This, coupled with the complexities surrounding diagnosing Lyme disease, has the potential to result in treatment delays which are costly to both patients and society as a whole (9). Furthermore, this underreporting of cases could contribute to the uncertainty about the actual burden Lyme disease has on Canada's public health system, which adds to the controversy that occurs around this infection (9).

2.11 Lyme Disease in Nova Scotia

With Nova Scotia almost at the point of having a suitable climate for ticks all across the province, Lyme disease has become an important provincial public health concern (11). The first locally acquired case of Lyme disease occurred in Nova Scotia in 2002, and the number of cases in the province has been growing rapidly since, along with the size and number of tick populations and Lyme disease awareness (11). Between 2002 and 2014, 447 cases were diagnosed in Nova Scotia, with approximately 94.8% of them believed to be transmitted by ticks resident in the province (39). The rate at which cases is increasing is a cause for concern, with 54 for 2011 and 115 for 2014 (11, 39). While this jump in cases may be partly attributable to changes in the case definition for Lyme disease in the province, it is unlikely that this is the only cause. It is not unrealistic to expect that Lyme disease cases have truly increased in Nova Scotia along with the endemic areas and risk, similar to other areas of Canada and the US. Furthermore, greater Lyme disease awareness may also have affected the number of cases in the province, as it would lead to improved recognition of the disease, causing more infected individuals to seek health care services and doctors to confirm the diagnosis.

Lyme disease is a reportable disease in Nova Scotia. Cases in Nova Scotia from 2002-2011 ranged from 3-83 years of age, and six cases were hospitalized, although no deaths have occurred to date (11). Risk factors for Lyme disease in Nova Scotia include being very young (0-9 years of age) or elderly (60-69 years of age) and being male (64% of cases) (11). Spending large amounts of time outside for work or leisure is also considered to be a risk factor (11). Although there has been a large effort on the part of public health in Nova Scotia to gain information on Lyme disease rates and risk factors in the province, much is still unknown, which is partially due to the suspected underreporting of cases (11). There are currently six endemic areas for Lyme disease in Nova Scotia, which include: Yarmouth, Pictou, Queens, Lunenburg, and Shelburne County, and parts of the Halifax Regional Municipality (31, 39). Consequently, there is an active tick surveillance program in place, along with the legally required reporting of human cases, to assist in finding new endemic areas.

To prevent and manage cases of Lyme disease, Nova Scotia uses the guidelines set in place by the Infectious Diseases Society of America (31). Consequently, preventive practices are encouraged as the best way to avoid getting Lyme disease, including proper tick removal as soon as possible after being bitten to prevent *B. burgdorferi* transmission (31). The two-tiered testing system of ELISA and a Western-blot is used to serologically confirm cases of Lyme disease in the province when required (31). Over 1000 Lyme disease screening tests have been performed annually on Nova Scotia residents from across the province during the last few years, a number which has more than doubled; less than 500 tests occurred annually in the 2001-2002 and 2002-2003 fiscal years (11). However, a 2012 report acknowledges that a better understanding should be gained about why physicians do or do not test, as well as their reporting practices (11). This would improve knowledge of testing practices and the extent of case underreporting in the province, specifically in regard to probable cases that do not require serological testing in order to meet the case definition (11). Unfortunately, this sort of research is noted to be beyond the scope of routine public health surveillance, as it requires an exploration of the knowledge, attitudes and behaviours of physicians in Nova Scotia (11).

2.12 Societal Impact of Lyme Disease

Lyme disease does not only come with a high cost for patients, due to the potential for considerable morbidity associated with an infection, but also for society in general. A study found that the estimated annual nationwide economic impact of Lyme disease for the United States in 2002 was 203 million US$ (6). However, this is believed to be a low approximation due to the commonly underreported rates of Lyme disease. This is supported by a study conducted in 2008, which found the cost for only testing Lyme disease was approximately 492 million US$, which does not include other costs such as treatment (3). Consequently, Lyme disease is a great burden to public health globally, and more resources need to be invested to increase knowledge and intervention measures.

Furthermore, although much is currently understood about the symptoms, disease trajectory, and treatment of Lyme disease, misconceptions persist that continue to confuse both physicians and patients (12). These misconceptions have created a fair amount of controversy in the United States, some of which appears to have crossed the border into Canada (12-15). The controversy largely pertains to whether the lab testing protocols for Lyme disease are accurate and how to manage "chronic Lyme disease" or "post-treatment Lyme disease syndrome", about which confusion exists even among its terminology and existence (9, 12-15). This controversy has resulted in division within and between different sectors of society including the scientific, political, medical, and public (14). This led the US Institute of Medicine to review the subject, and in the subsequent report it was noted that the result of this is "strong emotions, mistrust, and a game of blaming others who are not aligned with one's views" and a "heated and politicized debated" (14). This has created a division in the health care community between certain patients, doctors, and parts of the health care system which has had a detrimental impact on feelings of satisfaction and security in health services.

In medicine tension persists, even though it is acknowledged that Lyme disease diagnosis and treatment are now relatively well-understood (14). This is partially due to a separation between the traditional inductive approach that relies on observation and the newer strategy of evidence-based medicine (14). Furthermore, chronic Lyme disease and post-Lyme

disease syndrome in particular cause confusion among physicians in terms of their terminology and management; in Canada, most physicians support the concept of post-Lyme disease syndrome (9). Lyme disease controversy is especially troublesome when it occurs between physicians and patients, and a number of Lyme disease advocacy groups have been formed as a consequence (15). Some public organizations have gone on record to state that Lyme disease is rare in Canada, and that over-diagnosis and overprescribing practices should be avoided (9). This has created a population of patients who feel that they are not being accurately and promptly diagnosed with Lyme disease, and that their health concerns are not being heard. While the controversy in Canada does not appear to have reached the extent of that in the US, that which does occur only serves to worsen the public health issue that Lyme disease has become, and has the potential to grow along with the number of cases if persisting misconceptions are not resolved. Additionally, the situation is not improved by uncertainty around accurate human case rates and a lack of Lyme disease knowledge; however, it still unclear if this becomes problematic in physician or public populations in regard to negative health outcomes. Consequently, the ongoing debate highlights a need for further research to help address this issue and to pinpoint exactly where the break in effective communication is occurring between different sectors of Canadian society.

2.13 Epidemiological Studies on Lyme Disease Awareness and Behaviours

To assist in resolving some of the controversy surrounding Lyme disease, a handful of studies have been undertaken to measure the awareness of both physicians and the public, and in some cases how it affects behaviours (7, 16-22). Physicians' awareness and knowledge about Lyme disease was assessed in multiple regions with different levels of endemicity through similarly structured questionnaires (17-22). Topics included demographics, general Lyme disease knowledge, attitudes towards Lyme disease, and diagnosing and treating guidelines (17-22). It was found that overall, physician knowledge of Lyme disease was adequate, with an average knowledge score of around 75% (17, 18); however, the knowledge score varied based on which category of question was asked. Physicians' lowest scores were questions pertaining to diagnosis of Lyme disease, diagnostic testing, and reporting of cases (17-19), which is problematic because physicians

are primarily responsible for these activities. For example, physicians were found to rarely know that EM itself is diagnostic for Lyme disease in an endemic area, without any further testing required (average knowledge score of 26.1-28.3%) (17). This lack of knowledge could result in an increased number of unnecessary tests, which is further complicated by the possibility of false results due to the specificity and sensitivity issues of Lyme disease testing. Basing a patient's diagnosis on either false positive or negative test results would lead to inappropriate treatment.

Other research projects have targeted the general public to assess their knowledge and behaviours, typically through questionnaires as well (7, 16, 40). Questions were asked regarding: if prevention measures were undertaken and how frequently; risk perception of tick bites or infection; and belief in effectiveness of interventions (16). In the US, it was found that 92% of those who knew about Lyme disease believed that their chance of getting it was less than 50% (16) and only 40% of those surveyed practised preventive measures (7, 16). Being greatly concerned about getting bitten was highly associated with undertaking prevention activities, with an odds ratio of 8.34 (16). Having seen ticks, having a prior tick bite, hearing about Lyme disease, being concerned about Lyme disease, or knowing someone with Lyme disease were also associated with undertaking preventive behaviours (16, 40). However, it was found that individuals in endemic areas who said Lyme disease was a serious illness with high risks were actually less likely to undertake preventive measures, perhaps because they were "too experienced" (16); another study concluded that an increase in knowledge did not change levels of tick bites in a population (7). It is acknowledged that studies assessing behavioural risk factors and prevention for Lyme disease are rare, and that further research is required to address this.

One study evaluated the effect of preventive behaviours on the risk of contracting Lyme disease (37). It was found that a variety of protective measures have the possibility of significantly reducing the risk of becoming infected, such as checking for ticks within 36 hours of being outside (odds ratio of 0.55, 95% confidence interval 0.32-0.94), bathing within two hours of being outside (odds ratio of 0.42, 95% confidence interval 0.23-0.78), and employing fencing as a barrier (odds ratio of 0.54, 95% confidence interval 0.33-0.90)

(37). However, it is recognized that the effectiveness of preventive behaviours is not well understood (37).

The previously conducted studies on the topics of physician and public knowledge, awareness, and behaviours show that these factors are likely to have a great impact on Lyme disease outcomes. However, more research needs to be conducted in this area to discover precisely how they have an effect, how they are related, and how they are affected by variations in endemicity. This will assist in targeting susceptible populations with the most effective strategies to reduce negative Lyme disease outcomes, depending on different environments of awareness and behaviours.

2.14 Future Directions for Lyme Disease Research

Lyme disease is becoming an increasingly important public health concern, as it has a detrimental impact on both individuals affected by the disease and society as a whole, particularly because of escalating Lyme disease rates worldwide. Although the biology, ecology, and epidemiology of Lyme disease are fairly well understood, there is still much to learn about how awareness and behaviours surrounding this infection affect patient outcomes. Attempts have been made to measure the effect of these influences in both physicians and the public, but very little is known about how precisely differing levels of behaviours and awareness impact Lyme disease outcomes either positively or negatively. To efficiently direct public health resources it would be particularly useful to determine the best strategies, within specific contexts, with which to target the public and physicians to achieve the greatest effects in reducing negative Lyme disease outcomes.

Part of the reason for this failure is that the relationships between these factors are very dynamic, as they interact in different ways based on the environment in which they occur and how they influence one another. Previous studies that have evaluated physician and public behaviours and awareness have not taken into account how they inter-relate and change over time according to different societal perceptions of Lyme disease. These factors are also highly susceptible to varying levels of disease endemicity, but no consideration has been given to how the relative effects of physician- or public-based interventions may

change depending on the prevalence of the infection in the environment. For example, in a location with low Lyme disease endemicity, public and physician awareness is also likely to be relatively low, along with the practice of preventive behaviours. However, studies that analyse such complex interactions are next to impossible to conduct in the real world, because of limitations such as poor subject compliance, limited resources, and insufficient time (41). Additionally, many of the previously conducted studies on this topic have relied on questionnaires as their data source, a method that is known to have poor response rates, especially in physician populations. The end result of this approach is often small sample sizes for drawing inferences and the introduction of multiple biases that can affect study outcomes. Using a questionnaire also allows for results to only be gathered from a single moment of time, like a snapshot, instead of displaying how an issue progresses. Therefore, traditional methodologies have been found to be generally inadequate to address questions that deal with dynamic relationships such as those encountered with Lyme disease, so it would be worth exploring new approaches to rectify this issue (42).

Objectives:

In order to further understanding about Lyme disease awareness and behaviours, and to address the limitations and gaps in knowledge created by previously conducted studies, the research objectives for this study are:

1. To model how public and physician awareness and behaviour surrounding Lyme disease evolves with increasing disease prevalence, and how this affects incidence, diagnosis, progression to treatment, and patient outcomes.
2. To apply the model to determine the best intervention strategies for targeting the public and physicians to minimize negative Lyme disease health outcomes.

The results from this study will help clarify how health care systems should approach the management of Lyme disease, specifically in regard to how both public- and physician-based intervention strategies can be improved, and will identify areas requiring further research. Determining the best methods for targeting populations with Lyme disease interventions will also help direct health care resources in the most efficient way to achieve the greatest effects in reducing negative Lyme disease outcomes. However, to respect those

involved with the complexities surrounding Lyme disease, great care will be taken not to assign blame either to physicians or the general public for the negative outcomes of the disease. Instead, the focus will be on each group's relative contribution to the prevalence of Lyme disease, with an emphasis on how everyone has responsibility in resolving this public health issue. If this principle is successfully applied, the study outcomes will assist in resolving the controversy Lyme disease has created in Canada's public health system by providing further information to all stakeholders, from the general public to health care professionals. Consequently, this research provides an ideal opportunity to bring together different constituents of the health community such as public health authorities, patients, physicians, and researchers. As a result, knowledge translation and dissemination were key components of this project, as well as learning how to translate health research into public health policy.

CHAPTER 3: METHODS

3.1.1 Research Design: Rationale

It is typical for areas of public health research to have complications that limit the use of traditional methodologies, such as delays between cause and effect, nonlinear relationships between variables, feedback processes, and unexpected system behaviour (42). For example, increasing awareness and knowledge around health issues can prompt the undertaking of prevention measures, which modifies the relationship between these factors, as well as the dynamics of disease patterns (43). This mechanism is referred to as "feedback". A classic example of this in public health is the epidemiologic triad consisting of an external agent, a susceptible host, and an environment that brings the host and agent together (44). Used traditionally to model infectious disease, the variables of this triad interact in a variety of complex ways to produce disease (44).

A promising approach for gaining a further understanding of how public and physician awareness affects Lyme disease outcomes is simulation modelling, or systems science methods (42, 43, 45, 46). Modelling is used to help comprehend the relationships between a system's structure and its behaviour, and how these change over time (42). It is particularly useful as a method for resolving real world problems where experimentation is not possible due to either ethical or realistic constraints (46, 47). While simulation can be considered a relatively new method for addressing some areas of public health research, it has a long history in other areas such as infectious disease agent-based modelling (42). Modelling is particularly helpful for exploring health intervention programs because it permits decision-makers to visualize how the consequences of certain actions might play out over time in specific contexts (46). A variety of modelling methods exist, with the key types including: system dynamics simulation, agent-based modelling, network analysis, microsimulation, decision trees, discrete event simulation, and Markov modelling (42, 48). Once a model has been created, variables can be controlled and manipulated to understand how they interact in the system and affect outcomes. There is the potential for dynamic interplay between the variables under analysis within this study, which varies over time and according to different environments of Lyme disease endemicity. As the concepts of

dynamic interaction, system evolution over time, and relationship complexity are all central to simulation, this method is well justified for this study.

It is important to note that the strength of simulation is not to accurately predict outcomes for specific circumstances (*i.e.*, forecasting), as the number of factors and interactions that occur in real life situations are too complex to imitate. Instead, simulation is most successfully used as a powerful conceptual tool to provide and communicate insights on system behaviour and outcomes. Consequently, using simulation as the method for this research project has the potential to assist in clearly conveying the impact of policy options to interested stakeholders, thus supporting knowledge translation and dissemination. Furthermore, simulation is useful for investigating relationships between variables and synthesizing evidence on various cause-and-effect relationships to understand system consequences. The current literature on Lyme disease contains separate pieces of evidence within different studies regarding factors such as physician and public awareness, endemicity, testing sensitivity, and incidence. Using simulation will allow for the available pieces of evidence to be synthesized within a model in order to understand the implication of combining them, specifically in regards to Lyme disease outcomes.

3.1.2 Research Design: System Dynamics Simulation

The particular type of modelling used for this study is system dynamics simulation, which was invented in the 1950s by Jay W. Forrester and has been effectively employed since the 1970s for health research (42, 46, 48). System dynamics is based on endogenous theory, which means that it looks for explanations for events in the interactions between variables within systems (27). This type of simulation relies on causal diagrams, which are illustrations of the variables of interest and their cause-effect relationships, to help visualize mental models of systems (42). System dynamics works through dynamic modelling of stocks (*i.e.*, quantities) and flows (*i.e.*, inflow and outflow rates that modify the quantities), incorporating feedback processes, time delays, and information that determines the value for flows by employing a system of differential equations (46, 47). These systems of differential equations describe the interactions between variables over time. Computer programs numerically apply them to enable the study of model behaviour and

experimentation (42). Model development can be informed by literature or other sources of information to determine the directionality of relationships and to predict effect sizes (42). However, system dynamics models can also employ theory and conceptualization to include variables that do not have evidence readily accessible. Simulating a variety of realistic causal factors has been found to create more effective solutions to complex issues (48).

System dynamics has been successfully employed in public health research. Examples of topic areas system dynamics has addressed in public health include: disease epidemiology, including projects on HIV/AIDS and dengue fever; substance abuse epidemiology; health care capacity and delivery; and interactions between health care and disease epidemiology (48). System dynamics provides a way to frame, understand, and discuss the difficulties present within complicated systems (42). This particular type of modelling attempts to comprehend the possible impact of interventions or other problems during a specific time period where the trajectory to outcomes can be slow, complex, and is most easily shown through computer simulation (42). As a result, this approach is considered ideal for dealing with the dynamic relationships that occur within public health research (48).

System dynamics was selected for this study based on its strength in managing complex and evolving relationships at the population level. The objectives of this study include exploring disease endemicity and incidence, their relation to public and physician awareness and behaviours, and how this in turn affects diagnosis, progression to treatment, and outcomes. Therefore, the variables of interest function largely at the population level. System dynamics uses a compartmental model, which means that groups of people are represented in categories, which are occasionally further divided into subgroups such as sex or age (42). System dynamics is less adept than microsimulation methods at handling multi-variable attributes of individuals, or agent-based models at handling interaction between agents, but these were not requirements for this study. System dynamics is thus well suited to manage population level circumstances in which a variety of factors, such as diseases, health care, and risk factors, interact and evolve over time.

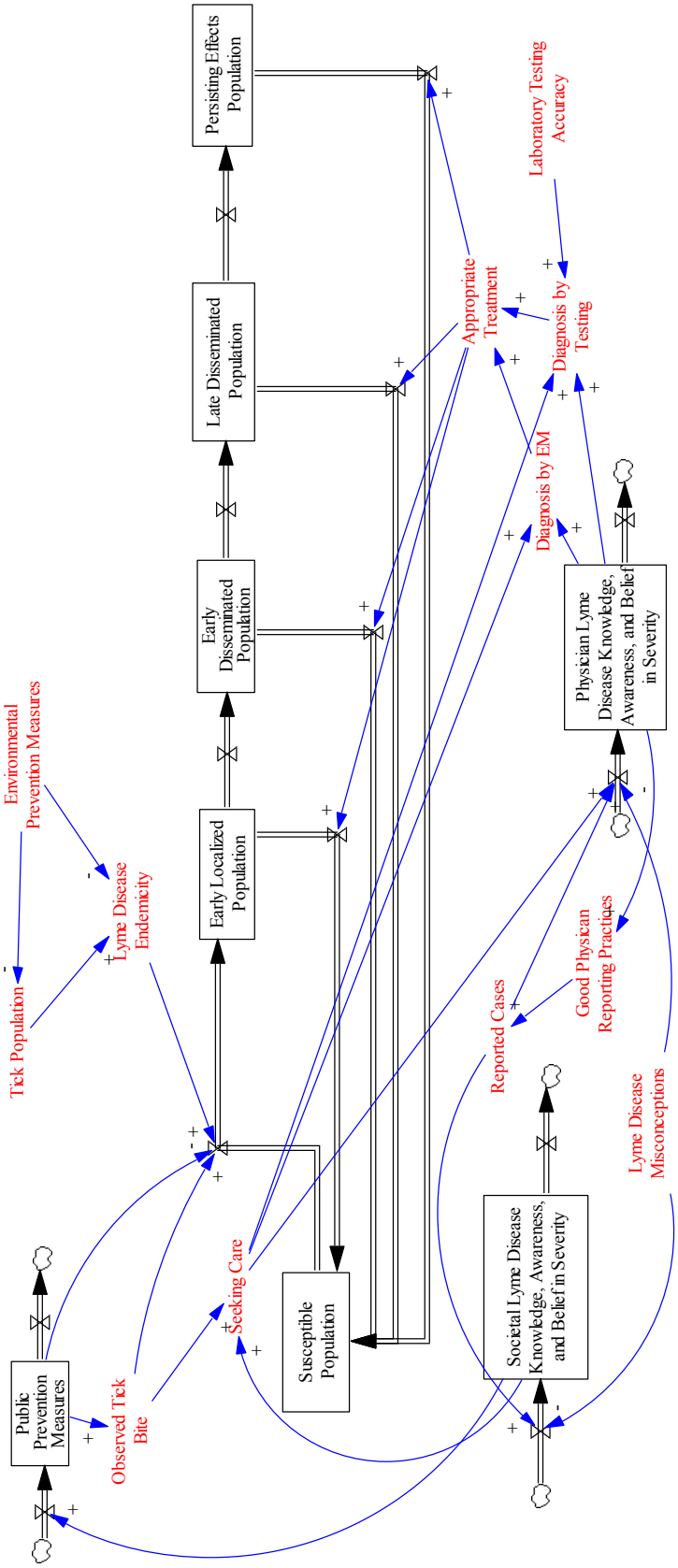
3.1.3 Research Design: Procedural Overview

Based on the research objectives of this study, a preliminary conceptual model was generated to explain the interactions between public and physician behaviours and awareness and Lyme disease endemicity, incidence, progression to treatment and diagnosis, and patient outcomes (Figure 3.1). It was used to map hypothesized causal processes and identify key variables (48). Vensim Professional 6.3®, by Ventana Systems Inc., was used as the specific simulation software for creating, running, and displaying the model (49).

System dynamics simulation uses a number of diagramming conventions. Boxes are referred to as stocks, and represent quantities of entities. All stocks in the final model represent numbers of people (Figure 3.2). These stocks accumulate people through inflows and outflows, which are rates of flow (units/time). The units of all inflows and outflows in the final model are people/day. Inflows and outflows are represented by pipes and arrows entering into and leaving the stocks. These inflows and outflows use valves, which are pictorially displayed, to control the flows. Normally, these rates depend on exposure, or the size of the stock, which is demonstrated by arrows pointing to the valve from the stock. Vensim calculates the amount of people in a particular stock at a given time by integrating its inflows minus its outflows. The small cloud shapes at the beginning of some inflows are called sources, which represent the origin of people from outside the model boundaries. When these cloud shapes are at the end of flows they are called sinks, and represent where people end up, again outside the model boundaries. The blue arrows within the model are used to indicate relationships between variables, which are accompanied by an underlying structure of equations.

Different variables related to Lyme disease that were considered in the preliminary model include: endemicity, public awareness or knowledge, preventive practices, seeking health care, physician awareness or knowledge, belief in severity, physician reporting practices, the accuracy of laboratory testing, and the stage of disease when treatment occurs (*see* Appendix A, Table 1). Environmental factors affecting tick density and Lyme disease endemicity are clearly important determinants of the likelihood of humans becoming

Figure 3.1 Preliminary Conceptual Simulation Model



infected, but this variable was kept exogenous to reduce the model's complexity. The focus of the study was to better understand the relative contribution of interventions directed to the public or the clinical community in managing an outbreak. Environmental interventions and biological systems supporting Lyme disease have been the most focused area of research, and are outside the scope of the simulation.

Based on the conceptual model, a review of the literature was conducted to find useful evidence from previously conducted studies and public health resources to quantify variables and their interrelationships within the model. This led to an iterative process of ongoing conceptualization and refinement of the simulation variables and model, which in turn changed data requirements. After the model was developed, calibrated, and validated, planned experiments were run by varying the values of key variables in the model to satisfy the study objectives. Variables were chosen ahead of time based on their importance to model behaviour and relative level of uncertainty. All other variables were held constant while these variables were changed, and the effect on outcomes of interest was observed. These outcomes include: the number infected, the total of which is the cumulative incidence of Lyme disease within the population; the number cured, which describes the number of diagnosed cases; and development of persisting effects, which are the number of cases that reach the final disease stage (*see* Appendix A, Table 1). For example, to determine how physician awareness affects the cumulative number of diagnosed and treated cases, the level of physician awareness was varied while the values for all other model variables, such as public awareness, were held constant. After developing and running the models, sensitivity analyses were used to test the robustness of conclusions regarding variables based on assumptions.

3.2 Data and Measurement

All variables in the final model (*see* Appendix A, Table 4) required input values, and all relationships between variables had to be specified as formal equations representing model relationships. This determined the requirements for data and evidence, which in many cases could not be fully met by the current body of evidence. Equations could be as simple as multiplying a given stock by a constant decay rate, which is how disease progression rates

were formed. Many equations were written using joint probabilities, such as the infection rate which included the risk of getting bitten by a tick, the probability of that bite being infectious, and the exposure time. The probabilities were, in turn, affected by other variables in the system (e.g. public awareness affected the probability of susceptible persons being bitten by a tick). The specification and quantification of the simulation equations relied heavily on what evidence was able to be obtained from the literature, and what form they were in.

The process of identifying and evaluating evidence sources and inputs was thus an important aspect of model validation. Evidence included in the models, such as the accuracy of Lyme disease laboratory tests, was identified and taken from information sources through an iterative process of model conceptualization and data collection. Evidence was collected from locations such as previously published research or public health resources through review of the literature. To obtain the most comprehensive collection of evidence for simulation variables, a rigorous search strategy was employed to find relevant studies; using a variety of data sources allowed for triangulation and cross-checking (47). This included using multiple databases, such as PubMed, searching for grey literature online, conducting backward citations searches, and prior planning of relevant keywords. The quality of studies was then assessed before their evidence was extracted and incorporated in the model. If similar evidence was replicated in multiple contexts it was considered to be of greater validity. More recent research was generally preferred over older studies, and properly conducted systematic or literature reviews which displayed the variability of results were also favoured. Studies were examined for a proper description of methodology, no matter which kind of study design they used; if they were found to be lacking in this regard the results were described with a degree of uncertainty. However, because of the lack of reported evidence around many of the model variables, it was often necessary to rely on whatever studies were available to identify appropriate values, whether they had high levels of internal validity or not. As a result, no specific bias ascertainment tool was used in validity assessment.

Both qualitative and quantitative evidence were taken from the literature to inform the model variables. Qualitative evidence tended to be used in cases where quantitative evidence was not available to justify the assumptions made for the value. For example, the sensitivity of Lyme disease testing was quantitative, while both qualitative descriptions and quantitative evidence on the general effectiveness of public-based interventions were used to assist in generating a plausible value for public awareness rates (*see* Appendix A, Table 3). When there were significant discrepancies between studies, the most frequently cited evidence, or a conservative average of the different values, was used. Collected evidence was occasionally transformed or re-expressed in order to be used in the simulation model. For example, some studies reported multiple values for what was considered to be a single variable within the model, so they were averaged into a single value to facilitate inclusion. Outcomes were measured quantitatively and included: cumulative incidence, the number of cases in each disease stage, and the percentage diagnosed.

It was important that the model results be generalizable and not specific to a particular context. To this end, when evidence existed from a variety of different study locations, all of it was used to attempt to represent the range of possible values. Although these methods do not make the results specific to a particular population or region, the generalities of the included evidence and results should make the outcomes adaptable and applicable to a variety of populations. Study context was particularly important in terms of Lyme disease endemicity. For the model, a representative range of different levels of endemicity with accompanying characteristics was desirable, but this was carefully balanced with not incorporating evidence from locations with extremely low or high levels: if endemicity was too low, not enough cases would even occur in the model to produce any measurable results, and if endemicity was too high it would overinflate results compared to what most commonly occurs. Additionally, North American evidence was preferred. The different genospecies that occur in Europe, for example, result in significant differences in symptoms and characteristics of infection; the goal was to make this model generalizable with respect to *Bb* specifically.

3.3 General Model Validation and Calibration

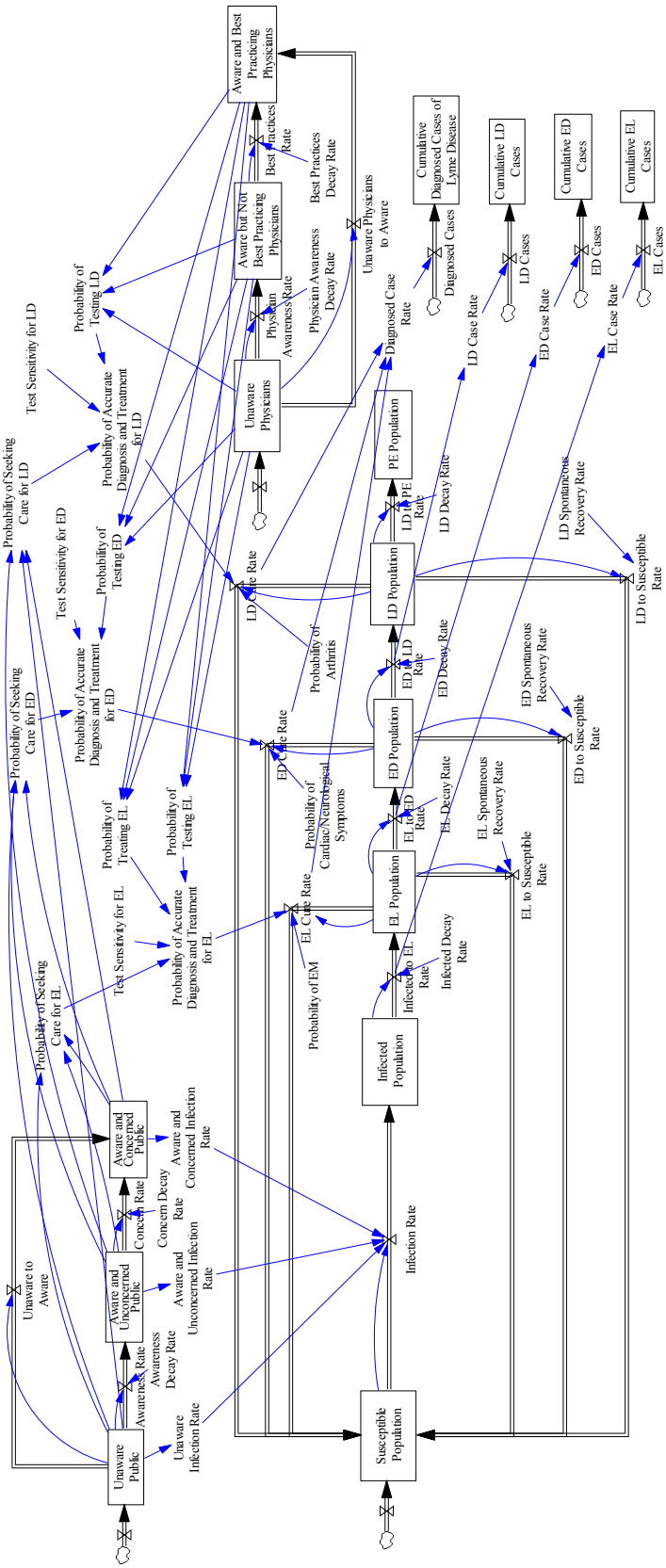
To validate the model, reflective modelling was employed to reveal errors and assumptions so that the model might be improved (32). This included carefully documenting the methodology for the sake of transparency. Using a rigorous process to obtain the evidence used in the model, including a quality assessment of the evidence, also served as an important validation method. Additionally, the iterative process used to collect evidence and refine model variables provided additional opportunities to improve the model structure. Data replication, which tests a model's ability to provide realistic outcomes based on what is found in the literature, is an important calibration method. No detailed population data were available in the literature, so replicating a documented outbreak could not be used as a method of model calibration. However, data replication was still used broadly for this purpose. For example, the range of annual Lyme disease incidence reported in the literature was used to calibrate the model.

Sensitivity analyses were used to reveal assumptions and errors in the model by demonstrating how model behaviour varied when variables were tested over a reasonable range of uncertainty (32). Comprehensive sensitivity analysis is not possible, based on the number of combinations of assumptions, so only parameters and relationships that were highly uncertain and predicted to be influential were tested (32). Examples of these variables include: public awareness and its relationship with preventive practices, concern, and Lyme disease prevalence; and the associations between physician awareness, best-practices, and diagnosis. Specific details on the validation and calibration methods used during model development are described in the following sections.

3.4.1 Model Development: Final Model

To facilitate model development, the model was built in four component modules which were combined to produce the final model (Figure 3.2). These include the natural history module, tick module, health services module, and public and physician awareness module.

Figure 3.2 Final Model

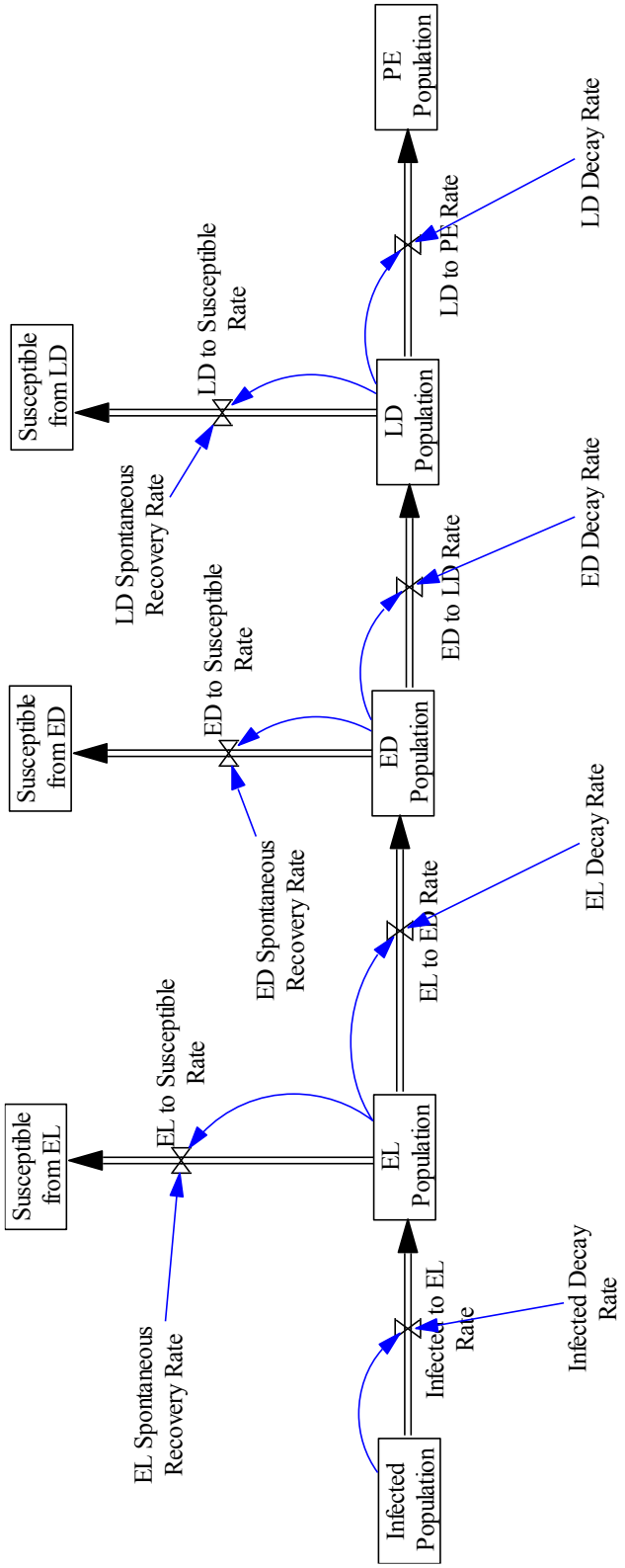


The natural history module forms the base of the finalized module. It interacts with the tick module to cause human infections, which then progress through the clinical stages of Lyme disease. The tick module includes three infection rates based on interaction with the stocks in the public and physician awareness module. In the natural history module people return to susceptible by spontaneously recovering, or being diagnosed and cured through interaction with the health services module. The health services module contains variables relating to the diagnosis, treatment, and curing of infected persons who present to the health care system. This module allows for the cumulative number of cases in each disease stage to be accumulated in separate stocks and cumulative incidence to be calculated. The health services module is also affected by the public and physician awareness module, which informs three levels of probabilities for the seeking care, testing, and treating variables based on awareness. The development of each module followed an iterative process of conceptual development, calibration, and validation to bring it in line with existing evidence and knowledge, which is described in detail in the following subsections.

3.4.2 Model Development: Natural History Module

The natural history module is the base for the entire model (Figure 3.3). In this module, the population moves between different stages of the natural history of Lyme disease: infection, early localized Lyme disease (EL), early disseminated Lyme disease (ED), late disseminated Lyme disease (LD), and persisting effects (PE). The module was initially built by assuming the population received no intervention and was calibrated by using the estimated proportion of people that spontaneously recover at each stage. Thus, it is a "natural history module", as it demonstrates how a population would progress through the various stages of Lyme disease without any treatment. Each disease stage is represented by a stock with an inflow (new entrants to the stage) and two outflows: one leading to the stock of the next disease stage, and one returning to the susceptible stock. The flow returning to susceptible represents those who spontaneously clear the infection. For example, the EL stock has outflows leading to the ED stock and returning to the susceptible population stock, and an inflow from the infected stock (Figure 3.3).

Figure 3.3 Natural History Module



Only a handful of resources were available (50-54) which documented the natural history of Lyme disease in the absence of treatment, as only a short period of time existed after the disease was discovered in 1975 before guidelines recommended immediate antibiotic treatment. Although the causative bacterium was not identified until 1982, a study by Steere from 1977 concludes that an unknown epidemic (that is now known to be Lyme disease) was likely to be infectious in nature, and he documented some physicians already treating the mysterious illness with antibiotics (51). As a result, the majority of these studies were conducted a significant amount of time ago, and their validity to the present day is uncertain. At the time, much less was known about Lyme disease stages. Most of the studies had poor documentation of their methods, making it difficult to discern how exactly the study was conducted and the validity of results. Unfortunately, with the lack of available sources, these studies had to be relied on even though the strength of evidence was not very strong. As a result, additional steps were taken when building and calibrating this section of the model to address the uncertainty.

The first stage, early Lyme disease, had the most detailed evidence. This is because a large number of cases, approximately 80%, present with the distinctive erythema migrans rash (1, 5, 23). As a result, there was better documentation about the duration of this stage, which ranged from 1-39 days with an average duration of 6.7-7 days (53, 54). The model was built under the assumption that the duration of the EM rash was equivalent to the duration of early Lyme disease. The duration of the incubation period, when individuals are infected but have not shown symptoms yet, ranged from 1-27 days with an average duration of 7-10 days (50, 53). The later disease stages were described in terms of how long after a tick bite or EM rash they took to present instead of duration. As a result, this evidence had to be used to estimate the average durations of the later stages for the model. Early disseminated Lyme disease occurs from days to 1-6 months after a tick bite, and weeks to months after EM (50, 54). Late disseminated Lyme disease can present weeks to years after a tick bite, and 1-24 weeks after EM with a median of 4 weeks (51, 54). Reviewing this timeline, there is evidence of overlap in symptoms between stages, and thus the demarcation of stages is not always clear. A few further assumptions were thus necessary. The first was that Lyme arthritis was considered to be equivalent to late

disseminated Lyme disease, as this is the stage where it most often occurs. The second was that the disease stages were modelled so that no overlapping occurs.

In order to deal with the significant amount of uncertainty regarding the duration of the various stages of Lyme disease, an upper and a lower bound for these parameters were created for the purpose of sensitivity testing. The incubation period was modelled with an average duration of 7 and 10 days; early Lyme disease was considered to have an average duration of 6.7 and 7 days; early disseminated Lyme disease was modelled with an average duration of 10.5 and 21 days; and late disseminated Lyme disease used both 10.5 and 24.5 as average durations.

Once the bounds for the average durations were decided upon, transition rates between stages were calibrated with an exponential distribution. Rates were selected such that application of the rates to the exposed population yielded a desired average duration. The module was calibrated based on the percentage of an infected population that spontaneously recovers at each stage, and what percentage moved on to the next stage, with no intervention (52). The only stock that this did not apply to was infected individuals, as its entire population was assumed to enter the first disease stage. Prospectively following a population that presented with EM, the proportion that spontaneously recover at each stage was found to be: 20% of early localized Lyme disease, 18% of early disseminated Lyme disease, and 51% of late disseminated Lyme disease (52). This leaves 11% of the total population to develop persisting symptoms (52). These percentages were used to calculate the proportion that spontaneously recover from each stage based on the number that actually reached it: 20%, 23% and 82%. After initializing each stock with a population, these proportions and the decay rates based on the average durations of the stages were used to calibrate the model. Consequently, the final product was two sets of rates for each disease stage, a lower and an upper bound input (*see* Appendix A, Table 3).

Careful consideration was given to the influence of uncertainty in transition rates between stages, and sensitivity analyses were conducted for transitions. Uncertainty regarding the duration of the later stages of Lyme disease is unlikely to affect the study results. The

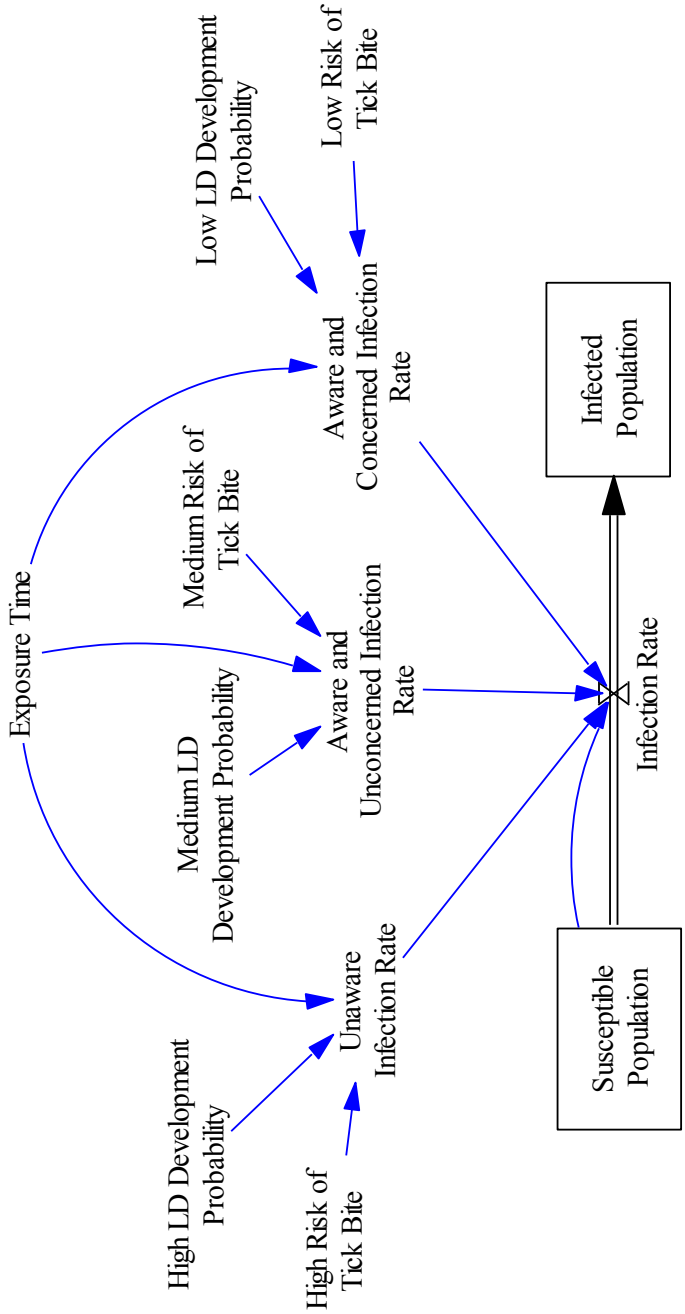
symptoms from these stages overlap in reality, so changing the length of these stages would probably not influence the relationship with variables of interest such as seeking care or being diagnosed. On the other hand, the duration of early localized Lyme disease is more likely to affect model results. The longer the duration of the EM rash, the more likely it is that it will be noticed and medical care pursued. Fortunately, the best evidence about the natural history of Lyme disease is from this stage, so with sensitivity testing of uncertainty in this duration, it was believed that the model would capture a suitable range of behaviours.

3.4.3 Model Development: Tick Module

The tick module (Figure 3.4) contains variables that affect transition of people from the susceptible population to the infected population. Although this module could be modelled in a very complex way, the environmental components, such as tick density and *Bb* prevalence, were treated as exogenous to the model. Environmental interventions and biological systems supporting Lyme disease have been the most focused area of research, and are outside the scope of the simulation. However, the aim of this study is to better understand the relative contribution of interventions directed to the public or the clinical community in managing an outbreak, so it was important for the model to be flexible enough to show how conclusions might change given different environments. Additionally, Lyme disease outbreaks have a seasonal component, occurring largely during six months from May to October; in a Nova Scotia report, 85% of cases occurred during this time (11). To avoid overcomplicating the model, this seasonal component was not modelled, but rather the model was run in six month seasons of May to October, for a total of 184 days. So if the model ran for two years (730 days), this would account for approximately four simulated Lyme disease seasons.

To estimate the risk of a person becoming infected, given different environmental factors, various types of evidence had to be pieced together from the literature. Additionally, the variables in this module had to be amenable to change based on the uptake of different kinds of prevention measures. As a result, the process of infection was reduced to three key variables: exposure time, risk of tick bite, and Lyme disease development probability.

Figure 3.4 Tick Module



Exposure time describes the average length of time the population spends outdoors per day. Risk of tick bite is the probability of being bitten by a tick per hour, while Lyme disease development probability is the likelihood of developing Lyme disease after being bitten by a tick. These three values were treated as independent probabilities, so they were multiplied together to achieve a joint probability for infection (*see* Appendix A, Table 3 and 4). Three levels of tick bite risk, Lyme disease development probabilities, and corresponding infection rates were used to differentiate between low, medium, and high preventive practices. Levels of preventive practice were determined by the public awareness module (see below). Preventive practices were used to alter the risk of tick bite, thus changing the risk of infection.

Uptake of prevention practices such as avoiding tick locations, using insecticides or covering up are represented by a lower risk of a tick bite. Increased use of interventions after being bitten, such as removing a tick, are displayed by lower risk of developing Lyme disease. A range of values was found in the literature for these two variables, from low endemic regions to extremely high risk populations in endemic areas (55-59). Additionally different values were available based on the use of preventive practices. For example, the probability of developing Lyme disease was shown to increase based on the number of hours a tick is attached, which can be altered by performing tick checks and removing any ticks found (59). Consequently, three different probabilities for both the risk of tick bite and the probability of developing Lyme disease were generated, corresponding to three different levels of preventive practice (*see* Appendix A, Table 3). Because the model is focused on determining the best strategies for handling different Lyme disease outbreaks, values were only taken from areas with adequate levels of Lyme disease endemicity. Regions with no or low endemicity typically only report a few cases, and most are not acquired locally (60). The exposure time, which directly affects the risk of tick bite, was held constant for all three risk levels at 0.25 hours per day.

Although a substantial number of studies were available to inform data inputs for the tick module, a significant amount of uncertainty had to be addressed. Studies were conducted in many different regions, with varying tick populations, types of ticks, levels of infection,

and exposure rates. For example, many studies were conducted in locations in Europe that only have *I. ricinus* ticks, which are known to transmit different levels of Lyme disease than *I. scapularis* ticks (55, 57). Furthermore, studies looked at different variables pertaining to this area of research, including nymphal tick density, incidence rates of Lyme disease, number of cases of Lyme disease, risk of tick bites, risk of developing Lyme disease after tick bites, and infection rates among ticks (55-59, 61-63). To deal with this uncertainty, reported incidence rates of infection were used for calibration (61-63). Although highly variable between studies, estimates of incidence rates were plentiful and obtained through more consistent methods than the other module variables. For example, many incidence rates were based on national surveillance data which, while known to underestimate incidence, provide a good conservative estimate. To match the values for other variables used in the model, only incidence rates from Lyme disease endemic areas were used.

Annual incidence rates were found to range from 9.4-912.9/100,000 (61-63). Lower values were obtained from surveillance data and considered to be conservative. For example, compared to a reported surveillance rate of 9.4, one study calculated incidence to instead be 44.8, which grew to 106.6 after corrections (63). For calibration, the aim was to produce rates roughly within the middle of this range. To do so, the risk of tick bite was varied, which was obtained from a single study in a very specific context and considered to have the greatest amount of uncertainty (57). As a result, an annual incidence rate of 321/100,000 was produced while calibrating this section of the model. While still somewhat high compared to some surveillance rates, it falls roughly in the middle of the reported range for endemic areas, and takes into account that much of this evidence is considered to be an underestimation.

3.4.4 Model Development: Health Services Module

The health services module (Figure 3.5) contains variables pertaining to the probability of: having recognizable symptoms of Lyme disease, patients seeking care, physicians appropriately treating and testing, and obtaining a positive test result. These variables differ for each stage of Lyme disease. This module transitions a proportion of those in each

disease stage back to susceptible through "cure rates". Once a person is diagnosed with Lyme disease they are assumed to be treated and cured. This is not an unreasonable assumption due to the high effectiveness of appropriate antibiotic treatment. To address persisting effects that are not resolved by antibiotics, as well as the reduced effectiveness of treatment for more severe disease, the persisting effects stage of disease cannot be cured in the model. Those who return to susceptible have a lower chance of being infected again because of higher levels of awareness and concern; this is discussed further in the public and physician awareness module section.

The literature was surprisingly consistent when reporting the probability of having an EM rash after being infected with Lyme disease. As many as 80% of those infected with Lyme disease develop EM (5, 23). As the most obvious and pathognomonic presentation of early localized Lyme disease and illness, it is likely to result in seeking care, so in this model behaviour is likely to be sensitive to this parameter. Infected persons who do not develop EM are unlikely to seek care or be diagnosed. For sensitivity analyses two values for this variable were tested: the commonly reported 0.80, and a much lower probability of 0.53 obtained from a single population-based study that attempted to produce a more accurate representation of cases with EM (64). One other study set the probability for having EM at 50-80% (29), further indicating that the value of 0.53 can be considered a conservative, low estimate for the probability of a Lyme disease case having EM.

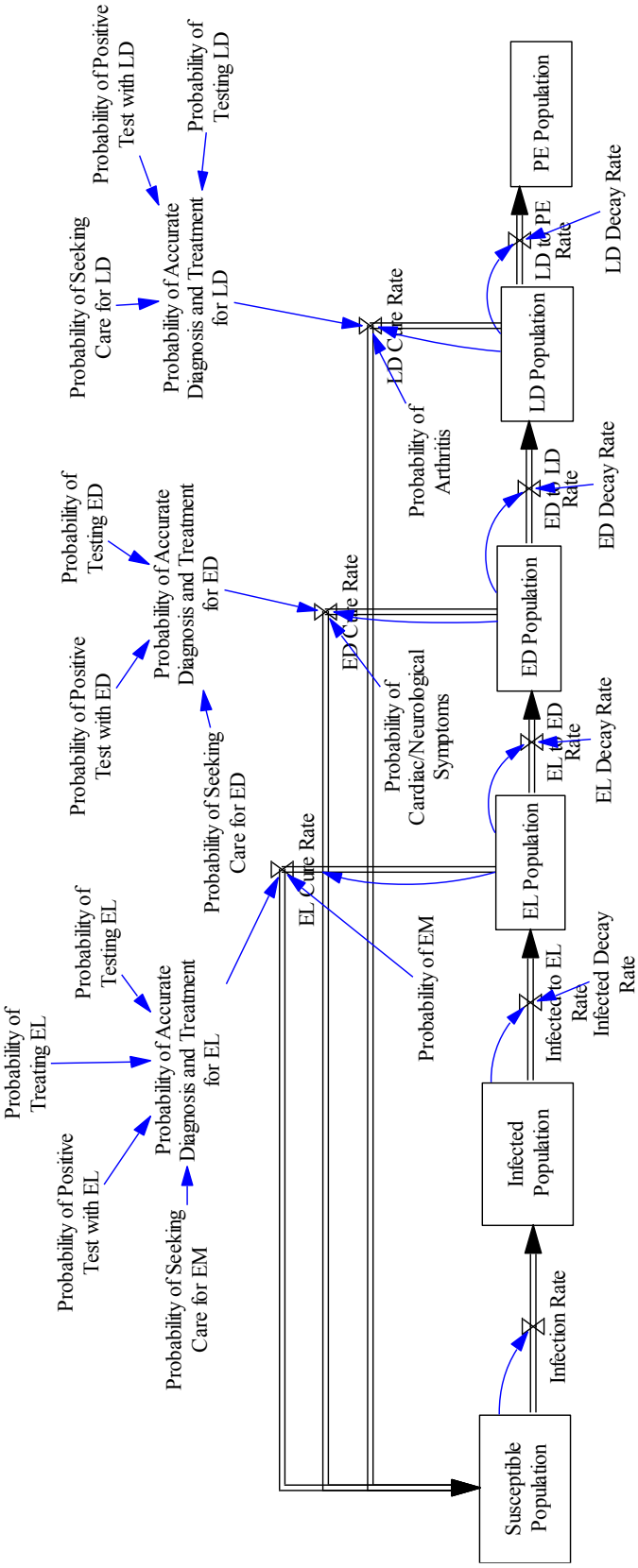
There was little evidence available in the literature to inform the probability of seeking care, as studies only include patients who seek care. While it is possible that a study could collect self-reported diagnoses in a population to compare to those reported by physicians, there was no evidence of this kind in the literature. However, this variable should have a small effect on model outcomes since a combination of an EM rash and feeling ill is in itself likely to prompt care seeking regardless of the patient's knowledge of Lyme disease. Alternatively, a person may only decide to seek care if the rash persists for a certain length of time. In these cases, physician awareness of Lyme disease may have a greater impact than public awareness on treatment. As a result, it is possible to assume that people both with and without awareness of Lyme disease are likely to seek care if they see the

distinctive and relatively severe EM rash (28). However, individuals who are aware of Lyme disease and its symptoms would probably be more likely to seek care, and as early as possible. As a result, separate likelihoods for seeking care were used depending on the level of population awareness and concern (*see* Appendix A, Table 3 and 4). A further description of this is available in the public and physician awareness module section.

A small number of studies were available in the literature that measured physicians' behaviours around diagnosing, treating, and testing for Lyme disease. Results were variable across contexts. While EM is supposed to be diagnostic for Lyme disease, requiring no further testing, many physicians, not knowing this, both treat and test. This does not affect outcomes if the physician continues treatment. By combining the probabilities found in physician behavioural studies for those who "treat" and those who "test and treat", the values obtained were: 58.3% of family practitioners in a low-endemic area (17); 85.5% of physicians in a moderate-endemic region (18); and 72% of physicians in an endemic region (21). These numbers were averaged to obtain a mid-level endemicity probability of 0.719. Since the model specifies three levels for the probability of a physician treating EM, depending on physician awareness of Lyme disease protocols, this value was used for moderate awareness. It was then increased and decreased by 25% to obtain the other two levels of probabilities, which is discussed further in the public and physician awareness module section (*see* Appendix A, Table 4).

The model also considers the scenario of physicians testing, and only treating if the test is positive. The reported probabilities of testing before deciding to treat are as follows: 36.0% of family practitioners from a low-prevalence area (17), 13.1% of physicians in a moderate-endemic region (18), 7% of physicians from an endemic region (21). One endemic study reported that 49% of physicians serologically tested EM rash patients, but as it was unclear if this was in addition to treating with antibiotics, this value was not included (19). This variable also requires different levels based on the awareness and practices of physicians, which is discussed further in the public and physician awareness module section. Consequently, three probabilities were used in the model: 7%, 13.1%, and 45%, the last of which was calculated by increasing the 36% reported in a low-prevalence region by 25%.

Figure 3.5 Health Services Module



The literature reports a range of serological test sensitivity values in the early localized stage of Lyme disease. Most studies differentiated between the acute and convalescent phase of EL, so these values were averaged to obtain a single sensitivity for each study. Estimated sensitivities were 35% (5), 47.5%, 45.5%, and 58.5% (14). In the study that reported a sensitivity of 35%, it was acknowledged that the reported accuracy may be overestimated because values were obtained from a case-control study (5). An average sensitivity of 0.466 was used in the model. Sensitivity analysis on this variable was not conducted, as it is unlikely to have a substantial impact on outcomes. Small variations in the sensitivity of a positive test are unlikely to greatly affect outcomes when multiplied by the relatively small probability of a physician testing at this stage (0.07-0.45).

For early and late disseminated stages, symptoms are similar to EL (*i.e.*, nonspecific viral) with the addition of more severe manifestations. For early disseminated Lyme disease, this primarily takes the form of various cardiac and neurological symptoms, which when combined together occur in 5-47% untreated Lyme disease cases (20, 22, 23). For the late disseminated stage, the most recognizable symptom is arthritis, which happens in 33-60% of untreated Lyme disease patients (22, 23). Reported probabilities for developing Lyme arthritis were consistent, but there was some difficulty in determining what actually constituted neurological and cardiac symptoms. For example, one study reported "cognitive" and "behavioural" symptoms (22), which could easily be classified as neurological, while another described "CNS issues" and "acute neurological signs" (20). Another issue was with the way studies reported the probability of having symptoms, since one patient could be counted twice if they had both reported symptoms. For example, one study states that 47% of patients presented with cognitive symptoms and 46% presented with behavioural symptoms (22), but it is unlikely that 93% of patients presented with some form of neurological symptom. As a result, some discretion had to be used when combining the different reported likelihoods of cardiac and neurological symptoms. Probabilities were combined to provide a reasonable, conservative estimate. A probability of 0.199 was assumed for having cardiac or neurological symptoms and 0.465 for having arthritis.

The probability of seeking care was assumed to increase by 5% with each successive stage, despite having less recognizable symptoms (*i.e.*, EM). The early disseminated and late disseminated stages of Lyme disease typically present with much more severe symptoms than that seen with early localized Lyme disease. Additionally, those suffering from Lyme disease at these stages would have had symptoms for a longer period of time than those with early disease and would also have experienced multiple disease stages, making the likelihood of having some severe or recognizable symptom greater. Both seeking care variables require three levels of probability which are multiplied by the proportion of people in each level of public awareness to obtain an overall probability for seeking care for each stage (*see* Appendix A, Table 3 and 4).

In the later stages, the probability of physician diagnosis and treatment depends on the probability of physicians associating the given symptoms with Lyme disease and consequently making a diagnosis. Regarding the various neurological and cardiac symptoms of early disseminated Lyme disease, studies commonly measured physician familiarity with third degree heart blocks, neuropathies, and meningitis (17, 18). From the studies, an average probability was of 0.805 was calculated for physicians associating these symptoms with Lyme disease (17, 18). For late disseminated Lyme disease, the same process was followed for arthritis, resulting in a cumulative average probability of 0.985 (17, 18). With a differential diagnosis more difficult in later stages, these reported values were considered to be a high estimate for the probability of treating. Since this probability requires three levels based on physician awareness, these reported probabilities were used for high levels of physician awareness. This is discussed in more detail in the public and physician awareness module. The probabilities for the other two levels of awareness and practices were obtained by using percentage reductions: 0.805 was decreased by 10% and 20% for the ED stage; and 0.985 was decreased by 15% and 35% for the LD stage (*see* Appendix A, Table 3 and 4). The LD stage's reported value was reduced more compared to the EL or ED stage. This is because in practice arthritis is more difficult to differentially diagnose from the many other etiologies that might cause it, even though Lyme arthritis is a well-known and distinguishing feature of Lyme disease. This is particularly true when compared to EM or Bell's palsy, which occur in the other two stages. However, arthritis is

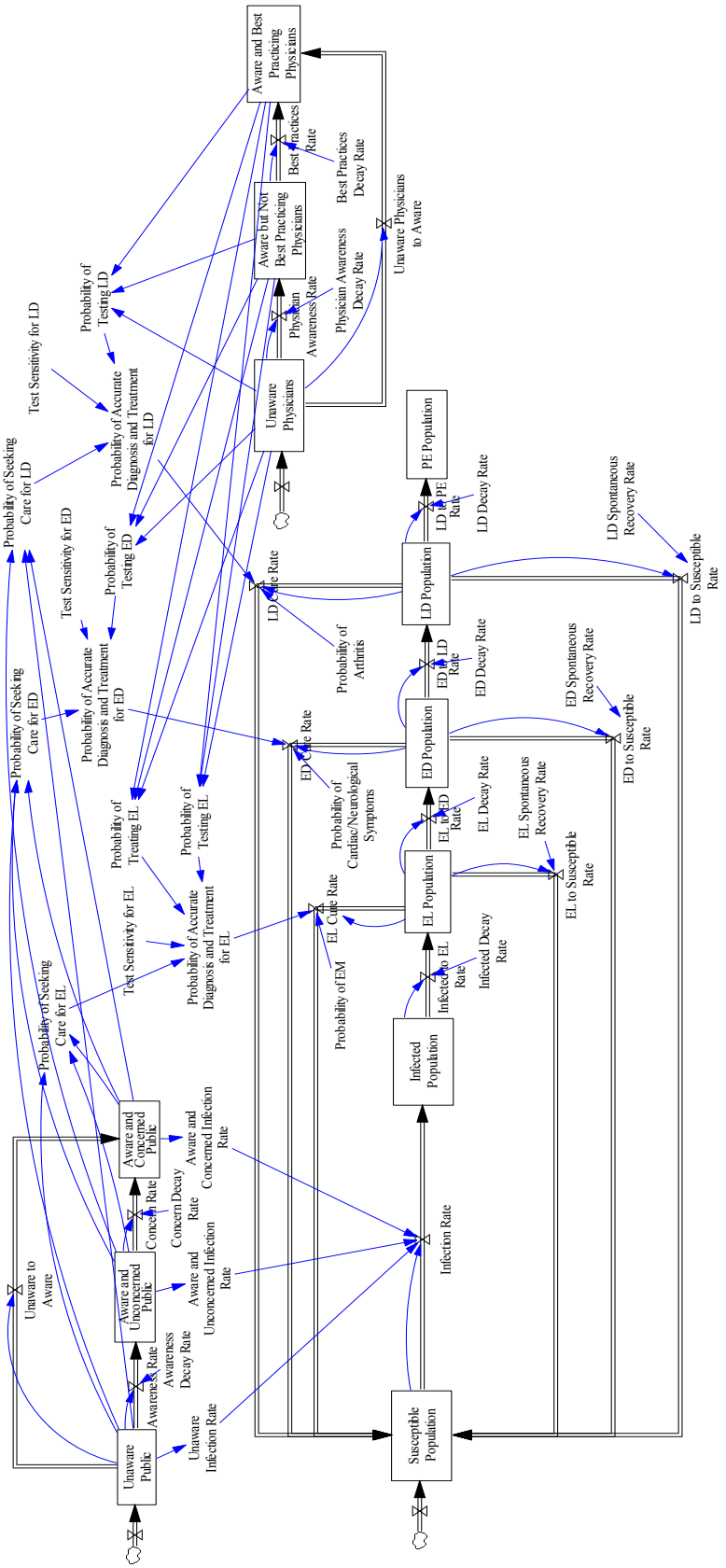
not typical in children, a population which is commonly infected with Lyme disease. Additionally, physicians generally reported to be more familiar with arthritis as a symptom. As a result, the probability for recognizing symptoms in this stage was not lower overall when compared to the other stages. The ranges obtained for the ED and LD stages were compared to those used for EL as a final validity check, to make sure they were not too much higher or lower and showed a similar range for values.

The literature provided clear guidance on test sensitivity at later stages. For the early disseminated stage, literature reported sensitivities of: 63%, 77.5%, 84.5% (14), and 71.5% (5). These were averaged to obtain a probability of 0.741. For late disseminated disease, estimated sensitivities were: 97.4%, 98.5%, 100% (14), and 100% (5). These values were again averaged to obtain a single probability of 0.990. While some of these sensitivities are acknowledged to be an overestimation (5), due to their consistency with the values reported from other studies they were considered valid enough to include when calculating an average test sensitivity.

3.4.5 Model Development: Public and Physician Awareness Module

The final module simulated changes in public and physician awareness of Lyme disease (Figure 3.6). The module groups each population into three stocks. For the public this includes those unaware of Lyme disease, those aware but not concerned, and those aware and concerned. For physicians this includes those unaware of Lyme disease, those aware but not best-practicing, and those aware and best-practicing. For both the public and physicians, the purpose of the stocks and flows was to model the percentage of each population who are at different awareness and concern levels. Simulated shifts in awareness and behaviour from this module affected the choice of other awareness specific model probabilities as described in each of the preceding modules.

Figure 3.6 Public and Physician Awareness Module



Specifically, simulated shifts in awareness and behaviour affected the probabilities of seeking care, testing, and treating employed in the health services module and the infection rates in the tick module. For the probability of seeking care, it was determined that there was unlikely to be a significant amount of change in behaviour, particularly between those who are unaware and those who are aware but unconcerned, since their motivation would minimally differ. For physicians treating, the range of probabilities was chosen to be wider than that used for seeking care, to permit behaviour to change more in response to higher awareness. Additionally, for the EL stage the range of treating probabilities was chosen to slightly extend beyond the values reported in the literature for low- to mid-endemic regions. This is because unaware physicians should have lower probabilities than those from low-endemic areas, while aware and best-practicing physicians should have higher probabilities than those reported from a mid-level endemicity area. To calculate an overall probability for each variable in the model affected by awareness, the three levels of probabilities were multiplied by the proportion of the population in the appropriate awareness level and then combined (*see* Appendix A, Table 4).

The initial shares of populations in each awareness stock, and the rates of transition between stocks were modified experimentally to observe their effect on model behaviour and outcomes. Transitions between awareness stocks also resulted from a feedback process whereby direct experience with a Lyme disease diagnosis (*i.e.*, being diagnosed with Lyme disease or being close to somebody diagnosed with Lyme disease) transitions people and physicians to being both aware and concerned. For the public, a multiplier was included in the model such that each diagnosed person resulted in five additional members of the public transitioning into aware and concerned. Similarly, physicians making a diagnosis transition to the highest awareness and practice level, with a multiplier of two (*i.e.*, they influence additional colleagues to be more aware and concerned). In both cases, these transitions were proportionally selected from the other awareness stocks.

To inform the transition rates for this module, the literature was searched for evaluations of educational interventions for both the public and physicians on behaviours and practice.

Studies on the effectiveness of public educational interventions are numerous but inconsistent. In part, this reflects the range of intervention types, which tend to be poorly described (65). Furthermore, few rely on psychological theories of behavioural change, which have been demonstrated to be a requirement for successful interventions (65). These theories include the theory of planned behaviour (66), health belief model, and protection motivation theory (65). All state that the success of public educational interventions is based on perceptions about threat severity, personal susceptibility, confidence in performing effective prevention measures, and favourable attitudes (65). The variability in success of interventions demonstrated in the literature, and their lack of psychological basis, indicates that their potential is currently unknown but possibly greater than what is reported.

The actual and potential effectiveness of interventions to improve public prevention of Lyme disease is uncertain. A systematic review which contained five before-after studies and four controlled trials determined that despite variability in study results, both knowledge and attitudes are amenable to change, although the permanence of this has not been determined (65). The review concludes that while education can be effective and Lyme disease is preventable, incidence is increasing partly because of the low uptake of prevention measures amongst the public (65). A study which assessed reasons for the uptake of prevention measures found that having Lyme disease in the past ($p=0.01$) and knowing someone well who has had Lyme disease ($p=0.02$) are both significantly associated factors (67). As incidence increases in the model, more of the public will have been diagnosed with Lyme disease or know someone who was through the multiplier effect, which will decrease the risk of infection through the uptake of prevention measures during simulations. Based on these findings, it was assumed for modelling purposes that post-intervention the public has higher levels of awareness and positive attitudes.

The results of similar studies conducted with physicians are also variable, from interventions having no effect to creating long term changes in awareness (68, 69). Part of the difficulty in assessing their effectiveness is attributable to the range of different kinds of interventions used, such as printed educational materials compared to educational

sessions, as well as the variability in study contexts (68, 69). Despite this uncertainty, the model assumes that physician awareness and best-practice rates would increase in the same way as public awareness post-intervention. In the model, physicians will be confronted with increasing numbers of Lyme disease cases to build experience, which is simulated through the multiplier effect. Additionally, physicians are also members of the general public, and as such it is reasonable that they would have a similar rate of increased awareness as others in the public. Consequently, all flows in the awareness module were given the same arbitrary, consistent rate at baseline (*see* Appendix A, Table 3). No evidence was found in the literature that described either awareness or concern being more amenable to modification, so these rates were kept equal as well.

3.4.6 Model Development: Final Model Calibration and Validation

Additional calibrations were done on the final model. First, the plausibility of numbers generated by the full model was assessed. With starting values, the model produced a total of 356 cases per population of 100,000. Since this is just slightly more than the 321 cases achieved during the tick module calibration, and still easily falls within the reported range of 9.4-912.9/100,000 cases annually, the model was considered reasonable in this regard. Next, the cumulative number of diagnosed cases was compared to the total number of cases, which resulted in a "diagnosis rate" of 84.8%. This was considered to be a reasonable estimate for this value taking into account the different reported probabilities for physicians recognizing and treating symptoms from various affected areas with differing levels of endemicity.

Second, when assigning a rate for the awareness module flows, different fractional values were tried to see how model output was affected. These rates were considered to be important to model behaviour, but were assumed values with little evidence as support, so the plausibility of model outcomes and behaviour were used as a means of calibration. Transition rates were chosen to shift the proportion of populations across the awareness categories in a reasonable way and to produce expected model behaviour. This included reduced infection rates for the public with higher levels of awareness, and changes in diagnosed cases based on physician awareness. Examples of tested values included

0.00001, 0.00005, 0.005, and 0.001, before a rate of 0.0001 was decided upon. For the public, this rate can be thought of as moving ten people per day into the next awareness stock.

Changes in the values of the other variables, stocks, and flows were checked with the goal of troubleshooting the model. The model behaviour of each variable was examined over time to make sure they were behaving as expected and that values remained within reasonable boundaries. This resulted in a number of model refinements. For example, over time the physician stocks in the public and physician awareness module were going to negative numbers because their flows were too high and their initial values were too low. To address this, conditions were included in the code to ensure the stocks did not fall below zero (*see* Appendix A, Table 4). The final date for evidence collection and model data incorporation was January, 2016.

3.5.1 Simulation Runs: Model Exploration

To meet the first objective, public and physician awareness surrounding Lyme disease was simulated under increasing prevalence to see how it affected incidence, diagnosis, and patient outcomes. This objective is broad, but its primary goal is to understand model behaviour to gain insights about the relative importance of different factors in determining outcomes.

Three scenarios were run. The first was a baseline scenario designed to simulate a typical outbreak. Two other scenarios were run to explore how more extreme scenarios affected model behaviour. In the baseline scenario, no changes were made to any variable values, including physician and public awareness rates. These rates were set at a level to mimic what might be typical of an area that is experiencing a first outbreak. Key variables of interest were: the infection rate, which reflects Lyme disease incidence; the number of cases in each disease stage, an important patient outcome; the cumulative number of cases, or cumulative incidence; the number of cumulative diagnosed cases, or diagnosed prevalence; and how the awareness stocks are behaving over time, in terms of how many people are progressing to the higher levels of awareness, and at what rate.

The two other scenarios were used to test model behaviour with higher levels of Lyme disease prevalence. In the first, the length of the outbreak was extended to both two and four seasons (*see* Appendix A, Table 5). As prevalence should continue to increase over time, this provides both a larger epidemic and a chance to see if any of the model behaviour varies with a longer study duration. For example, it was thought that the impact of some variables may take longer to produce visible results than others. In the second, the probability of getting a tick bite was increased to generate a higher infection rate (*see* Appendix A, Table 5). Elevating this risk is the same in effect as increasing the tick population or endemicity, and produces a larger outbreak more rapidly.

3.5.2 Simulation Runs: Model Experiments

A series of experiments were run to address the second study objective: comparing the impact of public health strategies targeting the public and physicians. To explore how public- and physician-based interventions affect patient outcomes, the public and physician awareness flow rates were altered to compare their effect on outcomes.

In the baseline run, neither public or physician flow rates were changed. In the public intervention experiment, the baseline value for the public awareness flow rates was doubled, while the physician flow rates were held constant; this mimicked the potential effect of low public educational interventions. It progressed the public more quickly to higher levels of awareness and concern, and thus lower infection rates and a higher probability of seeking care. In the physician intervention experiment, the public flow rates were held constant while the physician flow rates were doubled. This simulated the effect of a low educational intervention targeted at physicians, which increased awareness and the probability of treating cases. These experiments were then repeated with greater multiplications of rates to further compare the potential extent of effects (*see* Appendix A, Table 5). Study results were evaluated based on which rates for public and physician awareness had the greatest success in minimizing negative Lyme disease outcomes. Outcomes compared across scenarios included the cumulative number of cases, the number of cases in each disease stage, and the diagnosis rate.

3.5.3 Simulation Runs: Sensitivity Analyses

After both baseline and experimental scenarios were run in the model, sensitivity analyses assessed the robustness of study conclusions to uncertainty in model assumptions. It is impossible to test every variable in every combination, so key variables were identified for testing based on their relative uncertainty and importance to the model. This was guided by what was reported in the literature and baseline model behaviour. Two main categories of sensitivity analyses were identified, one for probability ranges and one for behavioural assumptions.

Sensitivity analyses for probability ranges focused on values for which high variation was found in the literature, and which were expected to have a large impact on model behaviour. This included the probability of developing EM, the progression and spontaneous recovery rates of disease, and interactions between these and the baseline and experimental scenarios (*see* Appendix A, Table 5). The probability of developing EM was predicted to be important since it is a key factor in seeking care and diagnosis. It was tested by using the lower bound probability of developing EM. The disease progression rates were altered to generate a "worst case scenario" in terms of disease progression. All rates from one disease stage to the next were increased at once, based on the higher bounds calculated from the literature, along with lower bound estimates of spontaneous recovery rates. The interactions between these variable changes and experimental scenarios were then analysed. For example, the interaction between a lower probability of EM and faster disease progression rates was tested to assess its effect on model results.

Sensitivity analyses for behavioural assumptions focused on model relationships in the public and physician awareness module, as they were considered to have the largest impact on model behaviour and findings. The goal of these analyses was to test the assumptions made about how higher levels of awareness manifest in behavioural modifications. There was little evidence found in the literature to guide these assumptions. There is some evidence that greater awareness leads to improved behaviours either in terms of prevention or best-practices, but the actual and potential magnitude of such effects is uncertain.

For the sensitivity analyses, the effect of awareness and concern on behaviour was decreased. This was accomplished by reducing the differential in probabilities of various behaviours between persons and physicians at different levels of awareness and concern (Table 3.1). To do so, the lowest probabilities for these variables were kept the same, then the other two levels were lowered to minimize the difference between the three. For example, at baseline the three levels of probabilities for seeking care were 0.7, 0.75, and 0.9. After altering the bounds, they became 0.7, 0.725, and 0.8. These probabilities were lower overall, producing less desirable behaviour, while the difference in behaviour between the three awareness levels was also reduced. As a result, someone who is aware but not concerned does not have a much higher probability for seeking care than someone who is unaware.

The second sensitivity analysis to test behavioural assumptions was simpler. The initial proportions of public and physician populations in the three levels of awareness were varied. At baseline, there are 0.90 in the first awareness stock, 0.09 in the second awareness stock, and 0.01 in the third awareness stock for both the public and physicians. This creates an initial environment of largely unaware and unconcerned public and physicians, such as might be found in an area experiencing a first outbreak. However, no evidence was identified in the literature that described the typical state of awareness and behaviour in such a population. So, different scenarios were created with greater levels of initial awareness (*see* Appendix A, Table 5).

When exploring model behaviour, all physicians were found to progress to the highest level of awareness close to halfway through the season. As a result, it was decided that the physician awareness stocks should undergo additional testing. Although this "ceiling effect" may be plausible, it was considered to potentially limit the impact of increased physician awareness on reducing negative outcomes. With all physicians reaching the highest awareness stock partway through the simulation, it eliminates the opportunity for an intervention to improve their awareness and behaviour. To test the effect of this on model behaviour, the progression of physicians to higher awareness levels was reduced so that fewer physicians reached this stock (*see* Appendix A, Table 5).

Table 3.1 Behavioural Bounds for Sensitivity Analyses

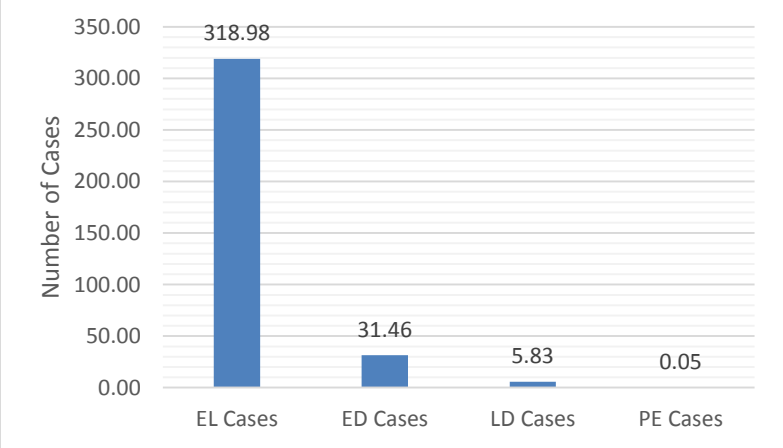
Variable	**Awareness Level**	**Baseline**	**Low Behavioural Bounds**
Probability of Seeking Care for EM	Unaware	0.7	0.7
	Aware/Unconcerned	0.75	0.725
	Aware/Concerned	0.9	0.8
Probability of Treating EL	Unaware	0.54	0.54
	Aware/Not Best-Practicing	0.719	0.608
	Aware/Best-Practicing	0.9	0.683
Probability of Testing EL	Unaware	0.45	0.36
	Aware/Not Best-Practicing	0.13	0.13
	Aware/Best-Practicing	0.07	0.10
Probability of Seeking Care with ED	Unaware	0.735	0.735
	Aware/Unconcerned	0.788	0.761
	Aware/Concerned	0.945	0.84
Probability of Testing ED	Unaware	0.644	0.644
	Aware/Not Best-Practicing	0.725	0.676
	Aware/Best-Practicing	0.805	0.708
Probability of Seeking Care with LD	Unaware	0.772	0.772
	Aware/Unconcerned	0.827	0.799
	Aware/Concerned	0.992	0.882
Probability of Testing LD	Unaware	0.64	0.64
	Aware/Not Best-Practicing	0.837	0.688
	Aware/Best- Practicing	0.985	0.752

CHAPTER 4: RESULTS

4.1 Model Exploration

Overall, the model behaved as hypothesized in all scenarios and produced reasonable results. The baseline run showed steady growth in cumulative cases, with slower accumulation in the later stages of disease. The majority of cases occurred during the EL disease stage, with the number of cases decreasing in each subsequent stage (Figure 4.1). There was a very low risk of progressing to the PE disease stage, which is partly attributable to the duration of the simulated season. These findings suggest that primary prevention is of great importance to reducing the cumulative incidence of Lyme disease, followed closely by early diagnosis.

Figure 4.1 Cumulative Cases in Disease Stages During the Baseline Run



The number of people in the infected population stock grew in the early stages of the outbreak, peaking around 30 days, then very gradually decreased (Figure 4.2). This rapid initial growth is due to model specification and may not mimic reality, although this might result from the incubation period of the disease. The inflow is steady (units/time) while the outflow depends on exposure (the number of people in the stock, which is initially very small). As cases accumulate in the stock, the outflow increases. The gradual but accelerating decline in the infected stock, seen after about 70 days, is attributable to the linear reduction of the infection rate (Figure 4.3). The infection rate is reduced through increased public awareness, as physician awareness does not impact this stage and the

infection rate is otherwise stable. Higher levels of public awareness (Figure 4.4) resulted in the uptake of prevention measures, so fewer people became infected and incidence was reduced.

Figure 4.2 Infected Population Stock During the Baseline Run

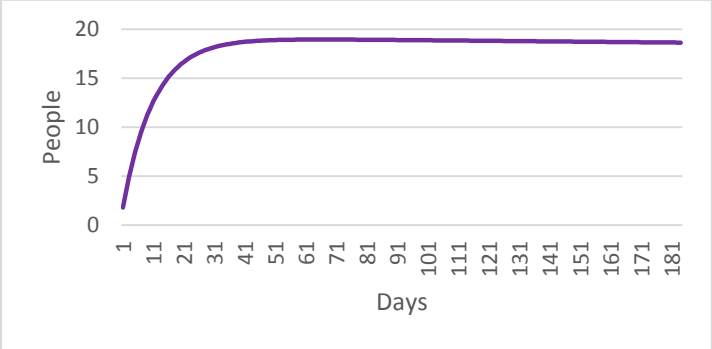


Figure 4.3 Infection Rate During the Baseline Run

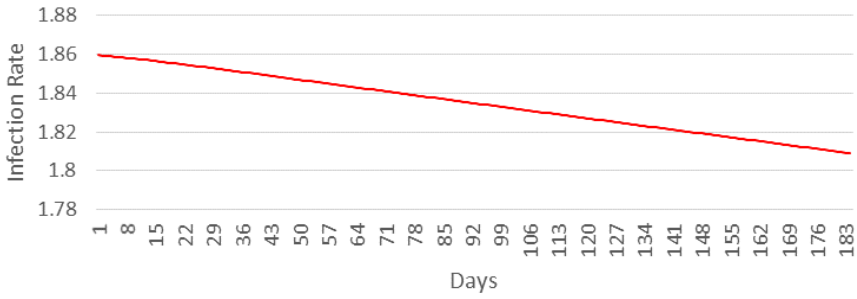
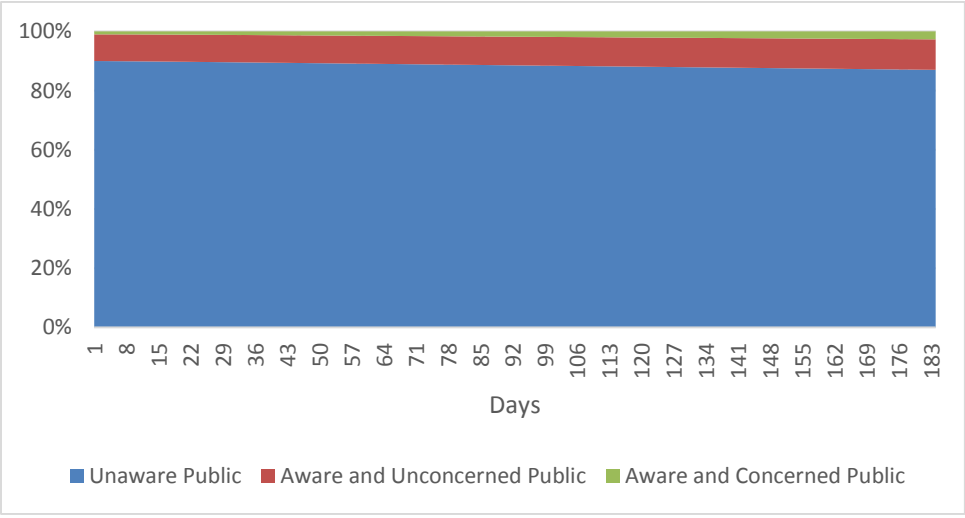


Figure 4.4 Percentages of Public in Awareness Levels During the Baseline Run



The EL and ED stage stocks showed more dynamic behaviour (Figure 4.5). The number of people in the EL stage peaked the earliest, around 29 days, after growing quickly for the same reasons as discussed for the infected population stock. The number of people in this stock then declined, and after a time levelled out to a gradual, consistent descent. The ED population stock showed similar behaviour, except the number of people did not grow as high and peaked slightly later. Implicit delays built into the model to mimic the progression of disease accounted for part of the early rapid growth, as seen in the infected stock. The decline in the stock populations can be explained by increased awareness and uptake of best behaviours in both the public and physician populations. However, the initial, quicker decline, before the descent becomes gradual, was largely attributable to physician awareness. All physicians moved into the highest level of awareness a little less than halfway through the simulation (Figure 4.6). Very few people progressed to the LD and PE stages of disease, so little change in the behaviour of these stocks was visible (Figure 4.5).

Figure 4.5 Disease Stage Population Stocks During the Baseline Run

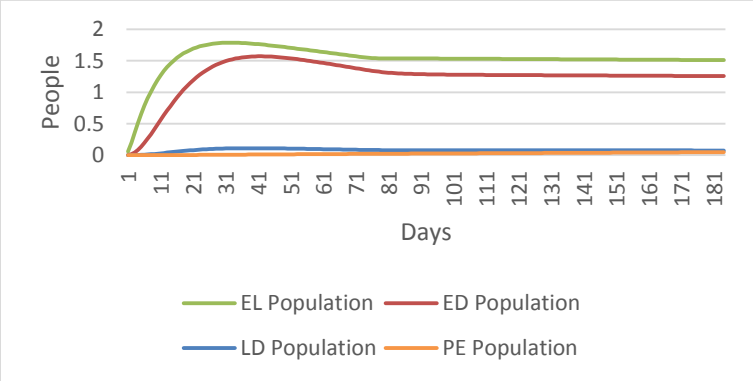
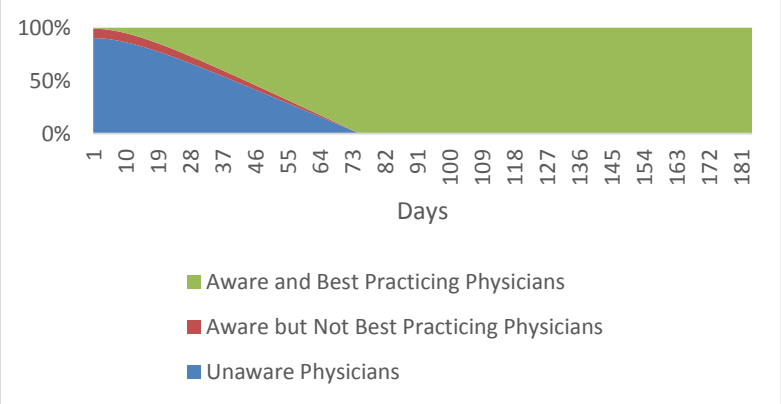
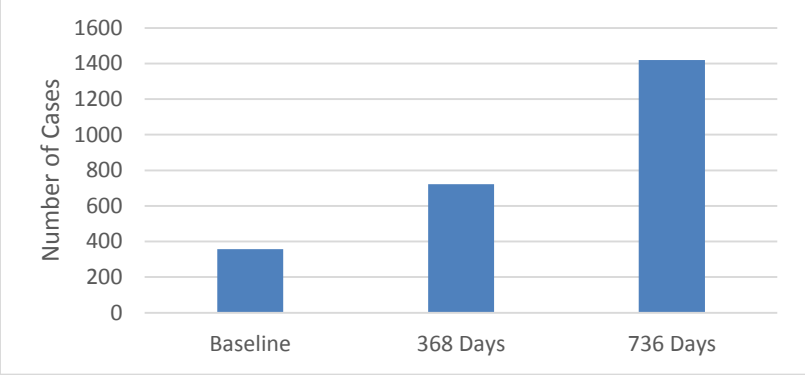


Figure 4.6 Percentages of Physicians in Awareness Levels During the Baseline Run



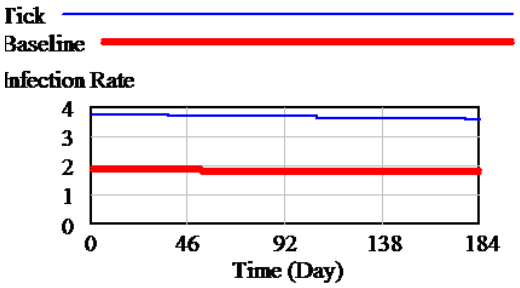
The model did not generate unusual results when the period of the epidemic was extended to two and four seasons to test behaviour. Doubling the length of time for the outbreak resulted in slightly more than double the baseline amount of cumulative cases, and quadrupling the duration caused similar behaviour (Figure 4.7). This means that model behaviour stayed relatively stable over time, particularly in terms of incidence rates.

Figure 4.7 Lyme Disease Cumulative Incidence for Different Outbreak Lengths



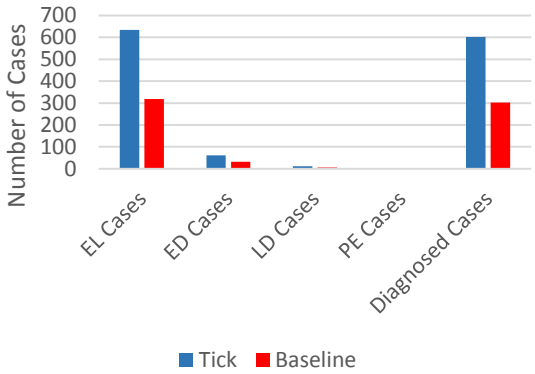
The model behaved as expected when the risk of tick bite was increased to test conditions of greater endemicity. Both the infection rate (Figure 4.8) and number of cumulative cases approximately doubled along with the risk of tick bite (Figure 4.9). However, the general behaviour of the infection rate stayed the same as during the baseline run, which is evident by its similar trajectory (Figure 4.8).

Figure 4.8 High Endemicity Infection Rate



*Tick=scenario with increased risk of tick bite

Figure 4.9 High Endemicity Case Totals



Similarly to what was seen in terms of the infection rate, with a higher risk of tick bite the public and physician awareness module rates increased but overall behaviour did not change (Figure 4.10 and 4.11). This increase in rates can be attributed to higher Lyme disease incidence, which causes people to progress to the greater levels of awareness more quickly. For the public, this resulted in more people reaching the third level of awareness than during the baseline run (Figure 4.10). Physicians completely progressed to the third awareness stock in approximately half the time as during baseline (Figure 4.11).

Figure 4.10 Percentages of Public in Awareness Levels During the High Endemic Run

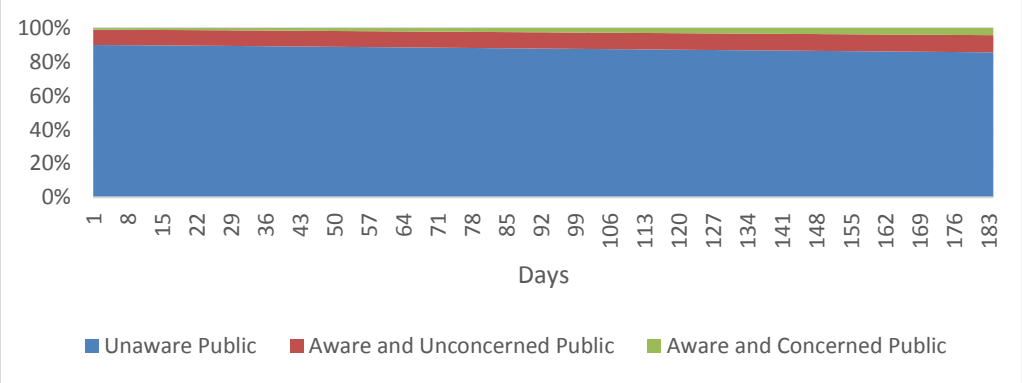
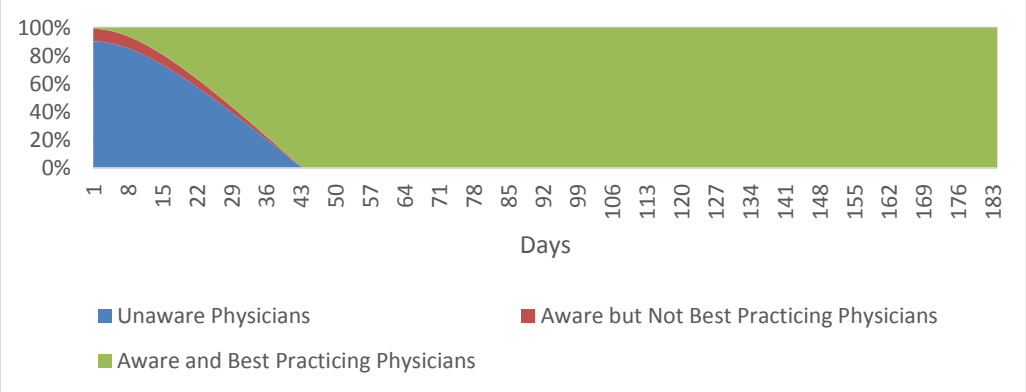


Figure 4.11 Percentages of Physicians in Awareness Levels During the High Endemic Run



4.2 Model Experiments

The results of the model experiments are summarized in Table 4.1. This table shows which experiment was conducted, the public and physician awareness flow rates used, and

outcomes including cumulative cases and the percentage diagnosed. Public-based interventions had a greater impact on reducing negative outcomes, a finding which was robust under all tested conditions. However, public-based interventions still did not produce dramatically different results from the baseline. A moderate intervention level was required to see a visible impact, but even this only resulted in a 5% reduction in cumulative cases (Table 4.1). This small change can be attributed to the small proportion of the population that shifts to higher awareness levels, which is not very different when compared to the baseline (Figure 4.12). However, even less of the public population shifted to higher awareness levels during the moderate physician intervention experiment (Figure 4.13), which explains its similarity in outcomes when compared to the baseline (Table 4.1).

Table 4.1 Experimental Results

Experiment	Flow Values*	EL Cases	ED Cases	LD Cases	PE Cases	Cumulative Cases	Cumulative Diagnosed Cases	Percentage Diagnosed (%)
Baseline	0.0001 0.0001	318.98	31.46	5.83	0.05	356.32	302.06	84.77
Low Public Intervention	0.0002 0.0001	317.11	31.27	5.79	0.05	354.22	300.32	84.78
Low Physician Intervention	0.0001 0.0002	318.98	31.46	5.82	0.05	356.31	302.07	84.78
Moderate Public Intervention	0.001 0.0001	302.62	29.76	5.51	0.04	337.93	286.80	84.87
Moderate Physician Intervention	0.0001 0.001	318.98	31.42	5.82	0.05	356.27	302.09	84.79
High Physician Intervention	0.0001 0.01	318.97	31.06	5.71	0.04	355.78	302.30	84.97
Very High Physician Intervention	0.0001 0.1	318.97	29.99	5.42	0.04	354.42	302.90	85.46

*Flow values are written as the public awareness flow rate over the physician awareness flow rate, with units of people/day.

The effect of public-based interventions was most evident in the decreasing cumulative cases for the first three disease stages. Public-based interventions did not produce fewer persisting effects cases, but this is likely because the number was already so low, being only a fraction of a case. Public-based interventions were most successful at reducing the number of early localized Lyme disease cases, which was not unexpected. This is because higher levels of public awareness and behaviour directly influence primary prevention

practices, decreasing the infection rate and most heavily impacting the number of early Lyme disease cases (Figure 4.15). Once people are infected, the only way a public-based intervention intervenes is by increasing the probability of seeking care, which has less effect overall on reducing negative outcomes than primary prevention. While public-based interventions resulted in fewer cumulative diagnosed cases, by creating lower Lyme disease prevalence the percentage diagnosed was actually slightly increased; in other words, the numerator decreased, but not as much as the denominator decreased. The number of diagnosed cases are reduced simply because with fewer people infected there are fewer diagnosed, while the greater likelihood of seeking care slightly improves the proportion of people diagnosed.

Figure 4.12 Moderate Public Intervention Public and Physician Awareness Levels

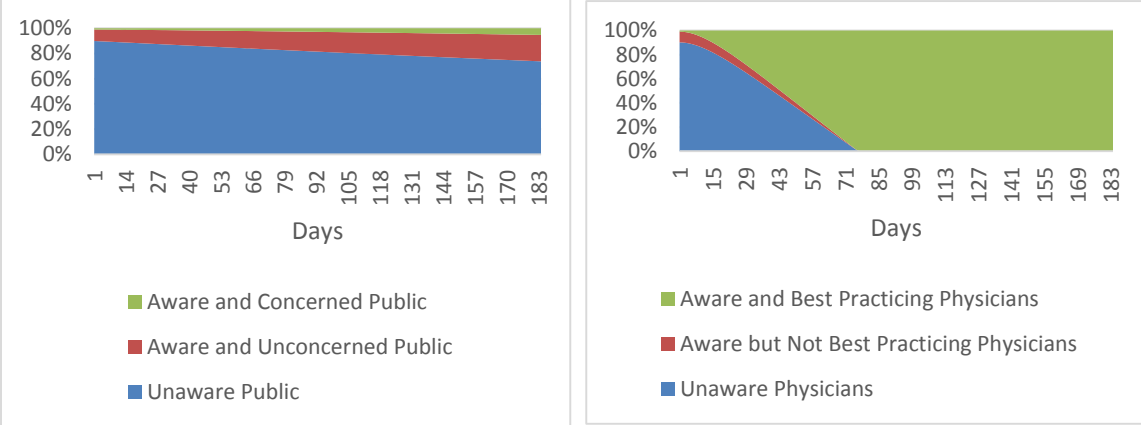
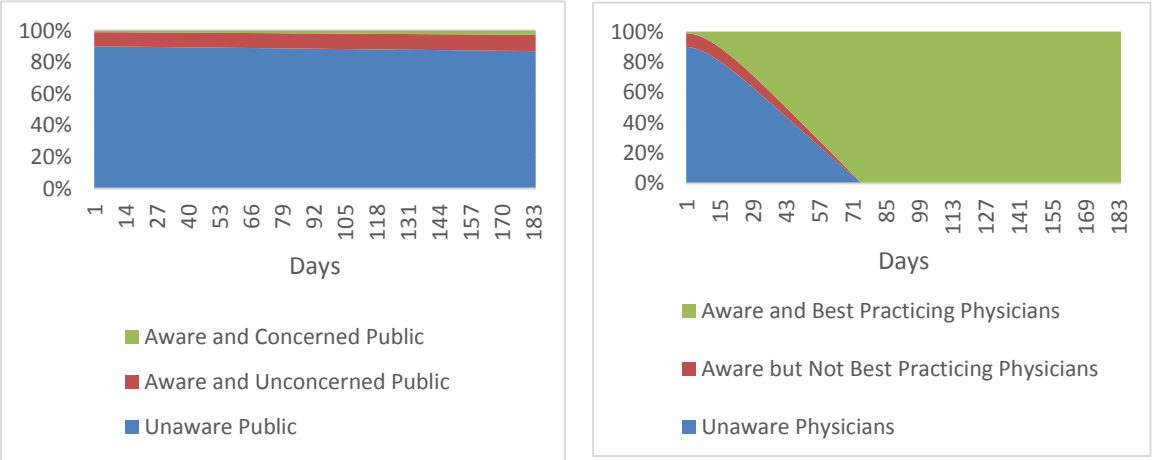


Figure 4.13 Moderate Physician Intervention Public and Physician Awareness Levels



While the public awareness rates had to be multiplied by a factor of ten from baseline to generate visible effects, when the physician awareness rates were multiplied by a factor of 1000 they still did not produce similar reductions in cumulative incidence. This very high physician-based intervention created slightly better results when compared to the low public-based intervention, with the exception of lower EL stage cumulative incidence. The moderate physician-based interventions produced slightly better diagnosed percentages when compared to the low public-based intervention or baseline. Since physician-based interventions only affect the probability of infected people being diagnosed and treated, these results were as predicted.

Figure 4.14 Experimental Lyme Disease Cumulative Incidence and Diagnosed Cases

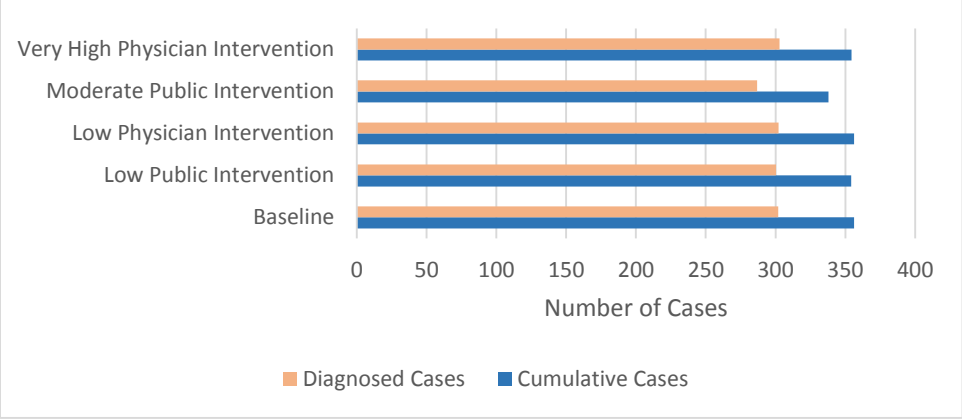
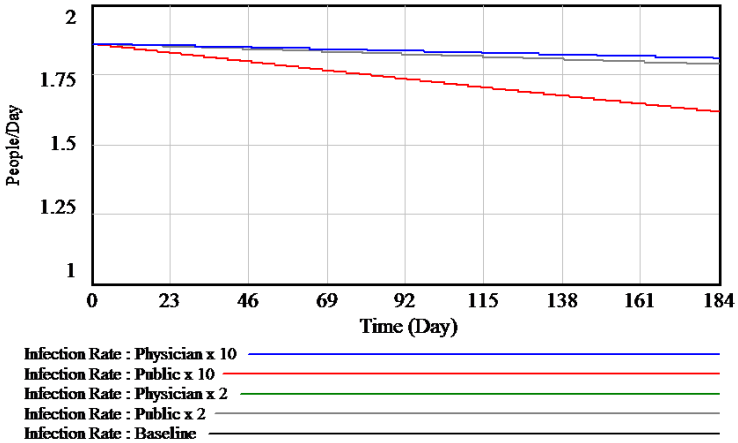


Figure 4.15 Simulated Daily Infection Rates Under Different Experimental Conditions



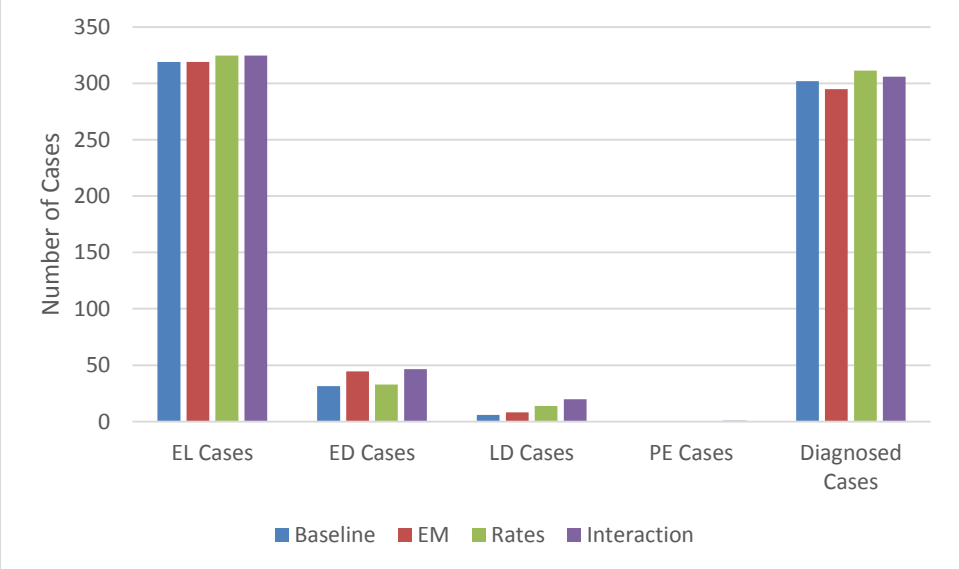
*Public x 2=Low Public Intervention, Physician x 2=Low Physician Intervention, Public x 10=Moderate Public Intervention, and Physician x 10=Moderate Physician Intervention.

4.3.1 Sensitivity Analyses: Probability Ranges

Sensitivity analyses showed conclusions were robust to all tested conditions. Public-based interventions were determined to consistently be more effective at reducing negative outcomes than physician-based ones. Additionally, model behaviour stayed relatively constant when different probabilities were employed for key variable values.

The first variable that was altered was the probability of developing EM, from 0.80 to 0.53 based on the range that was found in the literature. When the probability of EM was decreased, the cumulative cases in the three later disease stages increased slightly (Figure 4.16). The number of early localized Lyme cases did not change, as EM occurs during this stage and thus does not affect progression to it. Additionally, cumulative diagnosed cases of Lyme disease decreased marginally as well. While these behaviours were predicted, changing the probability of EM did not have as significant an impact on overall results as hypothesized, as it only caused moderate changes in outcomes of interest. Furthermore, when testing to see how this change interacted with the intervention experiments, it was not found to alter the experimental results; the difference between public- and physician-based interventions was maintained.

Figure 4.16 Cumulative Cases for EM, Rates, and Interaction Sensitivity Testing



*EM=scenario with a lower probability of EM, Rates=scenario with faster disease progression rates, Interaction=interaction between the EM and rates. All cases are cumulative.

The next variables to be tested were the disease progression rates. Quickening these rates increased the number of cases in all disease stages, as well as the cumulative diagnosed cases simply as a product of more cases overall (Figure 4.16). Both cure and spontaneous recovery rates were slower in this scenario, with more people quickly progressing to the next stage of disease. Cumulative cases increased in all disease stages more than what was seen after changing the probability of EM, with the exception of early disseminated cases. This is because the probability of EM most directly affects the rate from EL to ED. This is supported by the EL to ED rate generally being higher in the EM scenario and peaking at 0.284 compared to 0.214 for the rates scenario. Again, overall experimental results did not change when the interaction was tested.

The next step in the sensitivity analysis was testing interactions between the already identified and tested variables of interest. First, the interaction between a lower EM probability and faster disease progression rates was tested. There did not appear to be any interaction between these two variables, with the lower probability of EM decreasing the number of cumulative diagnosed cases similarly to what was seen with the slower disease progression rates. It did, however, create a "worst case scenario" in terms of cases, with a slightly higher number of cases in all disease stages than what occurred in either sensitivity test individually (Figure 4.16). Furthermore, when compared to the individual sensitivity testing for the probability of EM and the rates, the number of cumulative diagnosed cases falls somewhere in the middle of the two other runs. This interaction also did not change the results of the experiments.

The next interaction tested was a higher risk of tick bites with faster disease progression rates, a scenario that was thought to potentially produce very high numbers of cases, and comparatively more in the later disease stages. However, there were only minimally more cumulative cases in the first two stages or cumulative diagnosed cases overall. As predicted though, there were much higher numbers of cases in the late disseminated and persisting effects stages when compared to other simulation runs (Figure 4.17 and 4.18). This is expected model behaviour, since many additional infections are being generated with the higher risk of tick bite, and then they are moving quickly to the later stages of disease due

to the faster progression rates without recovering or being diagnosed. This interaction resulted in no changes to experimental results when compared to those obtained by running a higher risk of tick bite independently.

Figure 4.17 Tick and Rates LD Cases

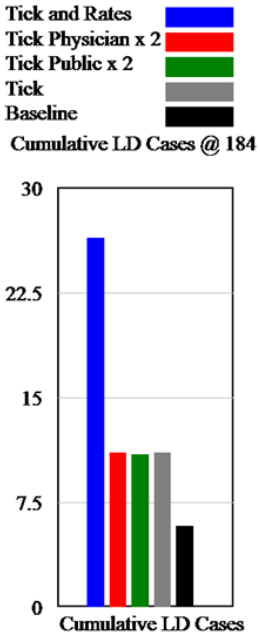
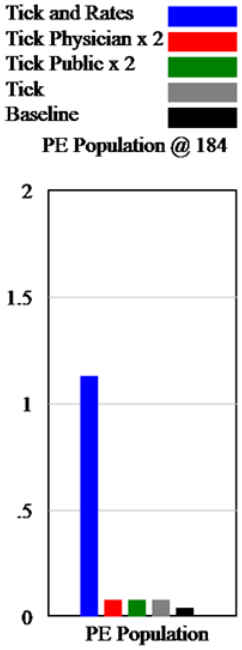


Figure 4.18 Tick and Rates PE Cases



* Tick and Rates=interaction between tick scenario and fast disease progression rates, Tick Physician x 2=interaction between low physician intervention and tick scenario, Tick Public x 2=interaction between low public intervention and tick scenario, Tick=scenario with increased risk of tick bite, cases are all cumulative.

Finally, the experimental results were tested with longer periods of seasonality, so that behavioural changes that require longer to manifest would not be missed. Testing both at 368 and 736 days, there were no alterations to experimental results, and the model behaved as hypothesized. Due to the extended length of time, there was a greater reduction in all cumulative cases when the public-based intervention was used when compared to the extended season baselines. However, when employing the physician-based intervention there was no change when compared to the baseline, since all physicians still reach the third level of awareness early on in the simulation.

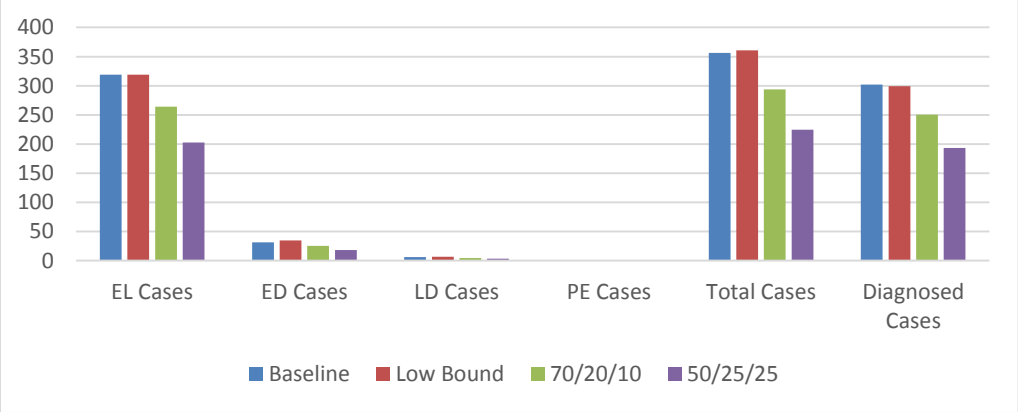
4.3.2 Sensitivity Analyses: Behavioural Assumptions

The most important sensitivity analyses involved the public and physician awareness module, as it was a key driver of model outcomes and a source of a high degree of

uncertainty. Sensitivity analyses revealed that the model behaviour was sensitive to the initial distribution of the public and physician populations by levels of awareness. Larger initial shares of the population in the highest awareness level greatly reduced Lyme disease cumulative incidence. Other behavioural modifications did not impact results in unexpected or extreme ways. However, the results of the experiments were still robust under all tested circumstances, with public-based interventions more successful than physician-based ones.

To initially test the assumptions made about how increased awareness affects behaviour, the bounds between probabilities associated with the different awareness levels were decreased. It was discovered that changing these had little overall effect on the outcomes of interest and model behaviour (Figure 4.19). Small expected variations occurred during testing but the experiments behaved the same way under these conditions and produced equivalent results (Figure 4.20).

Figure 4.19 Behavioural Sensitivity Testing Outcomes

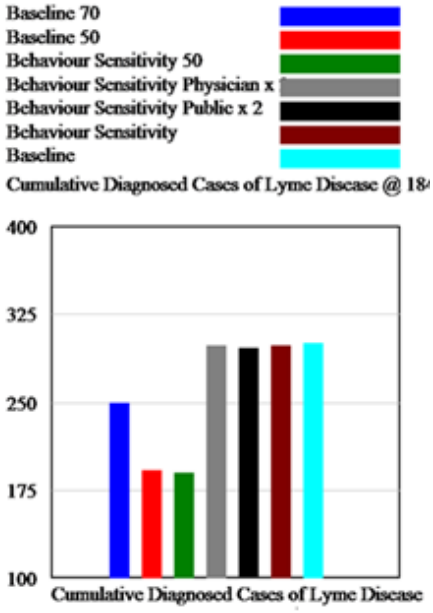


*Low bound=scenario with lower bounds on probabilities associated with behavioural modification, 70/20/10=scenario with awareness stocks initially set at 0.70, 0.20, 0.10, and 50/25/25=scenario with awareness stocks initially set at 0.50, 0.25, 0.25, all cases are cumulative.

For additional behavioural testing, the initial proportion of the population in each of the awareness levels was varied in a couple of different ways while keeping consistency between the public and physician awareness stocks. It was found that this had the greatest effect on model behaviour and outcomes, particularly in terms of decreasing the cumulative

incidence of Lyme disease (Figure 4.19 and 4.20). While the number of cumulative diagnosed cases decreased as well, this can be attributed to having lower cases overall. When decreasing the proportion in the first stock from 0.70 to 0.50, a similar reduction in cumulative incidence was observed when compared to changing the proportion from 0.90 to 0.70. However, these changes still did not alter the results of the experiments, with public intervention measures continuing to be more effective than physician-based ones, indicating that the results are robust (Figure 4.20).

Figure 4.20 Additional Behaviour Testing



* Baseline 70=scenario where the first awareness stock is initially set at 0.70, Baseline 50=scenario where the first awareness stock is initially set at 0.50, Behaviour Sensitivity 50=interaction between behavioural scenario and setting the first awareness stock initially at 0.50, Behaviour Sensitivity Physician x 2=interaction between behavioural scenario and low physician intervention, Behaviour Sensitivity Public x 2=interaction between behavioural scenario and low public intervention, Behavioural Sensitivity=scenario with lower bounds on probabilities associated with behavioural modification.

To test the effect of all physicians reaching the highest level of awareness partway through the simulation, the progression of physician awareness was reduced. After doing so, the physician awareness stocks behaved similarly to the public ones at baseline, although a comparatively smaller proportion of physicians reached the highest awareness level (Figure 4.21). This is due to the different way public and physician rates are increased during the simulation based on the number of diagnosed cases and the multipliers.

As expected, the cumulative number of EL cases only changed fractionally with a reduced progression in physician awareness, but the cumulative cases in all other stages increased at least slightly from baseline (Figure 4.22). This increase in later stage cases is due to the comparatively lower proportion of physicians in higher awareness levels, which decreased the probabilities for testing and treating Lyme disease. The greatest change in model behaviour after reducing the awareness progression of physicians occurred in the diagnosis rate, which decreased by approximately 4%.

Figure 4.21 Percentages of Physicians in Awareness Levels with Reduced Awareness Progression

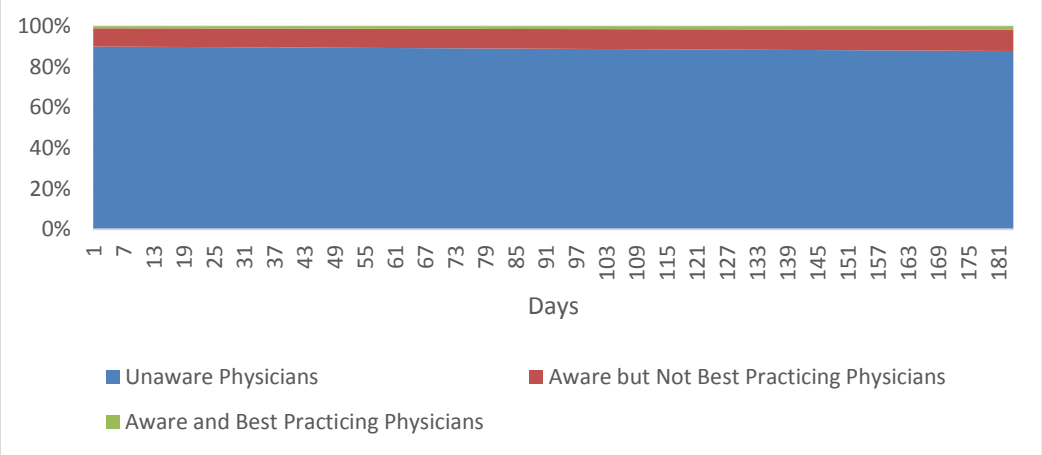
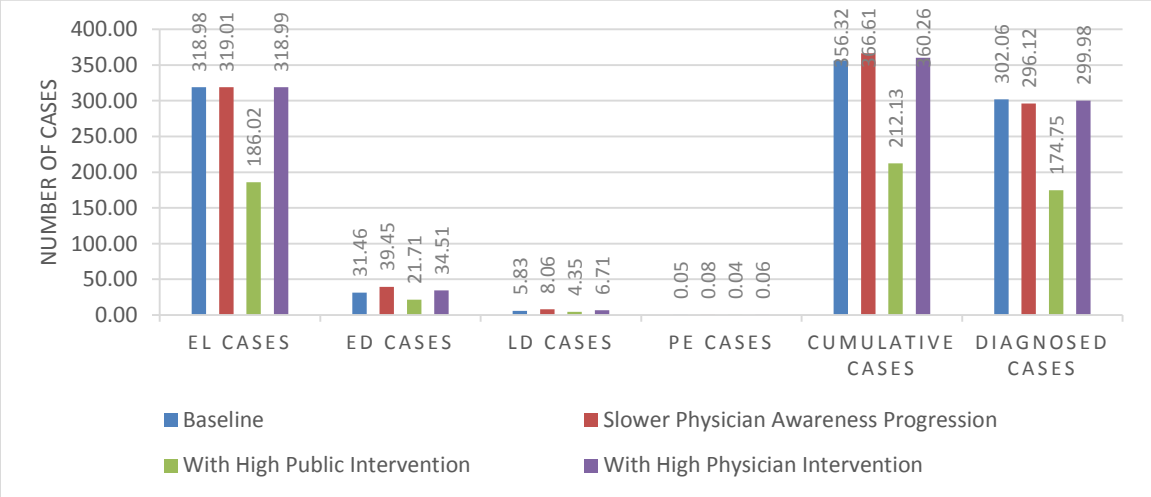


Figure 4.22 Experimental Results with Reduced Physician Awareness Progression



*With High Public Intervention and With High Physician Intervention are both simulated using a slower physician awareness progression.

Despite minor changes in model behaviour with a reduced progression in physician awareness, the experimental results were still robust (Figure 4.22). While public-based interventions were more successful at reducing negative outcomes than physician-based interventions during all experiments under these conditions, the differences were minimal until high intervention levels were modelled. A high public-based intervention produced lower numbers of cases in each disease stage, and as a result obtained a much lower cumulative incidence (Figure 4.22). The most dramatic reduction during the public-based intervention was in the number of EL cases, which physician-based interventions do not have the opportunity to change. However, a high physician-based intervention had a slightly greater diagnosis percentage, with 83.27% of cases diagnosed compared to 82.38% during the public-based intervention. Demonstrating that the experimental results do not change when tested under more extreme conditions indicates that they are robust, which contributes to model validity.

CHAPTER 5: DISCUSSION

This study found that public-based interventions had a greater impact than physician-based interventions on reducing negative outcomes of Lyme disease in emerging outbreak situations. These impacts included reducing the cumulative incidence of disease, reducing the number of cases in each disease stage, and slightly increasing the diagnosis rate for cases. This result was robust under a number of different conditions. Additional findings of interest were the importance of baseline awareness to the extent of disease, with higher initial levels of awareness greatly reducing the cumulative incidence, and the potential for the feedback of direct experience with Lyme disease to limit an outbreak.

While little evidence is available in the literature that specifically examines the effectiveness of public-based interventions for Lyme disease (65), the relative success of public-based interventions found in this study is supported by similar research on other health topics (70). For example, primary prevention is known to generally be more effective than other types of prevention for infectious diseases, since it reduces the infection rate for the entire at-risk population and prevents cases before they occur (70). The model incorporated multiple opportunities for public-based interventions to invoke behavioural change: a decreased risk of a tick bite; a decreased probability that a bite would cause infection; and an elevated probability of seeking care for an infection. Two out of three of these were primary measures. Improving the probability of seeking care was the exception to this, but it is a secondary measure that has an effect early on in the disease trajectory, and then again at each subsequent stage. Since diagnosing Lyme disease is easier in the first stage, increasing the likelihood of seeking care at this juncture would avoid having many cases progress to later stages where diagnosis is more difficult. With the model demonstrating that the majority of Lyme disease cases occur in the EL stage, primary prevention and early diagnosis are key in reducing the extent of an outbreak. Consequently, the results of this study provide further evidence that a primary approach to prevention is likely to be more successful than secondary methods. The outcomes are robust enough to recommend that in emerging outbreak situations, public-based intervention measures should be employed to reduce Lyme disease incidence.

The model used sensitivity analyses to explore the uncertainty around the extent of behavioural modification following educational interventions to test the robustness of results. Neither test impacted the study conclusions; public-based interventions were conclusively more effective at reducing Lyme disease cumulative incidence and other negative outcomes. The first test examined how higher awareness translates into preventive practices by lowering its effect on behavioural modifications. This was found to minimally influence model behaviour, indicating that although uncertainty persists around this aspect of educational interventions, it may not be of great importance in this particular situation. However, it was found that different initialized levels of the awareness stocks greatly influenced the number of Lyme disease cases within a population. When a population began with higher levels of awareness, and evidence-based behaviour, it dramatically decreased Lyme disease cumulative incidence. This indicates that a population with a certain level of awareness about a health issue is less likely to develop an outbreak of that kind, which is an important general concept to consider for disease prevention purposes.

Physician-based interventions were found to have a much smaller impact on reducing negative outcomes, even at high levels. These interventions were all secondary prevention measures, so it is unsurprising that they had less of an effect than primary public prevention. Additionally, behavioural changes based on physician awareness were limited to an increased probability of treating Lyme disease, and in the case of early Lyme disease, a decreased probability of inappropriately testing. As a result, there were fewer opportunities for physician-based interventions to invoke behavioural change and decrease negative outcomes in the model. It was expected that physician awareness would be most important in the early localized stage of Lyme disease, where it is key to treat and not test due to low testing sensitivity. However, it was reported in the literature that even with low levels of awareness few physicians were found to just test, with the majority testing and treating simultaneously (17, 18, 21). Consequently, improved physician awareness at this stage had less impact than initially hypothesized. At later stages, with testing sensitivity so much higher (5, 14), importance was primarily placed on physicians recognizing the symptoms as being attributable to Lyme disease. Due to the greater difficulty in distinguishing Lyme disease from other differential diagnoses in its later stages, the model

results support the concept that early diagnosis and treatment of Lyme disease is crucial. Furthermore, this highlights the importance of taking a patient's history to accurately diagnose Lyme disease, since it is challenging in the later stages to base a diagnosis of Lyme disease on symptoms alone.

It was thought that the physician awareness "ceiling effect" was part of the reason that physician-based interventions had low effectiveness in the model, with all physicians reaching the highest level of awareness approximately halfway through the simulation. However, with additional sensitivity testing, it was discovered that this was not the cause of the experimental results, which were robust. Furthermore, this "ceiling effect" is not unrealistic. While 100% of physicians in a population may not become highly aware about an emerging disease halfway through a season, it is possible that up to 80-90% may do so by the end of the season. Physician populations are much smaller than public populations, are exposed to both physician- and public-based interventions, and a component of their profession is continuing education and increasing their awareness about diseases they might encounter in their practice. These characteristics create a different distribution in awareness levels between public and physician populations. With the model only representing a proportion of an average-sized population, and no evidence available to determine otherwise, all physicians progressing to highest level of awareness can be considered plausible.

Even after the sensitivity analyses were conducted, uncertainty persisted around characteristics of the public and physician awareness module, for which no strong evidence is available in the literature. To maintain consistency between experiments, the rates for both public and physician awareness were increased equally. But the literature actually reported a lower level of educational uptake in physicians when compared to the public (68, 69). This was an unexpected finding, since it is logical that physician-based interventions are more successful in reality. High levels of awareness and best practices are a component of the profession, as is ensuring patients are appropriately treated; improving in these areas is less of an inconvenience, and more of a requirement. The lack of effectiveness of educational interventions reported for physician populations could be

explained by how busy their profession is, particularly in regards to lower long term effects. However, the results of these studies could also be highly influenced by the specific context in which they occurred, meaning that the outcomes may be underestimated if those physician populations had multiple competing demands or were not amenable to educational sessions. If what is found in the literature is accurate, making public and physician awareness rates increase equally during the experiments only served to have the study results overestimate the strength of physician-based interventions when compared to public-based ones. Since in all modelled scenarios public-based interventions were found to be more successful than physician-based interventions, this has no bearing on the outcomes except to indicate that public-based interventions may actually be even more effective comparatively than what was found. There is enough uncertainty around this evidence, however, to justify that both physician- and public-based interventions modify awareness at a similar rate for modelling purposes.

A finding of interest from the public and physician awareness module was that model behaviour suggested the effect of direct experience with Lyme disease may be an important driver of the disease dynamic. This is supported by existing research which indicates that direct experience with Lyme disease is key to increasing awareness, concern, and intervention measures (67). The impact of such experience should be explored further in the future, and additionally if it could be used by public health authorities in intervention measures for Lyme disease. Furthermore, the effect that geographic clustering may have on the potential impact of direct experience should be considered. For example, it is likely that someone diagnosed with Lyme disease would share their experience with people in proximity, such as their immediate family. The same could be true for physicians diagnosing Lyme disease, in which case they may discuss their experience with colleagues. Such situations would create a "geographic cluster effect", where those who have experience with Lyme disease are primarily restricted to a specific area. While this may be useful in areas of high Lyme disease risk, it could also limit the impact of direct experience on minimizing outbreaks by reducing the extent that awareness is able to spread.

While cumulative incidence increased over time during all simulation runs, the model results indicated that the rate at which it increased was reduced more by public-based interventions than those directed at physicians, which was supported by a 5% reduction in cumulative incidence from the baseline simulation. This suggests that immediately responsive public-based interventions are more effective than physician-based ones at reducing negative Lyme disease outcomes, but that their overall effect was minimal even at moderate levels. These results reflect what is currently encountered in public health practice. Public health authorities already target both the public and physicians regularly with educational interventions for Lyme disease, including specifically targeting high risk populations such a hikers or campers, but cumulative incidence continues to increase (24, 65). While this could be occurring because higher levels of awareness may cause more people to seek medical attention and get diagnosed, ultimately it could also indicate that such interventions are only minimally effective in reality. However, due to the lack of evidence around this issue, it is unclear if they are ineffective because they are not used by the public in practice or if they become less effective as endemicity increases in a region. Although current literature demonstrates that their effectiveness in reality is unclear (65), the model results indicate that public-based interventions do have a degree of effect and suggest that if more effective interventions could be developed, cumulative incidence may decrease even further. Since public-based interventions have the potential to greatly reduce health issues such as Lyme disease, perhaps this is an area deserving of further research to enhance public health programs.

Some theories to explain the possible low effectiveness of public-based interventions in practice have already been proposed in various health areas. These include the difficulty of motivating behavioural change and the lack of basing interventions on the appropriate psychological theories (65, 66, 70). While Lyme disease prevention strategies need to function largely at the population level, this does not preclude the application of these psychological theories, at least generally. Additionally, many recommended preventive measures, such as checking for ticks, are implemented at an individual level, which provides further opportunities to employ such psychological theories. Further research where the public is questioned directly in focus groups about barriers to behavioural change

could be particularly helpful in clarifying this issue. Specific areas that could be beneficial to explore further include an individual's perception of risk, which is considered to be particularly important when attempting to modify behaviour (65), and the feedback of direct experience with Lyme disease (67), which the model indicated could be key to motivating preventive measures.

Until the potential effectiveness of public-based interventions is determined, the model results support what the current literature suggests is the best strategy for prevention: approaching interventions from multiple angles increases the chance of success. A report that summarized Canada's 2014 Action Plan on Lyme Disease described a three-pronged approach of 1) education, engagement, and awareness 2) surveillance, prevention, and control, and 3) research and diagnosis (71). The first task specifically involved engaging and informing both the public and physicians to prevent cases and promote early diagnosis and treatment (71). While public-based interventions were found to be minimally more effective at moderate levels than physician-based interventions, the greatest success in the model from a public health approach could be considered to be the relatively high diagnosis rate. It remained between approximately 80-85% during all the model testing, and was achieved through a combination of public and physician awareness.

Additionally, while the study found that physician-based interventions had a small impact on population-level outcomes, early diagnosis and treatment is very important at the patient level. Furthermore, a prevention strategy used in practice is for educational interventions to come from a trusted authority figure, such as a physician for matters relating to health. A limitation of the model design is that this relationship could not be investigated, but its usefulness to public health interventions is worth considering in the future. As a result, using multifaceted interventions, with a focus on the public, may currently be the best option for public health in practice. These results could assist in resolving some of the current controversy around Lyme disease, as they support the idea that the public is at least as equally responsible for their own health as physicians, if not more so. The model provided a clear visual representation of how cases changed directly in response to the awareness and behaviour of the public, which could assist in communicating the

importance of individual responsibility to the general public. As such, both the public and physicians should work together to reduce Lyme disease instead of focusing on directing blame for negative disease outcomes.

Despite the robustness of study results, modelling can still be considered subjective in nature based on the necessity of employing assumptions or using judgement-based values for variables. This occurs in part because of the paucity of information in the literature from which evidence was collected. This created a significant limitation, as research was constrained by how the primary studies were performed, especially in terms of the study design including what evidence was collected and how variables were analysed. Using evidence from previously conducted studies was particularly problematic for this study, as the literature around the modelled aspects of Lyme disease, from disease progression, to testing and treatment, to seeking care, contained a number of gaps and discrepancies.

To address this limitation, a comprehensive literature search was conducted to achieve a representative sample of studies with a variety of methods and results. Evidence was preferentially included in the model if the original research was considered to be both internally and externally valid through a general assessment. If the literature permitted it, crosschecking between sources was used to obtain a plausible range for the variable values. Instances still occurred where evidence was unable to be found for certain variables or associations that were included in the simulation model, or varying levels of uncertainty persisted around what was found. In these cases, it was necessary to employ assumed values in the simulation model, many of which were based as least partly on logic. As a result, a number of the hypothesized associations or values for variables were not considered evidence-based. When evidence with questionable validity had to be used, the uncertainty around it was noted for transparency. Conducting validation tests throughout the modelling process helped address these validity issues, as limitations were found and resolved early on to improve the model. Additionally, sensitivity analyses were used for uncertain and important input parameters to test the assumptions that were made and their effect on model behaviour. When sensitivity analyses demonstrated that including any of these variables or relationships in the model significantly altered the study results, their

importance to the system was assessed. If they were then determined to be important to the model, this suggested that it would be valuable to fill those gaps in knowledge. By using this methodology, it was possible to make inferences about future research priorities and data requirements. Ultimately, employing different values for the majority of key variables did not affect the results of the experiments or drastically impact model behaviour. As a result, the model is considered to be robust.

An intrinsic limitation of modelling is the necessity of setting model boundaries. If it is even possible for a model to include all relevant variables from a complex system it would then likely be too complicated to be useful. But choices made about where to set model boundaries can prevent some potentially interesting interrelationships from being explored. A limitation of the current model is that the effect of personal environmental prevention measures could not be examined because of the decision to leave environmental components exogenous to the model. However, now that the model has been built it would be an easy task to perform minor adaptations including extending the tick module to include environmental measures such as tick density. Once the environmental components within the model are expanded upon, they could be integrated with the public section of the awareness module. This would permit the model to include personal environmental prevention measures, such as landscaping, so that their relative impact on reducing the extent of a Lyme disease outbreak could be assessed.

Both the study results and the process of modelling itself assisted in identifying a number of directions for future research. Since the model results indicated that moderate public-based interventions can have a larger effect than other methods, uncovering the reason for their apparent relative ineffectiveness in practice serves as arguably the most important area for future research. Additionally, the level of baseline awareness in populations of different endemicities could be a useful area to explore further, as sensitivity testing around this variable had the greatest impact on outbreak trajectory. Greater understanding about this topic may contribute to a better comprehension of why public-based interventions are not demonstrating high levels of effectiveness in practice. The threshold of an intervention required to visibly reduce outbreaks is another area that could benefit from more

investigation. The model showed some reduction in cumulative incidence with moderate levels of public awareness, but greater success occurred with higher intervention levels. As a result, it is worth exploring the extent of an intervention required to make significant population-level changes, and to determine if it is feasible in reality. In regards to physician awareness, it would helpful to identify how often physicians who treat and test stop a course of treatment if the test results are negative. In the model, it was assumed that such physicians would not, but it may increase the impact of physician awareness if those with low levels of awareness do not continue treatment with a negative test. Additionally, the reported ineffectiveness of physician-based interventions in practice could benefit from further exploration as to the reasons why, since logically physician-based interventions have the potential to be more successful than what is reported in the literature (68, 69). The feedback of direct experience with Lyme disease should also be further explored by working with the public and physician awareness module. This includes determining how direct experience with Lyme disease changes the extent of an outbreak by increasing awareness, concern, and the uptake of prevention measures, how it may be impacted by geographic clustering, and how it might be used by public health authorities to assist with interventions. The model could also be used to test the relative effectiveness of personal environmental prevention measures for Lyme disease, with the addition of environmental components to the tick module and its integration with the public section of the awareness module. Finally, the variable values that most greatly affected model behaviour during probability-based sensitivity testing were the rates for disease progression and spontaneous recovery. As a result, learning more about the stages of Lyme disease, accompanying symptoms, and how cases progress would be a good place for future research to begin.

Despite the inherent limitations of system dynamics simulation, the study results suggest that it could be more rigorously used as public health methodology. In an area where a lack of information, high costs, and ethical restrictions would make other study designs unfavourable, system dynamics provided a clear answer to whether public- or physician-based interventions are more effective at reducing the negative outcomes of Lyme disease by combining all the best evidence that is currently available. Furthermore, the evidence utilized in the model came from a variety of studies conducted in different geographical

locations, mainly within North America. Although it could be considered a limitation that the results are not applicable to a specific population, this may actually serve to make the results more generalizable and representative. The results, conducted with varying values for variables of interest from diverse regions, should be applicable to at least as many locations as those of the source studies. Additionally, now that the model is built, different values for variables could be entered to more accurately mimic certain environments and further explore model behaviour. For example, different scenarios could be run by employing various values for the risk of a tick bite or exposure time along with specific initialized populations to determine the potential extent of an emerging outbreak in particular locations.

Finally, the model is a useful communication tool, as it visually represents a complex system, including its components and interrelations, in a simplified manner. As such, this research provides an ideal opportunity to bring together different facets of the health care community such as patients, physicians, researchers, and public health authorities. If shared with these groups, it may lead to improved understanding and new discoveries about how the system functions, which could be used iteratively to improve the model. Consequently, knowledge translation and dissemination are key components of this project, as well as learning how to translate health research into public health policy. Lyme disease is an increasingly concerning health issue, and as the study results suggest, making a large audience aware of its existence and characteristics is important to the extent of disease outbreak.

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APPENDIX A SUPPLEMENTARY TABLES

Table 1. Definitions of Preliminary Model Variables

Variable	Definition/Notes	Model Relationships	Evidence Source
Population Disease Progression			
Susceptible population	A stock of the susceptible population that has not become infected with Lyme disease, or has been previously infected and cured. This population is initally fed into the simulation model.	A function of rate of infection and rate of return to susceptibility.	Published literature used as data sources for other variables, or set to a hypothethical number.
Early localized population	A stock of the early localized population where further disease progression is avoided through diagnosis and treatment.	A function of rate of disease progression and rate of return to susceptibility.	Computed through simulation.
Early disseminated population	A stock of the early disseminated population where further disease progression is avoided through diagnosis and treatment.	A function of rate of disease progression and rate of return to susceptibility.	Computed through simulation.
Late disseminated population	A stock of the late disseminated population where persisting effects are avoided through diagnosis and treatment.	A function of rate of disease progression and rate of return to susceptibility.	Computed through simulation.
Rates			
Rate of infection	The rate at which the susceptible population becomes the infected population.	A function of Lyme disease endemicity, public preventive practices, and if a tick bite is observed.	Published literature, specifically in regards to incidence rates in populations of different endemicities.
Rate of disease progression	The rate at which the infected population moves through the stages of Lyme disease.	Specifies each of the stages of disease progression.	Computed through simulation.
Rate of return to suceptibility	The rate at which the cured population returns to the susceptible population.	May depend on the severity of disease when cured. A function of appropriate treatment.	Computed through simulation.
Environmental Factors			
Lyme disease endemicity	If a location's established population of vector ticks have been demonstrated to transmit *B. burgdorferi*, and the proportion of the tick population which is infected.	This variable is a function of tick population.	Published literature, in particular survillance data.
Tick population	Size of the tick population.	This variable specifies Lyme disease endemicity and is a function of environmental prevention measures.	Published literature, in particular surveillance data or tick studies.
Environmental prevention measures	A parameter the includes the effect of all environmental preventive measures (such as acaricide or host removal) on tick	This variable specifies Lyme disease endemicity and tick population.	Published literature, in particular studies about the effectiveness of environmental

Variable	Definition/Notes	Model Relationships	Evidence Source
	populations and Lyme disease endemicity.		preventive measures.
Societal Factors			
Public prevention measures	A stock of preventive measures which includes protective behaviours such as checking for ticks, reducing time outdoors, and wearing protective clothing. Use of preventive practices reduces the chance of being bitten, and thus infected.	This stock is a function of Lyme disease knowledge, belief in severity, and awareness, and specifies the rate of infection and observed tick bite.	Published literature that involves studies measuring the effectiveness and use of preventive practices.
Observed tick bite	A parameter that describes if a tick bite has been observed.	This variable is a function of public prevention measures, and it specifies seeking care and the rate of infection.	Published literature that reports the proportion of those who observe a tick bite after being bitten.
Seeking care	A variable that describes seeking medical care for Lyme disease.	This variable is a function of both an observed tick bite and societal knowledge, awareness, and belief in severity. It specifies diagnosis by testing, diagnosis by EM, and physician knowledge, belief in severity, and awareness.	Computed through simulation.
Societal Lyme disease knowledge, belief in severity, and awareness	A stock of societal awareness, knowledge, and beliefs about Lyme disease. This includes information on characteristics of the infection such as symptoms and mode of transmission, the societal belief that Lyme disease can cause significant illness, the societal awareness that Lyme disease is an existing health concern, and whether it is endemic in a region.	This stock specifies public prevention measures and seeking care. It is a function of reported case and Lyme disease misconceptions.	Published literature that involves studies that measure different levels of Lyme disease knowledge, beliefs, and awareness in the public, and the effect of these factors on Lyme disease rates.
Reported cases	The number of human cases of Lyme disease reported within a population.	This variable increases the flow into both societal and physician knowledge, belief in severity, and awareness.	Computed through simulation.
Lyme disease misconceptions	A variable that describes persisting misconceptions that occur around Lyme disease within both society and the medical community.	This variable has a negative impact on the flow into both societal and physician knowledge, belief in severity, and awareness.	Published literature that has established the impact of misconceptions on overall Lyme disease knowledge. May alternatively be computed through simulation.

Variable	Definition/Notes	Model Relationships	Evidence Source
Health Care Factors			
Physician Lyme disease knowledge, belief in severity, and awareness	A stock of physician awareness, beliefs, and knowledge about Lyme disease. Includes information on characteristics of the infection such as symptoms and diagnostic protocols and how physicians diagnose, treat, report, and handle Lyme disease patients based on recommendations.	This stock is a function of reported cases, seeking care, and Lyme disease misconceptions. It specifies good physician reporting practices, diagnosis by EM, and diagnosis by testing.	Published literature that involves studies which measure different levels of physician Lyme disease knowledge, beliefs and awareness.
Laboratory testing accuracy	The sensitivity, specificity, and positive predictive value of Lyme disease serological tests.	This variable specifies diagnosis by testing.	Published literature which evaluates the accuracy of Lyme disease serological tests.
Diagnosis by EM	Whether human cases were diagnosed by EM.	This variable is a function of seeking care and physician knowledge, awareness, and belief in severity. Specifies appropriate treatment.	Computed through simulation.
Diagnosis by testing	Whether human cases were diagnosed by laboratory testing.	This variable is a function of seeking care, laboratory testing accuracy, and physician knowledge, awareness, and belief in severity. Specifies appropriate treatment.	Computed through simulation.
Appropriate treatment	Whether human cases received appropriate, effective treatment for Lyme disease.	This variable is a function of diagnosis by EM and diagnosis by testing. It specifies rate of return to susceptibility.	Published literature which involves studies that measure the effectiveness of appropriate treatment.
Good physician reporting practices	The level of physician reporting practices.	This variable is a function of physician knowledge, awareness, and beliefs. Specifies reported cases.	Published literature which involves studies that measure physician reporting practices.
Potential Outcomes			
Infection	Infection with Lyme disease due to being bitten by an infected tick and not stopping infection transmission before it occurs. Relates to use of preventive practices.	Cumulative number of cases in each disease stage.	Computed through simulation.
Persisting effects	Development of persisting effects that may be permanent. Most severe outcome.	A function of rate of disease progression.	Computed through simulation.
Return to susceptibility	Return of appropriately diagnosed and treated population to the	A function of the rate of return to susceptibility.	Computed through simulation.

Variable	Definition/Notes	Model Relationships	Evidence Source
	susceptible population after they are cured.		

Table 2. Example of Evidence Collection for Physician Awareness Variable

Author and Year	Study Population	Study Design	Results	Conclusions
Henry, 2012	Pediatricians, family practitioners, and internal medicine specialists licensed to practise in BC (low-endemic region). Response rate was 1673/5199 (32.2%).	Cross-sectional survey. 23-item questionnaire (questions on demographic characteristics, general knowledge, laboratory testing, and 3 clinical scenarios).	Overall knowledge score: 72.5% for family practitioners, and 75% for others. EM alone is diagnostic: 26.1% and 28.3%. Reportable disease: 62.1%. Treated a patient without believing they had Lyme disease: 30.5% and 12.1%. Underestimated occurrence of EM: 75.6% and 71.8%. Knew of possible co-infection (anaplasmosis): 10.1% and 15.2%. Belief that a patient requesting Lyme disease assessment has a different cause: 78.7% and 72.1%. Patient's risk after a tick bite: 82.9% and 84.9% said low risk.	Physicians are knowledgeable about the signs, symptoms, and risk, and are diagnosing and treating according to guidelines. Physician knowledge was lower concerning appropriate diagnosis and testing. Greater physician knowledge was not related to belief in a higher risk. Many more cases were reported by study participants than the number officially reported to public health. Education is needed to address the gaps in knowledge.
Magri, 2002	Randomly selected family practice physicians, internists, and pediatricians in New Hampshire (endemic region). Response rate was 296/523 (56.6%).	Cross-sectional survey. 21-item questionnaire (questions on demographics, knowledge, practices, patient scenarios, and beliefs/attitudes about local endemicity).	Median overall knowledge score: 76.9% (10/13). Underestimated the incidence of EM amongst Lyme disease patients: 73.6%. Would test and treat an asymptomatic patient with a tick bite: 41.2%. Gave antibiotic treatment solely at patient request: 44.8%. Knew EM is diagnostic: 52.4%. Belief that a patient requesting LD assessment has a different cause: 89.7%.	Physicians had good knowledge, but not knowing about diagnostic criteria could cause misdiagnosis through using laboratory testing too frequently. Inappropriate management of a tick bite and treatment without a confirmed diagnosis were both common. When compared to previous studies, it was found that varying levels of incidence in a

Author and Year	Study Population	Study Design	Results	Conclusions
			About ½ knew about co-infection with anaplasmosis.	region results in different diagnosis and treatment by physicians. More education is needed.
Murray, 2001	Sample of pediatricians, family physicians, internists, emergency medicine physicians, and dermatologists in Connecticut. Response rate was 267/573 (46.6%).	Cross-sectional survey. Questionnaire (questions on demography, scenarios, treatment practices, and testing).	Prescribed antibiotic prophylaxis for patients with tick bites: 26%. Serology ordered for patients with tick bites: 31%. Serology ordered for patients with EM: 49%.	Most physicians followed established guidelines, but many requested testing for tick bites or EM, which is not necessary.
Ziska, 1996	Sample of physicians from various US endemic areas. Response rate was 78/200 (39%).	Cross-sectional survey. Questionnaire to assess physician preferences in diagnosis and treatment (questions on clinical and lab diagnoses, and treatment at various stages).	Orders both ELISA and Western Blot: 86%. Believed that 25%+ LD patients were seronegative: 50%. Provides antibiotic treatment for tick bites: 20%. EM treated by all without serology. Believed EM only occurred in 30% of cases.	Significant differences were found between recommendations and practices. Need more physician education and clinical trials to clarify why.
Eppes, 1994	Family physicians, pediatricians, internists, and subspecialists in a seven-county endemic region in Delaware. Response rate was 124/600 (20.7%).	Cross-sectional survey. Questionnaire to assess physician beliefs and practices regarding LD (questions on number/nature of patients, testing, treatment, and scenarios).	Treat a patient for possible Lyme disease, even without EM or a positive test: 83%. Provides antibiotics for deer-tick bites: 35%. Knows EM is diagnostic: 85%. Did not specify which test when ordering LD serology: 45%.	Approaches vary significantly among practitioners. Most participants knew EM was diagnostic, but many believed that other non-diagnostic symptoms were as well (ex. Bell's palsy). Most physicians treated early Lyme disease appropriately. However, the vast majority of physicians would treat a patient without a clear

Author and Year	Study Population	Study Design	Results	Conclusions
				diagnosis, of which 25% would use IV antibiotics. In endemic areas physicians may feel pressured towards diagnosis and treatment.

Table 3. Simulation Model Data

Module	Stocks	Flows	Variables	Data for Variables and Calibration	Values for Variables	Sources and Example Search Terms
Natural History Module simulated	Infected Population	Infected to EL Rate	Infected Decay Rate	Exponential decay rates were based on a lower and upper value for the average duration of a stage in days. The population in each stock was multiplied by this decay rate to achieve the progression to the next disease stage. Cumulative cases for each stage were achieved by accumulating separately the disease progression rates for each stage. Calibrated using the proportion of cases that spontaneously recover at each stage (0%; 20%; 23%; 82%; 0%).	High: 0.1402 Low: 0.0972	Steere 1983 Steere 1977 Steere 1987 Nadelman 1996 Signs and Symptoms of Untreated Lyme Disease 2015 Lyme disease, *Borrelia burgdorferi*, borreliosis, disease progression, natural history, clinical spectrum or evolution
	EL Population	EL to ED Rate	EL Decay Rate		High: 0.1157 Low: 0.1122	
		EL to Susceptible Rate	EL Spontaneous Recovery Rate		High: 0.0289 Low: 0.0280	
	ED Population	ED to LD Rate	ED Decay Rate		High: 0.0707 Low: 0.0254	
		ED to Susceptible Rate	ED Spontaneous Recovery Rate		High: 0.0212 Low: 0.0063	
	LD Population	LD to PE Rate	LD Decay Rate		High: 0.0164 Low: 0.0033	
		LD to Susceptible Rate	LD Spontaneous Recovery Rate		High: 0.0754 Low: 0.0154	
	PE Population	-	-		-	
	Cumulative EL Cases	EL Cases	EL Case Rate		-	
	Cumulative ED Cases	ED Cases	ED Case Rate		-	
	Cumulative LD Cases	LD Cases	LD Case Rate		-	

Table 3. Simulation Model Data continued

Module	Stocks	Flows	Variables	Data for Variables and Calibration	Values for Variables	Sources and Example Search Terms
Tick Module initialized	Susceptible Population	Infection Rate	-	The overall infection rate was obtained by multiplying the susceptible population by the sum of the three awareness level infection rates. Each of these rates was based on multiplying the independent probabilities for the different levels of risk of tick bite/hour, LD development after a tick bite, and exposure time in hours/day by the fraction of people in each awareness stock to give levels for daily risk of infection. Calibrated using reported incidence rates of 9.4-912.9/100 000 (achieved 321 initially, then 335 when model was finalized).	0.0004	Stjernberg, 2002 Warshafsky, 2010 Wormser, 2006 Stanek, 2012 Huegli, 2011 Nelson, 2015 Kugeler, 2015 Hofhuis, 2015 Lyme disease, *Borrelia burgdorferi*, borreliosis, (global) incidence, prevalence, epidemiology, probability, risk, likelihood
		Unaware Infection Rate	High Risk of Tick Bite		0.20	
			High Lyme Disease Development Probability		0.000264	
		Aware and Unconcerned Infection Rate	Medium Risk of Tick Bite		0.099	
			Medium Lyme Disease Development Probability		0.000132	
		Aware and Concerned Infection Rate	Low Risk of Tick Bite		0.022	
			Low Lyme Disease Development Probability		0.25	
			Exposure Time		0.0004	

Table 3. Simulation Model Data continued

Module	Stocks	Flows	Variables	Data for Variables and Calibration	Values for Variables	Sources and Example Search Terms
Health Services Module initialized	Diagnosed Cases of Lyme Disease	EL Cure Rate	Probability of EM	Rates for each disease stage were calculated by multiplying the population within the stock by the probability of recognizable symptoms and the probability of accurate diagnosis and treatment. Cumulative diagnosed cases were accumulated by creating a stock into which flowed all the cure rates for the different disease stages.	High: 0.80 Low: 0.53	Griffin, 2014 Wright, 2012 Hatchette, 2015 Miraflor, 2015 Mullegger, 2008 Steere, 1987 Henry, 2012 Magri, 2002 Eppes, 1994 Ferrouillet, 2015 Murray, 2001 Ziska, 1996 Critical Needs and Gaps in Understanding, 2011 Lyme disease, erythema migrans, seeking care, physician, behaviours, knowledge, best practices, symptoms, disease progression, diagnosis, treatment, testing, ELISA, probability, likelihood, risk, sensitivity, accuracy
			Probability of Seeking Care for EL		Aware: 0.90 Unconcerned: 0.75 Unaware: 0.70	
			Probability of Treating EL		Aware: 0.90 No BP: 0.719 Unaware: 0.54	
			Probability of Testing EL		Aware: 0.07 No BP: 0.13 Unaware: 0.45	
			Test Sensitivity for EL		0.466	
			Probability of Accurate Diagnosis and Treatment for EL		-	
		ED Cure Rate	Probability of Cardiac/ Neurological Symptoms		0.199	
			Probability of Seeking Care for ED		Aware: 0.945 Unconcerned: 0.788 Unaware: 0.735	
			Probability of Testing ED		Aware: 0.805 No BP: 0.725 Unaware: 0.644	
			Test Sensitivity for ED		0.741	
			Probability of Accurate Diagnosis and Treatment for ED		-	
		LD Cure Rate	Probability of Arthritis		0.465	
			Probability of Seeking Care for LD		Aware: 0.992 Unconcerned: 0.827 Unaware: 0.772	
			Probability of Testing LD		Aware: 0.985 No BP: 0.837 Unaware: 0.64	
			Test Sensitivity for LD		0.99	
			Probability of Accurate Diagnosis and Treatment for LD		-	
		Diagnosed Cases	Diagnosed Case Rate		-	

Table 3. Simulation Model Data continued

Module	Stocks	Flows	Variables	Data for Variables and Calibration	Values for Variables	Sources and Example Search Terms
Public and Physician Awareness Module initialized	Unaware Public	Awareness Rate	Awareness Decay Rate	Exit rates are calculated by multiplying the given stock by the set initialized value for the rate after it is added to the cumulative number of diagnosed cases divided by 100. The cumulative number of cases is achieved by combining the proportions of the population exiting the disease progression through the three cure rates.	Low: 0.0001 High: 0.0002	Mowbray, 2012 Ajzen, 1991 Malouin, 2003 McKenna, 2004 Grudniewicz, 2015 Solano, 2008 Public, physicians, educational, intervention, prevention, behaviours, knowledge, awareness, concern, Lyme disease
		Unaware to Aware	-		-	
	Aware and Unconcerned Public	Concern Rate	Concern Decay Rate		Low: 0.0001 High: 0.0002	
	Aware and Concerned Public	-	-		-	
	Unaware Physicians	Physician Awareness Rate	Physician Awareness Decay Rate		Low: 0.0001 High: 0.0002	
		Unaware Physicians to Aware	-		-	
	Aware but not Best Practicing Physicians	Best Practices Rate	Best Practices Decay Rate		Low: 0.0001 High: 0.0002	
	Aware and Best Practicing Physicians	-	-		-	

Table 4. Simulation Model Variable List

Variable Name	Variable Type	Initial Value	Units	Equation
Initial Time	-	0	Days	-
Final Time	-	184	Days	-
Units for Time	-	-	Days	-
Time Step	-	0.25	Days	-
Save Per	-	-	Time Step	-
Susceptible Population	Level	100 000	People	ED Cure Rate+EL Cure Rate+LD Cure Rate+EL to Susceptible Rate +ED to Susceptible Rate+LD to Susceptible Rate-Infection Rate
Infection Rate	Auxiliary	-	People/Day	Susceptible Population*(Unaware Infection Rate+Aware and Unconcerned Infection Rate+Aware and Concerned Infection Rate)
Unaware Infection Rate	Auxiliary	-	1/Day	(Unaware Public/(Unaware Public+Aware and Unconcerned Public+Aware and Concerned Public))*High Risk of Tick Bite*0.2 *0.25
High Risk of Tick Bite	Constant	0.0004	-	GET XLS CONSTANTS('Range of Data Values.xlsx','Sheet2','E18')
Aware and Unconcerned Infection Rate	Auxiliary	-	1/Day	(Aware and Unconcerned Public/(Unaware Public+Aware and Unconcerned Public+Aware and Concerned Public))*Medium Risk of Tick Bite*0.099*0.25
Medium Risk of Tick Bite	Constant	0.000264	-	GET XLS CONSTANTS('Range of Data Values.xlsx','Sheet2','E20')
Aware and Concerned Infection Rate	Auxiliary	-	1/Day	(Aware and Concerned Public/(Unaware Public+Aware and Unconcerned Public+Aware and Concerned Public))*Low Risk of Tick Bite*0.022*0.25
Low Risk of Tick Bite	Constant	0.000132	-	GET XLS CONSTANTS('Range of Data Values.xlsx','Sheet2','E22')
Infected Population	Level	0	People	Infection Rate-Infected to EL Rate
Infected to EL Rate	Auxiliary	-	People/Day	Infected Population*Infected Decay Rate
Infected Decay Rate	Constant	0.0972	1/Day	GET XLS CONSTANTS('Range of Data Values.xlsx','Sheet2','E10')
EL Population	Level	0	People	Infected to EL Rate-EL Cure Rate-EL to Susceptible Rate-EL to ED Rate
EL to ED Rate	Auxiliary	-	People/Day	EL Population*EL Decay Rate
EL Decay Rate	Constant	0.1122	1/Day	GET XLS CONSTANTS('Range of Data Values.xlsx','Sheet2','E11')
ED Population	Level	0	People	EL to ED Rate-ED Cure Rate-ED to Susceptible Rate-ED to LD Rate
ED to LD Rate	Auxiliary	-	People/Day	ED Population*ED Decay Rate

Variable Name	Variable Type	Initial Value	Units	Equation
ED Decay Rate	Constant	0.0254	1/Day	GET XLS CONSTANTS('Range of Data Values.xlsx','Sheet2','E13')
LD Population	Level	0	People	ED to LD Rate-LD Cure Rate-LD to Susceptible Rate-LD to PE Rate
LD to PE Rate	Auxiliary	-	People/Day	LD Population*LD Decay Rate
LD Decay Rate	Constant	0.0033	1/Day	GET XLS CONSTANTS('Range of Data Values.xlsx','Sheet2','E15')
PE Population	Level	0	People	LD to PE Rate
EL to Susceptible Rate	Auxiliary	-	People/Day	EL Population*EL Spontaneous Recovery Rate
EL Spontaneous Recovery Rate	Constant	0.0289	1/Day	GET XLS CONSTANTS('Range of Data Values.xlsx','Sheet2','E12')
ED to Susceptible Rate	Auxiliary	-	People/Day	ED Population*ED Spontaneous Recovery Rate
ED Spontaneous Recovery Rate	Constant	0.0212	1/Day	GET XLS CONSTANTS('Range of Data Values.xlsx','Sheet2','E14')
LD to Susceptible Rate	Auxiliary	-	People/Day	LD Population*LD Spontaneous Recovery Rate
LD Spontaneous Recovery Rate	Constant	0.0754	1/Day	GET XLS CONSTANTS('Range of Data Values.xlsx','Sheet2','E16')
EL Cure Rate	Auxiliary	-	People/Day	EL Population*Probability of EM*Probability of Accurate Diagnosis and Treatment for EL
Probability of EM	Constant	0.8	1/Day	GET XLS CONSTANTS('Range of Data Values.xlsx','Sheet2','E24')
Probability of Accurate Diagnosis and Treatment for EL	Auxiliary	-	-	Probability of Seeking Care for EL*(Probability of Treating EL+ (Probability of Testing EL*Test Sensitivity for EL)+(1-Probability of Testing EL))
Probability of Seeking Care for EL	Auxiliary	-	-	(0.7*(Unaware Public/100000))+(0.75*(Aware and Unconcerned Public/100000))+(0.9*(Aware and Concerned Public/100000))
Test Sensitivity for EL	Constant	0.466	1/Day	GET XLS CONSTANTS('Range of Data Values.xlsx','Sheet2','E34')
Probability of Treating EL	Auxiliary	-	-	(0.54*(Unaware Physicians/225))+(0.719*(Aware but Not Best Practicing Physicians/225))+(0.9*(Aware and Best Practicing Physicans/225))
Probability of Testing EL	Auxiliary	-	-	(0.45*(Unaware Physicians/225))+(0.13*(Aware but Not Best Practicing Physicians/225))+(0.07*(Aware and Best Practicing Physicians/225))
ED Cure Rate	Auxiliary	-	People/Day	ED Population*"Probability of Cardiac/Neurological Symptoms" *Probability of Accurate Diagnosis and Treatment for ED
Probability of Cardiac/	Constant	0.199	1/Day	GET XLS CONSTANTS('Range of Data Values.xlsx','Sheet2','E35')

Variable Name	Variable Type	Initial Value	Units	Equation
Neurological Symptoms				
Probability of Accurate Diagnosis and Treatment for ED	Auxiliary	-	-	Probability of Seeking Care for ED*(Probability of Testing ED* Probability of Positive Test with ED)
Probability of Seeking Care for ED	Auxiliary	-	-	(0.735*(Unaware Public/100000))+(0.788*(Aware and Unconcerned Public/100000))+(0.945*(Aware and Concerned Public/100000))
Test Sensitivity for ED	Constant	0.725	1/Day	GET XLS CONSTANTS('Range of Data Values.xlsx','Sheet2','E42')
Probability of Testing ED	Auxiliary	-	-	(0.644*(Unaware Physicians/225))+(0.725*(Aware but Not Best Practicing Physicians/225))+(0.805*(Aware and Best Practicing Physicians/225))
LD Cure Rate	Auxiliary	-	People/Day	LD Population*Probability of Arthritis*Probability of Accurate Diagnosis and Treatment for LD
Probability of Arthritis	Constant	0.465	1/Day	GET XLS CONSTANTS('Range of Data Values.xlsx','Sheet2','E43')
Probability of Accurate Diagnosis and Treatment for LD	Auxiliary	-	-	Probability of Seeking Care for LD*(Probability of Testing LD* Probability of Positive Test with LD)
Probability of Seeking Care for LD	Auxiliary	-	-	(0.772*(Unaware Public/100000))+(0.827*(Aware and Unconcerned Public/100000))+(0.992*(Aware and Concerned Public/100000))
Test Sensitivity for LD	Constant	0.99	1/Day	GET XLS CONSTANTS('Range of Data Values.xlsx','Sheet2','E50')
Probability of Testing LD	Auxiliary	-	-	(0.64*(Unaware Physicians/225))+(0.837*(Aware but Not Best Practicing Physicians/225))+(0.985*(Aware and Best Practicing Physicians/225))
Unaware Public	Level	90 000	People	-Awareness Rate-Unaware to Aware
Awareness Rate	Auxiliary	-	People/Day	Unaware Public*(Awareness Decay Rate)
Awareness Decay Rate	Constant	0.0001	1/Day	GET XLS CONSTANTS('Range of Data Values.xlsx','Sheet2','E6')
Unaware to Aware Rate	Auxiliary	-	People/Day	IF THEN ELSE((Diagnosed Case Rate*5*(Unaware Public/ (Unaware Public+Aware and Unconcerned Public))>Unaware Public),(Unaware Public),(Diagnosed Case Rate*5*(Unaware Public/(Unaware Public+Aware and Unconcerned Public))))

Variable Name	Variable Type	Initial Value	Units	Equation
Aware/ Unconcerned Public	Level	9000	People	Awareness Rate-Concern Rate
Concern Rate	Auxiliary	-	People/Day	IF THEN ELSE((((Aware and Unconcerned Public*(Concern Decay Rate))+(Diagnosed Case Rate*5*(Aware and Unconcerned Public/(Unaware Public+Aware and Unconcerned Public)))) >Aware and Unconcerned Public),(Aware and Unconcerned Public),((Aware and Unconcerned Public *(Concern Decay Rate))+(Diagnosed Case Rate*5*(Aware and Unconcerned Public/(Unaware Public+Aware and Unconcerned Public)))))
Concern Decay Rate	Constant	0.0001	1/Day	GET XLS CONSTANTS('Range of Data Values.xlsx','Sheet2','E7')
Aware/Concerned Public	Level	1000	People	Concern Rate+Unaware to Aware Rate
Unaware Physicians	Level	203	Physicians	-Physician Awareness Rate-Unaware Physicians to Aware
Physician Awareness Rate	Auxiliary	-	Physicians/Day	Unaware Physicians*(Physician Awareness Decay Rate)
Physician Decay Rate	Constant	0.0001	1/Day	GET XLS CONSTANTS('Range of Data Values.xlsx','Sheet2','E8')
Unaware Physicians to Aware	Auxiliary	-	Physicians/Day	IF THEN ELSE((Diagnosed Case Rate*2*(Unaware Physicians/ (Unaware Physicians+Aware but Not Best Practicing Physicians)) >Unaware Physicians),(Unaware Physicians),(Diagnosed Case Rate*2*(Unaware Physicians/(Unaware Physicians+Aware but Not Best Practicing Physicians))))
Aware/ Not Best Practicing Physicians	Level	20	Physicians	Physician Awareness Rate-Best Practices Rate
Best Practices Rate	Auxiliary	-	Physicians/Day	IF THEN ELSE((((Aware but Not Best Practicing Physicians*(Best Practices Decay Rate))+(Diagnosed Case Rate*2*(Aware but Not Best Practicing Physicians/(Unaware Physicians+Aware but Not Best Practicing Physicians))))>Aware but Not Best Practicing Physicians),(Aware but Not Best Practicing Physicians),((Aware but Not Best Practicing Physicians*(Best Practices Decay Rate)) +(Diagnosed Case Rate*2*(Aware but Not Best

Variable Name	Variable Type	Initial Value	Units	Equation
				Practicing Physicians/(Unaware Physicians+Aware but Not Best Practicing Physicians)))))
Best Practices Decay Rate	Constant	0.0001	1/Day	GET XLS CONSTANTS('Range of Data Values.xlsx','Sheet2','E9')
Aware/ Best Practicing Physicians	Level	2	Physicians	Best Practices Rate+Unaware Physicians to Aware
Cumulative Diagnosed Cases of Lyme Disease	Level	0	People	Diagnosed Cases
Diagnosed Case Rate	Auxiliary	-	People/Day	ED Cure Rate+EL Cure Rate+LD Cure Rate
Diagnosed Cases	Auxiliary	-	People/Day	Diagnosed Case Rate
Cumulative EL Cases	Level	0	People	EL Cases
EL Case Rate	Auxiliary	-	People/Day	Infected to EL Rate
EL Cases	Auxiliary	-	People/Day	EL Case Rate
Cumulative ED Cases	Level	0	People	ED Cases
ED Case Rate	Auxiliary	-	People/Day	EL to ED Rate
ED Cases	Auxiliary	-	People/Day	ED Case Rate
Cumulative LD Cases	Level	0	People	LD Cases
LD Case Rate	Auxiliary	-	People/Day	ED to LD Rate
LD Cases	Auxiliary	-	People/Day	LD Case Rate

Table 5. Planned Simulation Scenarios

Scenario	Changed Model Variables	Baseline	New Value
Baseline	-	-	-
Low Public Intervention	Awareness Decay Rate	0.0001	0.0002
	Concern Decay Rate	0.0001	0.0002
Low Physician Intervention	Physician Awareness Decay Rate	0.0001	0.0002
	Best Practices Decay Rate	0.0001	0.0002
Moderate Public Intervention	Awareness Decay Rate	0.0001	0.001
	Concern Decay Rate	0.0001	0.001
Moderate Physician Intervention	Physician Awareness Decay Rate	0.0001	0.001
	Best Practices Decay Rate	0.0001	0.001
High Physician Intervention	Physician Awareness Decay Rate	0.0001	0.01
	Best Practices Decay Rate	0.0001	0.01
Very High Physician Intervention	Physician Awareness Decay Rate	0.0001	0.1
	Best Practices Decay Rate	0.0001	0.1
Tick Bites	High Risk of Tick Bite	0.0004	0.0008
	Medium Risk of Tick Bite	0.000264	0.000528
	Low Risk of Tick Bite	0.000132	0.000264
Two Seasons	Final Time	184	368
Four Seasons	Final Time	184	736
Rates	EL Decay Rate	0.1122	0.1157
	EL Spontaneous Recovery Rate	0.0289	0.028
	ED Decay Rate	0.0254	0.0707
	ED Spontaneous Recovery Rate	0.0212	0.0063
	LD Decay Rate	0.0033	0.0164
	LD Spontaneous Recovery Rate	0.0754	0.0154
Low Bounds	Probability of Seeking Care for EM: Unaware	0.7	0.7
	: Aware/Unconcerned	0.75	0.725
	: Aware/Concerned	0.9	0.8
	Probability of Treating EL: Unaware	0.54	0.54
	: Aware/Not Best-Practicing	0.719	0.608
	: Aware/Best-Practicing	0.9	0.683
	Probability of Testing EL: Unaware	0.45	0.36
	: Aware/Not Best-Practicing	0.13	0.13
	: Aware/Best-Practicing	0.07	0.1
	Probability of Seeking Care with ED: Unaware	0.735	0.735
	: Aware/Unconcerned	0.788	0.761

Scenario	Changed Model Variables	Baseline	New Value
	: Aware/Concerned	0.945	0.84
	Probability of Testing ED: Unaware	0.644	0.644
	: Aware/Not Best-Practicing	0.725	0.676
	: Aware/Best-Practicing	0.805	0.708
	Probability of Seeking Care with LD: Unaware	0.772	0.772
	: Aware/Unconcerned	0.827	0.799
	: Aware/Concerned	0.992	0.882
	Probability of Testing LD: Unaware	0.64	0.64
	: Aware/Not Best-Practicing	0.837	0.688
	: Aware/Best-Practicing	0.985	0.752
70/20/10	Unaware Public	90000	70000
	Aware and Unconcerned Public	9000	20000
	Aware and Concerned Public	1000	10000
	Unaware Physicians	203	158
	Aware but not Best-Practicing Physicians	20	45
	Aware and Best-Practicing Physicians	2	22
50/25/25	Unaware Public	90000	50000
	Aware and Unconcerned Public	9000	25000
	Aware and Concerned Public	1000	25000
	Unaware Physicians	203	113
	Aware but not Best-Practicing Physicians	20	56
	Aware and Best-Practicing Physicians	2	56
Reduced Physician Awareness Progression	Unaware Physicians	203	90000
	Aware but not Best-Practicing Physicians	20	9000
	Aware and Best-Practicing Physicians	2	1000
Interactions:	All scenarios and Public x 2 and Physician x 2	-	-
	EM and Rates	-	-
	Tick Bites and Rates	-	-