DISSERTATION

PUBLIC HEALTH CONSIDERATIONS FOR A POTENTIAL LYME DISEASE VACCINE IN THE UNITED STATES: COST OF ILLNESS, VACCINE ACCEPTABILITY, AND NET COSTS OF A VACCINATION PROGRAM

Submitted by

Sarah A. Hook

Department of Environmental Health and Radiological Health Sciences

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Doctoral Committee:

Advisor: Jennifer Peel

Brooke Anderson
Jude Bayham
Sheryl Magzamen

ABSTRACT

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Background

Lyme disease (LD) is a bacterial illness caused by infection primarily with *Borrelia burgdorferi*, which is mainly transmitted by the bite of infected *Ixodes scapularis* ticks in the United States (U.S.). Annually, over 30,000 cases of this multi-system disease are reported to the Centers for Disease Control and Prevention, but recent studies have provided evidence that the true number of cases is estimated to be over 300,000 each year, a substantial disease burden. Studies evaluating currently available prevention methods (e.g., repellent use, yard-based pesticides) have not demonstrated an effect on disease reduction. An LD vaccine was available 1998 – 2002 in the U.S. until it was voluntarily discontinued by the manufacturer due to low demand caused by several factors, despite it being both safe and effective. Since then, the number of LD cases reported annually has nearly doubled.

New vaccine candidates are currently in development with estimated availability during 2022 – 2024. However, before any future LD vaccine can be recommended by the Advisory Committee on Immunization Practices (ACIP), current research gaps must be addressed. Comprehensive estimates of the cost of LD to the patient and society are

lacking; there is a dearth of research regarding public acceptance of a potential LD vaccine; and the economic benefit of a hypothetical vaccination strategy in the U.S. is unknown.

Methods

To address the first gap regarding the cost of LD in the U.S., we conducted a prospective, cost of illness study to estimate the total costs incurred due to incident LD using a societal perspective (Chapter 3). Data were collected from participants and their providers to estimate medical costs, non-medical costs, and productivity losses attributable to LD in endemic states. Recruitment took place among physician-diagnosed, reported LD cases in Connecticut, Maryland, Minnesota, and New York. Sample-weighted, descriptive statistics were conducted to estimate the out-of-pocket cost of LD per patient and the total societal cost of LD per patient, overall and by LD category (confirmed localized, confirmed disseminated, and probable disease). Linear regression analysis was used to evaluate associations between total societal cost per patient and the following independent variables of interest: LD disease category, age group, gender, and state.

To address the second gap regarding public acceptability of a potential LD vaccine, we conducted a cross-sectional, population-based survey of persons living in LD endemic states (Chapter 4). A web-based survey was administered to a random sample of Connecticut, Maryland, Minnesota, and New York residents June – July, 2018. Sample-weighted, descriptive statistics were conducted to estimate the proportion willing to receive vaccination against LD. Multivariable, multinomial logistic regression

models were used to quantify the association of sociodemographic characteristics and LD vaccine attitudes with willingness to receive vaccination against LD.

Lastly, to address the third gap regarding the economic benefit of a LD vaccination strategy in the U.S., we conducted a cost-benefit analysis to estimate the net cost of vaccination against Lyme disease (Chapter 5). A decision-analytic model was used to compare a vaccination strategy to no vaccination among a hypothetical cohort of 100,000 individuals living in high incidence areas over a three-year time horizon. Probabilities and costs for vaccine and clinical parameters were estimated from the literature as well as from primary research (chapters 3 and 4). Deterministic sensitivity analyses were conducted. Model outputs included cases averted, the total net cost of the vaccination strategy, cost per case averted, and net cost per vaccinee.

Results

In the cost of illness study, patients had an average out-of-pocket cost of approximately $1,340 (median $270) and an average total cost of approximately $2,270 (median $770) (2020 USD) for LD. In stratified analyses by disease category, those with confirmed disseminated and probable disease had approximately double or more the total cost per patient compared to those with confirmed localized disease. Having disseminated or probable disease, being aged 18 – 65 years, and having residence in MN had the greatest impact on the total cost of LD. The aggregate cost of diagnosed LD could be upwards of $800 million annually in the United States.

In the LD vaccine acceptability survey, we estimated that 64% of residents were willing to receive a LD vaccine, while 30% were uncertain and 7% were not willing. Those who were uncertain had higher odds of being parents, adults 45 – 65 years of

age, non-white, having less than a bachelor's degree, or having concerns about the safety of a potential LD vaccine compared to those who were willing. Those who were unwilling also had higher odds of being non-white, having less than a bachelor's degree, or having concerns about the safety of a potential LD vaccine, but they also would not be influenced by a positive recommendation from a HCP, had low confidence in vaccines in general, and had low perceived risk of contracting LD compared to those who were willing.

Lastly, from the cost-benefit analysis, we estimated that 2,160 cases would be averted during a three-year period for a 100,000-person cohort residing in an area with an LD incidence of 0.01. The net cost of the vaccination strategy was $12,510,475, which translates to a cost per case averted of $9,301 and a net cost per vaccinee of $156 over a three-year period. The net cost per vaccinee was most sensitive to changes in vaccine price and disease incidence, with a $0 net cost resulting from a vaccine price of $45 at an incidence of 0.01 or a vaccine price of $476 at an incidence of 0.08.

Conclusions

This research provides critical information for public health considerations for a potential LD vaccine in the U.S., including new information on the economic burden of LD, the acceptability of a potential LD vaccine by the public, and the net cost of a potential vaccination program. In the cost of illness study, we found that most LD patients have low costs, but some experience very high costs related to LD; further, the total economic burden of diagnosed LD in the U.S. could be upwards of $800 million annually, a significant societal cost. These findings emphasize the importance of

effective prevention and early diagnosis to reduce morbidity and associated costs. Results can be used in economic evaluations of current and future prevention methods, such as a vaccine.

We also found that acceptance of a LD vaccine among potential consumers was high, with over 60% willing to receive vaccination, approximately 30% uncertain, and less than 10% unwilling. Effective communication by clinicians regarding safety and other vaccine parameters to those groups who are uncertain about LD vaccination (i.e., parents, adults 45 – 65 years of age, those who are non-white, and those with lower education) will be critical for increasing vaccine uptake and reducing LD incidence.

Using these cost and vaccine acceptability results, we estimated that a vaccination program in areas with a high incidence of LD could generate a net cost of approximately $150 per vaccinee over three years of vaccine effectiveness. Many counties in endemic states have annual incidence greater than 0.01, and while the price of a potential vaccine is currently unknown, it is possible that an eventual vaccine could be cost saving. This analysis should be repeated when price and performance parameters for a LD vaccine are available.

With currently available prevention measures failing to decrease LD incidence, new vaccine candidates have the potential to make a substantial impact on the morbidity and economic burden of LD in the U.S. The ACIP makes national recommendations for the use of licensed vaccines based on factors such as disease burden, public acceptance, public health impact, cost, vaccine supply, and other considerations beyond the safety and efficacy data used for FDA approval. The results from this research provide important, complementary information that may be

considered by the ACIP in making recommendations for a new LD vaccine, when available. Specifically, these results show the need for, potential public demand for, and economic benefit of a new LD vaccine.

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DEDICATION

This dissertation is dedicated to my mother, Nancy Coffey Mitchell (May 20, 1954 – August 17, 2020). She taught me, by her example, that there is profound courage in simply choosing to keep going, in both the momentous events and the minutiae of life. She made all things seem possible, including this doctoral work, and was a wellspring of faith and encouragement. It is with immense gratitude to her that I dedicate this work in tribute to her amazing life and legacy.

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CHAPTER 1: INTRODUCTION

Significance

Lyme disease (LD) is a bacterial illness primarily caused by infection with *Borrelia burgdorferi*, which is mainly transmitted by the bite of infected *Ixodes scapularis* ticks in the United States (U.S.). This multi-system disease is the most commonly reported vector-borne disease in the U.S. [1, 2]. Incidence is highest among children aged 5-10 years and adults aged 45-55 years [1]. Cases primarily occur in the northeastern, mid-Atlantic, and upper-midwestern states, though there is spatiotemporal variation in risk within these areas, depending on local ecology and human behavior [3, 4]. Incidence is increasing as the range of *I. scapularis* expands from historical foci and human development intensifies in tick habitat [1, 5].

Annually, over 30,000 cases are reported to the Centers for Disease Control and Prevention (CDC), but recent studies have provided evidence that the true number of cases is estimated to be over 300,000 each year [6, 7]. This disease burden represents considerable direct, and presumably, indirect costs to U.S. society [8], though existing economic studies lack comprehensive estimates [7-10]. Studies evaluating currently available prevention methods (e.g., repellent use, yard-based pesticides) have not demonstrated an effect on disease reduction [11-16]. The inability of these measures to stem rising LD incidence highlights the need for a prevention modality suitable for use at the population level, such as a vaccine [17].

A LD vaccine was available 1998 – 2002 in the U.S. until it was voluntarily discontinued by the manufacturer due to low demand caused by a number of factors, despite it being both safe and effective [18-20]. Since then, the number of LD cases reported annually has nearly doubled [21]. New vaccine candidates are currently in development [22-25] with potential availability as early as 2022. However, before any future LD vaccine can be recommended by the Advisory Committee on Immunization Practices (ACIP), current estimates of disease cost, potential vaccine uptake, and economic evaluation of a hypothetical vaccination strategy are needed [26, 27].

Summary of Aims

To address these research gaps, the specific aims of this dissertation are as follows:

Aim 1: Estimate the per-patient cost of Lyme disease and evaluate factors associated with cost.

I used a prospective, cost of illness study design to estimate the total costs incurred due to incident LD using a societal perspective (Chapter 3). Data were collected from participants and their providers to estimate medical costs, non-medical costs, and productivity losses attributable to LD in endemic states. Recruitment took place among physician-diagnosed, reported LD cases in Connecticut, Maryland, Minnesota, and New York. This Aim focused on three objectives: 1) Estimate the out-of-pocket cost of LD per patient; 2) Estimate the total societal cost of LD per patient; and 3) Evaluate associations between total societal cost per patient and the following independent variables of interest: LD disease category (confirmed localized, confirmed disseminated, or probable disease), age group, gender, and state. This Aim addresses

gaps in the existing literature by providing updated, comprehensive cost estimates from several LD endemic states using primary data sources. The results can be used in future economic evaluations of LD prevention methods, such as in the cost-benefit analysis of a LD vaccine strategy described in Aim 3 (Chapter 5) below.

Aim 2: Estimate uptake of a potential Lyme disease vaccine and evaluate factors associated with willingness to be vaccinated.

I conducted a cross-sectional, population-based survey of persons living in four LD endemic states to address the following objectives (Chapter 4): 1) Estimate the proportion of people in Connecticut, Maryland, Minnesota, and New York who would receive a vaccine that protects against LD if one were available; and 2) Evaluate associations between age, gender, state, LD vaccine cost concerns, LD vaccine safety concerns, and clinician LD vaccine recommendation with willingness to receive a LD vaccine. This estimate of vaccine uptake can be used for future economic evaluations for a LD vaccine, as is done in the cost-benefit analysis of a LD vaccine strategy described in Aim 3 (Chapter 5) below. Our characterization of the factors associated with willingness to receive a LD vaccine is the first of its kind and directly informs communication efforts with clinicians and the public to increase awareness and uptake of a future vaccine.

Aim 3: Estimate the net cost of a Lyme disease vaccination strategy.

I conducted a cost-benefit analysis using a decision-analytic model to estimate the net cost of vaccination against Lyme disease (Chapter 5). This Aim focused on the following objectives: 1) Estimate the net cost of vaccination; and 2) Evaluate which

variables have the greatest impact on the net costs of vaccination. The probability and cost estimates used in this analysis were derived from primary sources (Aims 1 and 2) and secondary sources (surveillance data, published literature). These results may be used in ACIP recommendations regarding a potential LD vaccine, and the model can be modified as more specific parameters for vaccine candidates become available.

An effective human LD vaccine may be the only intervention able to make a substantial impact on disease reduction, but several research gaps must be addressed if a new vaccine is to be successful. This complementary suite of Aims provides new information on the economic burden of LD, willingness to receive a LD vaccine, and the net costs of a hypothetical vaccination strategy. These results will inform recommendations and public health communications for a LD vaccine when one becomes available.

My role in the research

Since 2012, I have served as the study coordinator for the TickNET research program based out of the Bacterial Diseases Branch, Division of Vector-Borne Diseases at the Centers for Disease Control and Prevention (CDC). TickNET is a public health network composed of researchers at state health departments, universities, and the CDC who collaborate on tickborne disease research and surveillance [51]. The projects described in chapters 3 and 4 were conducted by a team of TickNET researchers in Connecticut, Maryland, Minnesota, and New York during 2014 – 2018. During this time, I was responsible for protocol development, gaining regulatory approvals, coordinating activities among the TickNET sites, data storage and management, data analysis, report writing, and preparing publications for both of these projects. The research

described in Chapter 5 was conducted solely by me, as part of my regular duties at CDC, yet it was only made possible with use of the primary data collected through the TickNET research described in chapters 3 and 4. In 2018, I received a scholarship from CDC to complete my PhD in epidemiology at Colorado State University (CSU). Both CSU and CDC allowed me to use the research I had conducted in my role with TickNET for my doctoral dissertation.

CHAPTER 2: LITERATURE REVIEW

Background on the burden of Lyme disease

Lyme disease (LD) is a tickborne bacterial illness caused by infection with *Borrelia burgdorferi sensu lato* genospecies complex [28, 29]. In the United States (U.S.), Lyme disease is primarily caused by infection with *B. burdgorderi sensu stricto*, and occasionally by the recently discovered *B. mayonii [30].* These bacteria are mainly transmitted by the bite of infected *Ixodes scapularis* nymphal ticks in the Northeast, Mid-Atlantic, and Upper Midwestern and, more rarely, by *I. pacificus* ticks in the Pacific Northwest of the U.S [31]. However, there is spatiotemporal variation in risk within these regions, depending on local ecology and human behavior [3, 4]. The bacteria are maintained in a complex ecologic cycle primarily involving *Ixodes spp.* ticks, rodent reservoirs of the bacteria upon which the ticks feed, and large mammal hosts responsible for sustaining tick populations. Humans are incidental hosts, with increasing exposure due to the range expansion of *I. scapularis* from historical foci and intensification of human development in tick habitat [1, 5].

LD consistently ranks within the top 10 nationally notifiable conditions and is the most commonly reported vector-borne disease in the U.S. [1, 2]. Annually, over 30,000 cases are reported from state and local public health surveillance authorities to the Centers for Disease Control and Prevention (CDC) [1]. Surveillance data show a bimodal peak in incidence among children aged 5 – 10 years and adults aged 45 – 55 years, along with a slight male predominance in most age groups [1]. However, surveillance for LD is resource-intensive due to the need for accompanying clinical

information with laboratory reports (described below), and reporting and surveillance practices vary across jurisdictions. As such, underreporting of LD has been recognized for decades [32-36]. Recent studies using laboratory testing data and insurance claims data have provided evidence that the true number of cases is estimated to be over 300,000 each year [6, 7], resulting in a substantial disease burden to U.S. society [8].

Early symptoms of localized infection include a characteristic bulls-eye rash known as erythema mirgrans (EM) as well as flu-like symptoms such as fever, headache, fatigue, myalgia, and arthralgia [29]. If left untreated, disseminated disease can cause facial paralysis, arthritis, neurologic involvement, and rarely, cardiac involvement, though this can be life threatening. LD is typically treated with a 10 – 14-day course of oral antibiotic, though treatment of late-stage disease may require more aggressive antibiotic therapy. Most patients will experience a full recovery after antibiotic treatment, although a small proportion (5 – 10%) may continue to experience symptoms related to disease sequelae for months to years [29, 37]. If these symptoms, usually subjective complaints, persist in a confirmed LD patient for at least six months following antibiotic treatment, the patient is said to have post-treatment LD syndrome (PTLDS) [37, 38]. With PTLDS there is no evidence of ongoing infection, and no benefit has been found for long-term treatment with antibiotics [39-42]. This syndrome is distinct from the term “chronic Lyme disease” used informally by some patients, clinicians, and patient advocates, and for which there is no agreed-upon definition. The controversial term is often applied by those outside of mainstream medical practice to patients with subjective symptoms and no evidence of infection, and diagnosis and

treatment of “chronic Lyme disease” has been linked to unproven, sometimes harmful, treatments [43-45].

For cutaneous manifestations of LD, i.e., EM, diagnosis of LD can be made based on clinical findings alone in areas endemic for LD. For non-cutaneous manifestations, diagnosis of LD is primarily supported by serologic testing [29]. Current recommendations for laboratory testing include using a two-step process [46]. The first step involves a sensitive enzyme immunoassay or immunofluorescences assay; if this test is negative, no further testing is necessary. If the first test is positive or equivocal, a second step involving either a western immunoblot assay or an additional enzyme immunoassay is recommended.

The national surveillance case definition for LD includes criteria for confirmed or probable cases [47]. A confirmed case of LD is defined as follows: 1) a case of EM ≥ 5 cm with a known exposure; or 2) a case of EM without a known exposure but with laboratory evidence of infection; or 3) a case with at least one late manifestation (arthritis, lymphocytic meningitis, cranial neuritis or facial palsy, radiculoneuropathy, encephalomyelitis, or second or third degree heart block) that has laboratory evidence of infection. A probable case is defined as follows: any other case of physician-diagnosed LD that has laboratory evidence of infection; additional clinical information may or may not be present.

Current prevention options

Available prevention methods include personal measures such as tick checks, repellent use, permethrin treated clothing, avoidance of tick habitat, and showering or

bathing after being in tick habitat. Current prevention options also include environmental controls such as yard-based acaricide treatments, host-targeted acaricide treatments, and landscape modifications [48]. These personal and environmental measures have been the mainstay of LD prevention for the past several decades. However, studies evaluating personal protective measures have shown that use is inconsistent, with minimal or no effect on disease reduction [11-16]. More recent randomized controlled trials have shown that yard-based and host-targeted acaricide treatments failed to reduce human tickborne disease ([49], Hinckley et al., in prep). The inability of these personal and yard-based measures to stem rising LD cases highlights the need for a prevention modality suitable for use at the population level, namely, a LD vaccine.

Lyme disease vaccines: past, present, and future

Two safe and effective vaccines for LD were independently developed and completed Phase III clinical trials in the 1990s. ImmuLyme was developed by Connaught Laboratories, and LYMErix was developed by SmithKline Beecham Pharmaceuticals. Both were designed to confer protection based on a recombinant outer surface protein A (OspA) of *B. burgdorferi;* the vaccines utilized a novel mode of action by stimulating human antibodies to OspA, which then neutralized *B. burgdorferi* spirochetes in the gut of the tick during its blood meal, thus preventing transmission of *B. burgdorferi* from the tick to the human host [50]. Two multi-center, randomized, placebo-controlled trials evaluated the efficacy of a 30 μg, three-dose series of each vaccine; they were both well tolerated, with only mild, self-limited reactions and no significant increase in arthritis or neurologic events in those vaccinated [51, 52]. Efficacy after two doses ranged from 40 – 68%; after three doses, efficacy increased to 76 –

92%. However, Connaught Laboratories never sought licensing by the Food and Drug Administration (FDA) for ImmuLyme. LYMErix sought and received licensing from the FDA, and the vaccine was available for persons aged 15-70 years from 1998 until 2002 in the U.S. [18, 19, 51, 52]. During the vaccine's availability, no effectiveness studies were conducted to determine its impact on disease incidence, and duration of immunity was not evaluated past three years post-vaccination.

In February 2002, LYMErix was voluntarily discontinued by the manufacturer, reportedly due to poor sales [20]. However, several factors have been highlighted as reasons contributing to low demand [50, 53-55]. There was vocal opposition by some LD advocacy groups who claimed that the vaccine caused Lyme arthritis, and a class-action lawsuit ensued. These claims were based on patient testimonies of vaccine harm and pointed to a mainstream scientific hypothesis at the time that OspA might cause treatment-resistant LD arthritis via molecular mimicry; the OspA protein was similar to a human protein, LFA-1, which was posited to play a role in autoimmune arthritis [56]. This molecular mimicry hypothesis was never proven, and post-licensure safety studies and CDC's Vaccine Adverse Events Reporting System (VAERS) never found evidence for vaccine-induced, LD arthritis, leading to the conclusion that LYMErix was indeed a safe vaccine, although sales had already begun to decline at the time of these determinations [53, 54].

Further, some have cited hedged recommendations for approval by the FDA and tepid, cumbersome recommendations for clinical use by the Advisory Committee on Immunization Practices (ACIP) at CDC as reason for low demand by physicians and the public [17, 19, 57]. The ACIP, composed of immunization experts from inside and

outside CDC, makes national recommendations for the use of licensed vaccines, which are based on epidemiology, public acceptance, public health impact, cost, vaccine supply, and other factors beyond the safety and efficacy data used for FDA approval [26, 27, 58]. These recommendations become CDC policy upon publication in the *Morbidity and Mortality Weekly Report* and are the primary guide for clinicians in vaccination decisions for individual patients. At the time of LYMErix's licensure, cases were not widespread, and incidence of 0.01 occurred in only a few highly endemic counties; in addition, LD is non-communicable, so vaccination against it would not offer the additional benefit of herd immunity that is a feature of most other vaccines [50, 59]. These facts limited the public health impact of a LD vaccine. Several cost-effectiveness analyses (CEAs) concluded that the vaccine was only cost-effective for residents in high incidence areas who had elevated individual risk for LD [60-62]. These conclusions had a major role in informing ACIP's recommendations for use of the LYMErix vaccine [19]. In addition, it was not available for children under 15 years, the highest risk age group; it was presumed that booster doses would be needed; and many saw LD as a mild, easily treatable disease that could be prevented with other options [50]. Lastly, LYMErix's marketability was not helped by the coincident rise of the most recent anti-vaccination movement in modern history [55].

Since LYMErix's withdrawal, the number of LD cases reported annually has nearly doubled [21]. After almost two decades without an effective prevention method, a new vaccine candidate called VLA15 [22-25] is being developed by the French biotech company, Valneva, in partnership with Pfizer [63-65]. Using a similar, recombinant OspA technology as past LD vaccines, this vaccine candidate is being evaluated as a

three-dose series, but with several important improvements. First, it is being evaluated for use in the general population, including children aged 2 years and older. Second, it is designed to protect against the primary LD causing strains found in both the U.S. and Europe. Third, the alleged arthritis-causing epitope of OspA has been removed. Randomized, observer-blind, placebo-controlled Phase II trials were completed in 2020 in LD endemic areas of the U.S. and Europe, with results showing both a favorable safety profile and high immunogenicity across all tested age groups. If successful, VLA15 may be licensed for use as early as 2024.

In addition, a passive vaccination approach using a single monoclonal antibody administered annually is also in development [66-68]. This product, called Lyme pre-exposure prophylaxsis (Lyme PrEP), is being developed by MassBiologics, a non-profit vaccine manufacturer overseen by the University of Massachusetts Medical School. MassBiologics plans to initiate Phase 1 trials in 2020 with potential availability in 2022 [66].

Data gaps

In the absence of other validated prevention methods, an effective human LD vaccine may be the only intervention able to make a substantial impact on disease reduction. However, several research gaps must be addressed if a new vaccine is to be successful. While recent studies have shown that the disease burden of LD is high, the current economic burden of LD to patients and society in the U.S. is unknown [69]. Estimating this aspect of disease burden is crucial for future health economic evaluations of a vaccine. Further, while rising LD incidence would ostensibly result in increased demand for a new vaccine, the controversial climate surrounding LD [45], the

failure of LYMErix [50, 55], and general vaccine hesitancy among some groups [70-73] necessitate further investigation into the acceptability of a LD vaccine among potential consumers. This information will be critical for targeting vaccine communications to patients and providers pre- and post-licensure. Finally, as was seen in the ACIP recommendations for LYMErix, cost is an important factor in making guidelines for use of a vaccine. When the CEAs for LYMErix were conducted, incidence rates close to 0.01 occurred only in a few counties in the northeastern U.S., which limited the overall economic benefit of the vaccine. With the number of reported cases currently growing and recent studies estimating true cases at more than 300,000 annually [6, 7], there are now many more areas of the U.S. where incidence meets or exceeds 0.01, warranting an updated economic evaluation for a potential, new LD vaccine.

Gap1: Economic burden of Lyme disease

Cost of illness studies

Cost of illness studies are economic evaluations that show the impact of an illness, beyond morbidity and mortality, by presenting disease burden in monetary terms [74, 75]. Researchers conducting these essentially descriptive studies aim to itemize, value, and sum the costs of an illness from different payer perspectives. These different perspectives may include those of the patient, healthcare provider, third-party payer, government, employer, or society as a whole; for the societal perspective, all costs of an illness are taken into account, regardless of who pays those costs [76]. Cost of illness studies may be prevalence-based, wherein the costs attributable to an illness for any cases within a predetermined time period (usually a year) are collected, or incidence-

based, wherein costs attributable to new cases only are collected from onset of disease to recovery or death [77]. Cost of illness studies may also be conducted retrospectively or prospectively. Retrospective studies require that sufficient data are available, and this methodology is more efficient for diseases of long duration. Prospective studies are better suited for diseases of short duration and allow for data collection systems tailored to the illness under investigation; non-medical costs and productivity losses are more easily measured with this methodology. Costs are typically categorized as direct (including medical and non-medical costs), indirect (i.e., productivity losses), and intangible costs (e.g., the psychosocial cost of pain and suffering), though intangible costs are difficult to quantify and are typically omitted from cost of illness studies [78].

Some economists are critical of cost of illness studies because many of the included costs do not reflect true opportunity costs in terms of welfare economics because healthcare markets often do not operate perfectly (or fail), compared to other markets [79]. Further, many cost of illness studies use the human capital approach to value productivity losses (vs. willingness-to-pay methods). Lastly, retrospective studies can potentially suffer from recall bias and high-level approximation [77]. Despite these criticisms, prospective, incidence-based cost of illness studies, while demanding in terms of data collection, can be very detailed and highly informative. The results help inform public health resource use by allowing for relative comparisons of the economic burden of different diseases. Further, incidence-based cost of illness results provide estimates of the cost savings per case averted (i.e., the potential benefit of an intervention), which can be used in cost-benefit analyses [77].

Economic evaluations for Lyme disease

Previous studies have estimated certain components of the costs of LD morbidity in the U.S., though very few have made comprehensive evaluations using an incidence-based, cost of illness approach [7-10, 33, 69, 80, 81]. Two older studies conducted more comprehensive analyses from the societal perspective for the total cost of LD in the U.S., including direct and indirect costs, albeit utilizing different methodologies. Maes et al. (1998) conducted a retrospective, incidence-based cost of illness study by modeling total U.S. expenditures for LD based on disease outcome probabilities developed by an expert panel, cost data from medical claims of the privately insured, and productivity losses from the National Health Interview Survey (NHIS). The authors estimated a total societal cost of $843M (2020 USD) annually [9, 82]. This study was limited by the lack of research at the time of publication on probabilities for disease outcomes, necessitating numerous assumptions in the model. In addition, costs were extracted for LD patients based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code for LD, 088.81, which has been shown to have low sensitivity and specificity in identifying true LD cases. Lastly, indirect costs were identified from the NHIS based on ICD-9-CM codes for symptoms related to LD (e.g., dermatologic symptoms), but not specifically for LD patients. Zhang et al. (2006) collected direct and indirect costs from LD patients identified via health records in a retrospective, incidence-based study conducted in five counties in MD [10]. LD patients were categorized into five diagnosis groups: clinically defined early-stage LD, clinically defined late-stage LD, suspected LD, tick bite, and other related complaints. Charges were used to estimate direct medical costs for 3,415 patients; questionnaires assessing

patient out-of-pocket medical costs, non-medical costs, and productivity losses were available for 284 of these patients. The authors estimated a mean total cost attributable to LD at $3,030 and a median cost of $433 per patient; they estimated an aggregate cost to U.S. society of $298M (2020 USD) annually, though this estimate was based on reported cases in 2002, not accounting for underreporting. This study was limited in scope geographically and may not reflect costs in other endemic areas. Further, indirect cost data were only available for 8% of the study population but were extrapolated to the entire study population for total cost; this approach may have affected the validity of the results, though whether it resulted in an over- or under-estimation of costs is unclear.

A more recent, retrospective, incidence-based study by Adrion et al. (2015) used nationwide private insurance claims data to compare direct medical costs of LD cases (n = 52,795) with matched controls (n = 263,975) from 2006 – 2010 using the healthcare payer perspective [8]. The authors estimated an increase of $3,305 (2020 USD) per patient in direct medical costs attributable to LD over a 12-month period compared with matched controls. The authors extrapolated these results to the estimated number of cases per year from Hinckley et al. (2014) for an estimated total aggregate cost per year of $793M (2020 USD) [7, 8]. This study is limited in that LD patients and controls were restricted to persons under 65 years of age with commercial health insurance plans; direct costs for those older than 65 years with non-private insurance may be very different due to other comorbidities or likelihood of having public insurance (i.e., Medicare), so results may not be generalizable to all LD patients. However, a strength of this study is that authors evaluated costs for LD patients from

across the U.S.; costs and healthcare utilization for LD in areas where the disease is not endemic likely varies from that in endemic areas. In this way, the results are more representative of nationwide costs.

Hinckley et al. (2014) conducted a retrospective study to estimate the total direct cost of LD testing in the U.S. as charged by large commercial laboratories [7]. The authors reported a national, annual cost of $596M (2020 USD) for 3.4M LD diagnostic tests representing approximately 2.4M people; only 10 – 18.5% of testing represented true infections, suggesting that many patients undergo unnecessary, costly testing. Strickland et al. (1997) and Fix et al. (1998) drew similar conclusions from their retrospective studies conducted in Maryland in the 1990s [80, 81]. Strickland et al. estimated an annual testing burden for LD of 30,000 tests at a cost of $3.5M (2020 USD) in direct medical costs in Maryland alone, much of which was for inappropriate use of serologic testing as a test of cure after treatment. In a smaller study of 232 patients, Fix et al. estimated that serologic testing costs for LD accounted for 33% of the total direct medical costs among patients, with the largest share (43%) of testing conducted inappropriately for those with tick bite.

There are several more comprehensive cost of illness studies for LD conducted from the societal perspective in Europe [83-85]. In a recent study in the Netherlands, Van den Wijngaard, et al. (2017) used a societal perspective to estimate a total cost of $145 for patients with EM only and $6,858 (2020 USD) for those with disseminated Lyme borreliosis for an aggregate national cost of $24.8M (2020 USD) [85]. Joss et al. (2002) reported an annual cost of $788,705 USD for LD in Scotland, while Lohr et al. (2015) estimated an annual national economic burden of $43.8M USD in Germany

(2020 USD) [83, 84]. Comparability to U.S. studies may be limited by differences in disease incidence, healthcare financing systems, or variations in clinical manifestations due to infection with different *B. burgdorferi* sensu lato strains [83-85].

In summary, most existing cost of illness studies report direct medical costs but lack data on productivity losses and non-medical costs [8, 10, 80, 81]. Several studies were conducted two decades ago in a small number of Maryland counties where LD was emerging [10, 80, 86], and the age of these studies and limited geographic scope prevents generalizability to other endemic areas. More recent studies have used diagnosis codes, e.g., ICD-9-CM, to identify LD patients from insurance claims databases. However, the low sensitivity and specificity of these codes in identifying true cases [87, 88] may lead to incorrect estimates of direct medical costs attributable to LD. Further, data available from insurance claims is often restricted to those with private insurance who are under 65 years of age, again, limiting generalizability. The research project described in Aim 1 (Chapter 3) addresses these gaps by conducting a prospective, incidence-based, cost of illness study among physician-diagnosed, reported LD cases in four high incidence states to estimate the total direct and indirect cost per patient from both the societal as well as the patient perspectives.

Gap 2: Acceptability of a potential Lyme disease vaccine

As noted above, LD vaccine candidates are in development that have the potential to substantially reduce disease incidence. However, if the pitfalls of the failed LYMErix vaccine are to be avoided, it is necessary to understand motivators for and barriers to receiving a new LD vaccine among potential consumers. Lessons may be drawn from general vaccine acceptability/hesitancy research, but specific considerations arise with

a LD vaccine. For example, LYMErix is notable for being the only vaccine withdrawn from the U.S. market that was proven to be both safe and effective [50, 55]. Further, vaccination against LD will not prevent infections with other pathogens transmitted by *I.scapularis* ticks such as *Anaplasma phagocytophilum*, *Babesia microti*, Powassan virus, and *B. miyamotoi*. While these diseases are rare compared to LD [2], this fact may influence potential consumers' view of acceptability of a LD vaccine given that the same prevention measures will still be required to prevent other *I. scapularis* transmitted infections. In addition, there are discrepancies in how potential consumers view how easily detected, how severe, and how treatable the disease is, with some viewing it as mild and easily treatable and others believing it to be a debilitating, life-long illness [43, 45]. It is unclear how these discordant views may affect overall demand for a LD vaccine.

General vaccine hesitancy considerations in U.S.

The term "vaccine-hesitant" includes those who refuse some or all vaccines, those who delay or use an alternative schedule of vaccination, or even those who accept all vaccines but still harbor concerns [73]. The causes of vaccine hesitancy are complex and varied, but many stem from a perception of the risk of vaccines as greater than they actually are, largely due to societal unfamiliarity with the diseases vaccines prevent (i.e., lower perceived risk of contracting a vaccine preventable disease and lower perceived risk of the severity of vaccine preventable diseases) [89]. Further, higher risk perception is attributable to the compulsory nature of some vaccines; the coincidental temporal relationship between vaccination and other, unrelated adverse health outcomes; general lack of trust in corporations and public health agencies; and

an abundance of misinformation about vaccines on the internet [73]. The upshot is that for any vaccine, including a potential LD vaccine, safety and efficacy concerns are paramount among potential consumers and must be adequately addressed to increase acceptability [71-73, 90-94].

While vaccine hesitancy is certainly a barrier to receiving vaccinations, there are also important logistical and structural barriers to receiving vaccinations by patients that should also be considered with a potential LD vaccine. The uninsured, underinsured, and those with interruptions in insurance experience lower coverage of recommended vaccines [95], particularly among adults where there are fewer safety nets compared to childhood vaccinations (e.g., health department clinics). Other structural barriers include the fact that many are simply not aware of non-compulsory vaccine recommendations; not all ACIP-recommended vaccines for adults are covered by public and private insurance; many providers lack resources to properly store, recommend, and deliver adult immunizations; immunization histories can be difficult to access or determine; and finally, convenient locations for immunization in nontraditional settings (e.g., workplaces, pharmacies) are often not readily available [96]. In addition, demographic disparities in vaccination coverage are well documented among adults and children; these disparities may be related to hesitancy and/or structural barriers [70, 71, 90, 97-99].

Lyme disease vaccine acceptability studies

Two vaccine acceptability studies were conducted for LYMErix when it was available. A 2002 study among parents (n = 186) in Nassau County, New York evaluated whether parents would request the LYMErix vaccine for their children, if it became available, and what factors might influence this decision. The vast majority of

parents reported that they would “definitely” (23%) or “likely” (65%) request it, followed by those “unlikely” (9%) to request it and those who would not (3%) [93]. Parents with greater concern for LD, those with children who participated in high-risk activities, and those with lower LD knowledge scores were more likely to request the vaccine for their children. Parents also reported that clinician recommendation for the vaccine would have the most influence on their decision (71%), followed by personal research (23%), and media reports (6%) [93]. Another study evaluated a LYMErix vaccination program among New York State Department of Health employees (n = 190) at risk for occupational tick exposure. This study aimed to assess attitudes affecting the employees’ vaccination decision. While only 16% of employees chose to receive vaccination, they did so because of an anticipated risk of tick exposure (e.g., working in leaf litter or brushy areas). Among those who declined vaccination, the majority (64%) reported safety as a major concern, followed by the novelty (56%) and efficacy (48%) of the vaccine [94]. These studies shed light on motivators for LD vaccination specifically (e.g., hypothetical availability for children) and barriers (e.g., safety and efficacy concerns). However, both studies were small and conducted among very specific populations; as such, there is little empirical research available to adequately assess the exact reasons for low acceptability of the LYMErix vaccine among the broader population living in endemic areas.

There has been limited research conducted on the acceptability of a potential, new LD vaccine. In a 2016 convenience sample survey conducted among residents (n = 1883) in Connecticut and Maryland counties with a high incidence of LD, Niesobecki et al. (2019) found that the majority of respondents were likely to be vaccinated.

Specifically, 49% reported being “very likely”, followed by 35% being “somewhat likely”, 8% being “somewhat unlikely”, and 7% being “very unlikely” to receive a LD vaccine [100]. Similarly, in a nationwide population-based survey conducted in 2014 and 2015, Nawrocki et al. found that 65% of respondents in high incidence states would be “likely” to receive a LD vaccine [101]. Additionally, a qualitative research study conducted in 2018 using focus groups comprised of those at high risk for LD showed that 57% would be “very likely” to receive a LD vaccine (Devchand et al, submitted).

While these concordant results across different study designs are encouraging for the acceptability and potential uptake of a new LD vaccine, only one of the three studies was population-based. Further, gaps remain regarding understanding the motivators for and against receipt of a LD vaccine. The research project described in Aim 2 (Chapter 4) addresses these gaps using a cross-sectional, population-based survey of persons living in four states with a high incidence of LD to estimate the proportion who would be willing to receive a potential LD vaccine if one were available and to evaluate factors associated with willingness to vaccinate (e.g., demographic characteristics and specific vaccine concerns). The estimate of vaccine uptake can be used for future economic evaluations for a LD vaccine, as in Aim 3 (Chapter 5), and the characterization of factors associated with willingness to vaccinate will inform future communication efforts with clinicians and the public to increase awareness and uptake of a vaccine.

Gap 3: Economic benefit of a potential LD vaccine

Key features of economic evaluations for health interventions

There are three main approaches to health economic evaluation: cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and cost-benefit analysis (CBA). All three are comparative analyses that use the costs (i.e., monetized resource use) of an intervention as inputs and the benefits of that intervention as outputs (e.g., improved health, healthcare savings) [102, 103]. These analyses differ with respect to how benefits are defined. CEA defines benefits as a standardized unit of non-monetary effectiveness, such as number of cases treated, cases prevented, or lives saved. CUA is a form of CEA in which the unit of effectiveness is a quality-adjusted life year (QALY) or disability-adjusted life year (DALY), which incorporates time and utility [104]. Limitations of CEA and CUA include the potential for great variability in estimation of the measures of effectiveness [103] and inability to capture non-health benefits, i.e., non-health cost-savings [105]. CBA, on the other hand, defines effectiveness of the health intervention in monetary terms, that is, monetary value must be assigned to life or health status. While the need to monetize health status has been criticized by those who view life as invaluable, CBA has the advantage of allowing for cost comparison across a range of interventions and illnesses [105]. Further, CBA is the recommended approach for public health vaccines to determine whether they are worthwhile [102].

For all three types of health economic evaluations, it is important to evaluate uncertainties and variabilities in the parameters used to understand how valid the data are or how robust the conclusions [103]. Sensitivity analysis may reveal areas where more research is necessary to accurately estimate the variable to which the result, e.g.,

net cost of an intervention, is sensitive [106]. Sensitivity analysis usually takes one of two forms: deterministic sensitivity analysis (DSA) or probabilistic sensitivity analysis (PSA). In DSA, the most common form of sensitivity analysis, one or more parameters in an economic evaluation is varied across a plausible range. With one-way DSA, each parameter is varied individually while the other parameters are held at their base-case specification; in this way, the impact on results can be evaluated separately for each parameter. In multi-way DSA, two or more parameters are varied across plausible ranges at the same time; however, variation of many parameters can complicate presentation of results. PSA requires that plausible ranges plus probability distributions be specified, then Monte Carlo simulations simultaneously select values at random for each parameter from each specified distribution; the result of the economic evaluation for each simulation is stored and results in its own probability distribution. Other forms of sensitivity analysis include threshold analysis and analysis of extremes. In threshold analysis, the goal is to identify the value of one or two parameters above or below which the conclusion about the study's result will change (e.g., the point at which an intervention goes from having a net cost to net savings). This type of sensitivity analysis is particularly useful when a certain parameter is unknown, such as the price of a vaccine before it is available. Lastly, analysis of extremes, sometimes referred to as "worst/best case analysis", uses the extreme estimates of each parameter under either optimistic or pessimistic assumptions (e.g., a low cost, high effectiveness scenario or a high cost, low effectiveness scenario, respectively).

Decision analysis refers to the use of a systematic, quantitative approach to decision-making under uncertainty, and this methodology has been increasingly used to

evaluate public health and clinical interventions, including health economic evaluations [107]. Decision-analytic models often take the form of a decision tree or a Markov model, and they can be used in cost-benefit analyses to estimate the net costs (or savings) of an intervention, such as vaccination, while incorporating uncertainty. Decision tree modeling presents a mathematical structure for the decision of interest, the probabilities of resultant events, and disease states over a certain time horizon [107]. This approach is particularly appropriate for acute, non-communicable diseases occurring over a short, fixed time horizon, such as LD. A decision tree is composed of branches and nodes, which are classified as either decision, chance, or terminal nodes. The terminal nodes represent the outcomes of interest at the end of a specified time horizon.

Economic evaluations for a Lyme disease vaccine

Three CEAs were conducted for the LYMErix vaccine from 1999 – 2002 in the U.S., all comparing a vaccination strategy with a no vaccination strategy and using vaccine performance parameters of the LYMErix vaccine available at the time [60-62]. Meltzer et al. (1999) used a decision-analytic model to estimate the main outcome of the cost per case averted in a vaccination strategy that assumed universal vaccination of the cohort and included a yearly booster [60]. Parameters included the cost of vaccination, effectiveness of vaccination, annual probability of contracting LD (i.e., incidence), direct and indirect costs of treating LD (including early LD or sequelae and associated costs), probability of successfully treating early LD, and the probability of sequelae. Because of uncertainty in the parameter estimates due to lack of data at the time, particularly for the cost of the vaccine and the cost of treating disease, the authors

defined the probability distributions of these parameters and employed Monte Carlo simulations to generate a probability distribution of the cost per case averted and resulting summary statistics. Their main finding was a cost per case averted of $10,143 (USD 2020) annually with a vaccination cost of $100 per year, vaccine effectiveness at 0.85, and an incidence of 0.01 [60]. The authors concluded that the incidence of LD is the most important factor influencing the cost per case averted, followed by the cost of treating sequelae and the probability of successful early treatment of LD. However, many of the model parameters changed the net results from cost to savings upon variation; therefore, the authors also noted that a "single answer regarding the cost effectiveness of vaccinating a person against Lyme disease cannot be calculated" [60]. In terms of policy implications, i.e., ACIP guidelines for use of LYMErix, the authors suggested that use of the vaccine should be based on a combination of community- and individual-level risk. The main limitation of this study was the lack of data available on the cost of the vaccine and the cost of treating LD, resulting in a high level of uncertainty in the results.

Shadick et al. (2001) similarly used a decision-analytic model to evaluate the cost effectiveness of a vaccination strategy, but the authors' main results included the number of cases averted, cost per case averted, and cost per quality-adjusted life-year (QALY) gained. Other differences from Meltzer et al. included the use of a Markov model to simulate a cohort of individuals through 10 seasons, and an additional parameter of vaccine compliance, varied by three shots (full compliance), two shots, or one shot. The authors assigned a base-case estimate and plausible range to each parameter in the model and performed DSA. The quality of life weights used in the

estimate of QALY gained were derived from a random sample of 105 residents from a high incidence area. At a vaccination cost of $150 and an incidence of 0.01, the authors estimated that 202 cases of LD would be averted during a 10 year period for every 10,000 persons vaccinated, which results in a cost per case averted of $11,346 and a cost per QALY gained of $118,507 (USD 2020) [62]. These authors also concluded that LD incidence had the largest impact on results, and that vaccination against LD in endemic areas with incidence ≥ 0.01 “compares somewhat favorably with other preventive treatments” [62]. The major limitations of this study again included lack of definitive data on the cost of vaccination or the cost of treating LD, as well as a lack of inclusion of indirect costs in treating LD. Incorporating the latter cost would influence results in favor of vaccination.

Hsia et al. (2002) also conducted a CEA using a Markov decision-analytic model to estimate the cost effectiveness of LD vaccination [61]. The authors used a hypothetical cohort of individuals aged 15 – 70 years and a 10-year time horizon with yearly cycles. Two vaccine strategies were evaluated: one with an annual booster and one with a booster every three years. Otherwise, parameters were similar to those used by Shadick et al. One-way deterministic sensitivity analysis was conducted for all parameters, and two-way sensitivity analysis was conducted for LD incidence and certain components of the costs of treatment and probability of disease. In addition, best-case and worst-case scenarios were evaluated. The authors estimated a cost per case averted of $9,309 for the strategy with booster vaccination every 3 years or a cost of $17,975 (USD 2020) for the strategy with an annual booster [61]. Similar to the other two studies, the authors concluded that LD incidence was the most important factor in

determining cost-effectiveness for a LD vaccine, and that at > 0.01 incidence, a LD vaccine was potentially cost-effective, but that individual risk should be taken into account when recommending the LYMErix vaccine. The major limitations of this study again included the lack of available, comprehensive cost of illness data, most notably the lack of indirect costs.

When these CEAs were conducted, incidence rates close to 0.01 occurred only in a few counties in the northeastern U.S., which limited the overall economic benefit of the vaccine. With the number of reported cases currently growing and recent studies estimating true cases at approximately 10 – 12 fold higher [6, 7], there are now many more areas of the U.S. where incidence meets or exceeds 0.01. Further, more recent cost of illness studies, described above and including Aim 1 (Chapter 3), allow for use of more robust data sources for cost parameters in future economic evaluations of a LD vaccine. Lastly, with two vaccines currently in development, an updated economic evaluation for a potential, new LD vaccine will be useful for ACIP considerations and recommendations, even prior to such a vaccine coming to market. In Aim 3 (Chapter 5), I aim to improve upon past CEAs of the LYMErix vaccine by conducting a CBA, which provides an estimate of the net cost (or savings) of a new, potential vaccine, plus identification of the most important drivers of this estimate. An additional benefit is that the model can be modified as more specific information on vaccine parameters for VLA15 or LymePrEP becomes available.

Summary

In the absence of other validated prevention methods, an effective human LD vaccine may be the only intervention able to make a substantial impact on disease

reduction. However, several research gaps must be addressed if a new vaccine is to be successful. The research described herein will provide new information on the economic burden of LD, willingness to receive a LD vaccine, and the net costs (or savings) of a hypothetical vaccination strategy. These results will inform recommendations and public health communications for a LD vaccine when one becomes available.

CHAPTER 3: THE ECONOMIC BURDEN OF REPORTED LYME DISEASE IN HIGH INCIDENCE AREAS OF THE UNITED STATES

Summary

There are over 300,000 cases of Lyme disease (LD) in the United States annually, yet comprehensive economic evaluations are lacking. We estimated the total out-of-pocket and total societal cost per patient due to LD in a prospective study among patients in LD endemic states. Additionally, we evaluated disease and demographic factors associated with total societal cost. Patients had an average out-of-pocket cost of approximately $1,200 (median $240) and an average total societal cost of approximately $2,000 (median $700 (2016 USD)). Those with confirmed disseminated and probable disease had double the costs of those with confirmed localized disease. The aggregate cost of diagnosed LD could be upwards of $800 million annually in the United States. These findings emphasize the importance of effective prevention and early diagnosis to reduce morbidity and associated costs. Results can be used in cost-effectiveness analyses of current and future prevention methods, such as a vaccine.

Introduction

Lyme disease (LD) is a bacterial illness caused by infection with *Borrelia burgdorferi*, or, less commonly*, Borrelia mayonii,* which is transmitted by the bite of infected *Ixodes scapularis* and *I. pacificus* ticks in the United States (U.S.). Early symptoms of LD include a bull's-eye rash known as erythema migrans (EM) as well as flu-like symptoms [29]. Disseminated infection can cause neurologic, musculoskeletal, and cardiac complications; in rare cases, cardiac involvement can be fatal [1, 29, 108, 109]. Most patients will experience a full recovery after antibiotic treatment, although a small proportion may continue to experience symptoms related to disease sequelae [29, 37].

LD case numbers consistently rank in the top 10 among all nationally notifiable conditions, and LD is the most commonly reported vector-borne disease in the U.S. [1, 2]. Annually, over 30,000 cases are reported to the Centers for Disease Control and Prevention (CDC) [1], but recent studies have provided evidence that the true number of cases exceeds 300,000 each year [6, 7]. This figure represents a substantial disease burden, but the total economic burden to U.S. society is unknown [69].

Existing economic evaluations for LD have limitations [69]. Most studies report direct medical costs, but lack data on productivity losses and non-medical costs [8, 10, 80, 81]. Several studies were conducted two decades ago in a small number of Maryland counties where LD was emerging [10, 80, 86]; yet, this limited scope prevents generalizability to other endemic areas, and results may not be representative of today's costs due to changes in disease management and healthcare structures. More recent studies have used diagnosis codes, e.g., International Classification of Diseases, Ninth

Revision, Clinical Modification (ICD-9-CM), to identify LD patients from insurance claims databases. However, the low sensitivity and specificity of these codes in identifying true cases [87, 88] may lead to incorrect estimates of direct medical costs attributable to LD. The few studies that provide more comprehensive cost estimates of LD were conducted in Europe under healthcare systems with financing structures different from the U.S. [83-85]. As such, updated estimates of the total societal cost of LD in endemic areas of the U.S., including direct and indirect costs, are needed [69].

We aimed to address current research gaps by conducting a prospective cost of illness study to estimate the economic burden of reported LD in high incidence areas of the U.S. The main objectives of this study were to estimate the total out-of-pocket costs incurred per patient and the total societal cost per patient due to LD. The secondary objective was to evaluate the association of selected disease and demographic factors with the total societal cost per patient. The results can be used by public health officials and communities to assess the cost-effectiveness of interventions to reduce the incidence of LD.

Methods

Study design

This study was conducted as part of TickNET, a public health network of researchers who collaborate on tickborne disease research and surveillance [110]. We conducted a prospective, cost of illness study to estimate total costs incurred per patient due to LD in four high incidence states: Connecticut (CT), Maryland (MD), Minnesota (MN), and New York (NY). We used an incidence-based design, which measures the

cost of an illness from onset to resolution [76, 77]. Cost categories included direct costs (i.e., medical costs and related non-medical costs) and indirect costs (i.e., productivity losses). We used a patient perspective to estimate the total out-of-pocket cost incurred per patient, including medical costs, non-medical costs, and productivity losses. We used a societal perspective to estimate the total societal cost per patient, including total direct medical costs, non-medical costs, and productivity losses, regardless of who pays, whether the patient, third-party payer, or the government [74, 75].

Study population

The source population included pediatric and adult patients with clinician-diagnosed LD reported to state and county public health surveillance authorities in CT and MN and in select counties in MD and NY (Appendix A, Table A.1). Eligible participants included those who met the national surveillance case definition for confirmed or probable LD during the study period [47]. For our study case definition, we used additional exclusion criteria to ensure enrollment of incident cases only. We excluded probable cases with no symptoms reported by the clinician, cases with a previous LD diagnosis within two calendar years of current diagnosis date, and cases with a diagnosis date > 12 months prior to date of enrollment. Non-English speaking participants were not enrolled due to limited resources for interpreters.

Eligible patients were classified into three disease categories. Those with confirmed LD were divided into two groups: confirmed localized disease (i.e., those with EM rash) and confirmed disseminated disease (i.e., those with arthritis, lymphocytic meningitis, cranial neuritis or facial palsy, radiculoneuropathy, encephalomyelitis, 2nd or 3rd degree heart block) [47]. The third category included probable cases with symptoms

reported by a clinician. To ensure enrollment of patients with a range of disease severity, we stratified recruitment by disease category and, using quota sampling, aimed to recruit approximately equal numbers of patients in each category each month. This strategy also allowed us to enroll patients as close to their diagnosis date as possible to reduce patient recall error regarding their costs. Each state aimed to enroll a minimum of 50 participants per disease category, with an overall minimum enrollment goal of 150 total participants per state. Recruitment and enrollment occurred September 2014 through January 2016.

Data collection

Participants consented to data collection for either out-of-pocket costs and direct medical costs, or just the former. For out-of-pocket cost data, study coordinators conducted phone-based surveys with participants (or their legal guardians for pediatric participants) to collect age, gender, annual household income, insurance coverage, and LD onset date. Participants completed follow-up surveys at approximately one-month intervals using web-based or phone surveys [111]. Follow-up surveys ceased when participants reported no LD-related expenses for two consecutive surveys or when they completed the maximum of 12 surveys. The following were collected on all surveys: length of illness, symptoms, treatments, dates for LD-related healthcare visits, clinician contact information, out-of-pocket medical costs (prescription and non-prescription medicine, co-pays, medical bills), non-medical costs (roundtrip distance for healthcare visits; amount paid for assistance with self-care, dependent care, or house/yard maintenance due to LD), and productivity losses (amount of time taken off work or school due to LD symptoms or healthcare visits).

We collected direct medical costs for consenting participants by requesting billing codes (i.e., Current Procedural Terminology (CPT), 4th edition) directly from participants' clinicians, as reported in surveys. Codes were requested for one month prior to the self-reported disease onset date to the date of final survey. We used a date range instead of the individual visit dates reported by the participant in the event participants had incorrectly reported dates. The requested codes represented clinician visits, consultation and related in-office procedures, diagnostic testing, therapy, hospitalization, emergency department (ED) visits, or other procedures or relevant costs. Mean reimbursement for each CPT code collected for participants with private insurance was extracted from IBM® MarketScan® Research Databases, which include national medical claims data for privately insured persons up to age 65 and their dependents. Reimbursements for CPT codes collected for non-privately insured participants were extracted from the Physician Fee Schedule from the Centers for Medicare and Medicaid Services (CMS) [112]. Both MarketScan and CMS costs reflect reimbursements made for charges for medical procedures and services and include the amount paid by the insurer as well as the beneficiary (such as deductibles, copays, and coinsurance). The costs of reimbursements were extracted according to state, year, and inpatient vs outpatient status.

Analysis

In order to provide an overall weighted mean and median set of reimbursements and costs, disease category sampling probabilities were estimated from proportions derived from surveillance data [1] to approximate stratified random sampling. The inverse of the sampling probabilities was then used to weight the data for all analyses

described herein. Medical costs were adjusted to 2016 USD using the Consumer Price Index (CPI) for medical care, and nonmedical costs and productivity losses were adjusted using the general CPI [113]. We estimated the mean, median, 10^{th} and 90^{th} percentiles, and standard deviations of the patient out-of-pocket costs, direct medical costs, and total costs per patient. The Kruskall-Wallis rank sum test was used to evaluate differences in cost among the three disease categories (confirmed localized, confirmed disseminated, probable). Participants who did not complete three consecutive surveys were considered lost to follow-up and were excluded from all analyses.

To estimate the out-of-pocket costs per patient, we summed self-reported medical costs, non-medical costs, cost of productivity losses, and other related costs over all surveys. To calculate the direct medical cost per patient, we summed the mean cost per CPT code collected for each patient. Further details for these calculations for out-of-pocket and direct medical costs are described in Section 1 of Appendix A. Finally, the total societal cost of LD per patient was calculated by summing the direct medical costs, self-reported non-medical costs, and the cost of lost productivity per patient.

We conducted multivariable linear regression analysis using the weighted dataset to evaluate associations between total cost per patient and the following independent variables: disease category (confirmed localized, confirmed disseminated, probable), age group (< 18, 18 – 45, 46 – 65, > 65 years), gender (male, female), and state (CT, MD, MN, NY), controlling for insurance status (private or non-private insurance), income (< or ≥$60,000, which was the approximate median household income for participating states in 2015), and study year (2014, 2015, 2016). These potential confounders were identified *a priori* using directed acyclic graphs [114]. As is

typical for healthcare cost data, the distribution of total cost was highly skewed, resulting in heteroskedasticity of the residuals in the model [115]. Therefore, we transformed total cost per patient using natural logarithms and conducted sampling-weighted least squares regression. For interpretability, we exponentiated resulting regression coefficients and subtracted 1 to get the percent change in baseline cost for each independent variable of interest. The regression equation is given in Appendix A, Equation A1.

Research approval was obtained from institutional review boards at CDC, Connecticut Department of Public Health, Maryland Department of Health, Minnesota Department of Health, New York State Department of Health, and Yale University. Extraction and calculation of mean cost per CPT code from IBM® MarketScan® Research Databases were conducted using SAS® 9.4; all other analyses were conducted using R version 3.5.2 [116-121].

Results

During the enrollment period, 2,991 LD patients were identified and classified as confirmed cases or probable cases with symptoms reported (Figure 3.1). Of the 1,360 (45%) reached, 1,118 (37%) consented to out-of-pocket cost surveys, with 901 (30%) participants with complete survey data included in the out-of-pocket cost analysis. Lastly, 613 (20%) participants had complete out-of-pocket and direct medical cost data and were included in the total cost analysis.

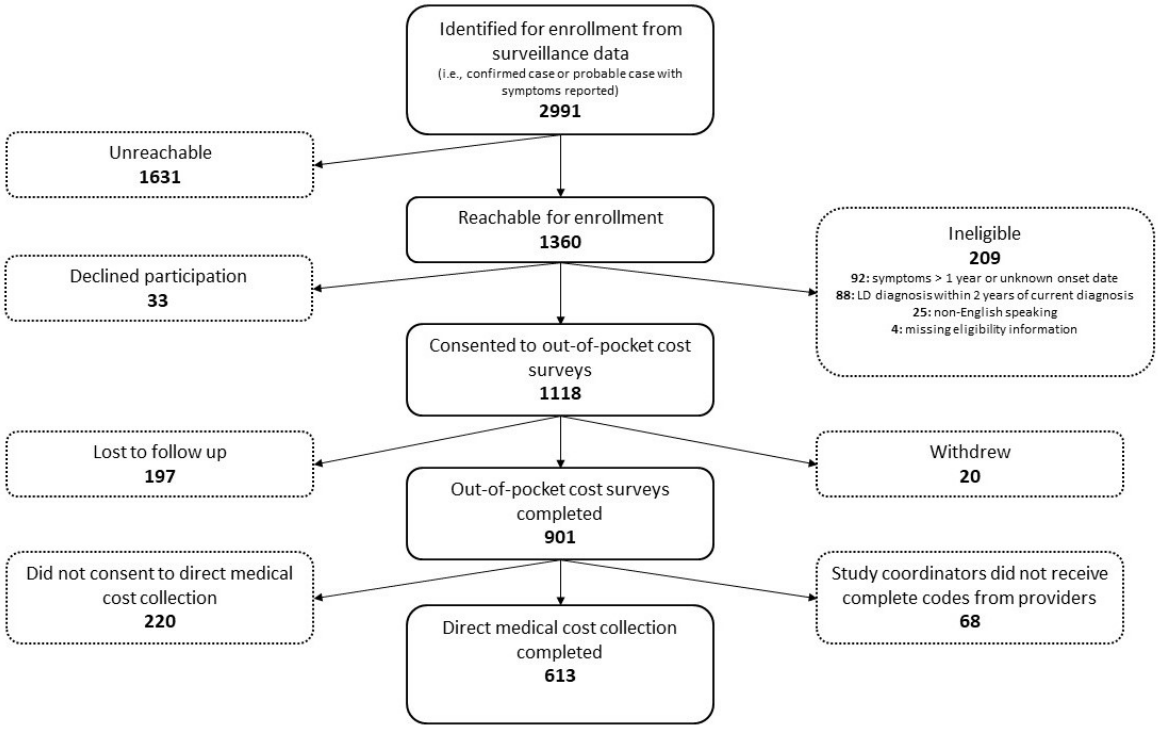

Figure 3.1 Flowchart of study enrollment and completion by participants

In weighted analysis, the study population included 402 (55%) confirmed localized, 238 (21%) confirmed disseminated, and 261 (24%) probable LD cases (Table 3.1). Overall, 36% of participants were 46 – 65 years of age, 57% were male, and 94% were white. Most had income > $60,000 (71%) and private health insurance (70%). Appendix A, Table A.2 includes these results for the subset of our sample who completed out-of-pocket cost surveys and direct medical cost collection (n = 613).

Table 3.1 Participant demographic characteristics, N = 901

Characteristic		N	Unweighted %	Weighted %*
Disease category	Confirmed localized	402	44.6	54.5
	Confirmed disseminated	238	26.4	21.2
	Probable	261	29.0	24.2

Age group (years)	< 18	259	28.7	28.4
	18 – 45	145	16.1	16.1
	46 – 65	326	36.2	36.1
	> 65	171	19.0	19.4
Gender	Female	385	42.7	43.1
	Male	516	57.3	56.9
Race	Non-white	59	6.5	6.4
	White	842	93.5	93.6
State	CT	225	25.0	23.7
	MD	239	26.5	26.8
	MN	268	29.7	29.6
	NY	169	18.8	20.0
Income[**]	≤ $60,000	238	29.2	28.8
	> $60,000	576	70.8	71.2
Insurance	Private	632	70.1	70.2
	Other	269	29.9	29.8

[**] Data were weighted according to disease category sampling probabilities derived from surveillance data.
[**] Participants were not required to provide information on income; n = 814

Participants reported a median of two provider visits and completed a median of three surveys (Table 3.2). Those with confirmed disseminated disease had the highest number of healthcare provider visits, reflecting the highest health care utilization, while those with probable disease had the highest number of surveys completed, reflecting the longest duration of costs incurred. Forty participants (4%) were still reporting symptoms and 25 (3%) were still incurring costs at survey 12, which is the maximum number of surveys before completion of the study.

Table 3.2 Clinician visits and duration of costs incurred, by LD category

		LD category		
Characteristic	All	Confirmed localized	Confirmed disseminated	Probable
Median provider visits (range)	2 (1 – 47)	2 (1 – 25)	3 (1 – 45)	2 (1 – 47)

Median surveys (range)	3 (1 – 12)	2 (1 – 12)	3 (1 – 12)	4 (1 – 12)

Overall, the total out-of-pocket cost per patient ranged from $0.46 to $30,628. The median cost was $244, and the mean cost was $1,242, reflecting a highly positively skewed distribution (Table 3.3). Participants with confirmed disseminated LD had the highest median and mean cost ($358 and $1,692, respectively), followed by those with probable disease ($315 and $1,277, respectively), then confirmed localized disease ($170 and $1,070).

Table 3.3 Out-of-pocket cost of LD per patient, by disease category

	Out-of-pocket cost per patient* (2016 USD)						
Disease category	**N**	**Median**	**Mean**	**Standard deviation**	**10th percentile**	**90th percentile**	**Range**
All	901	244	1,252	2,972	29	3,139	0 – 30,628
Confirmed localized	402	170	1,070	4,164	27	2,535	1 – 26,686
Confirmed disseminated	238	358	1,692	7,323	32	4,116	2 – 30,628
Probable	261	315	1,277	4,629	34	3,987	0 – 18,833

* The estimates for the overall population use the sample-weighted data except the range.

Figure 3.2 shows the median and mean cost per component of the total out-of-pocket cost by disease category (see Appendix A, Table A.3 for values). For all disease categories, productivity losses had the highest mean cost of all cost components, at $727 for those with confirmed disseminated disease, $627 for those with probable disease, and $540 for those with confirmed localized disease. However, the median cost of productivity losses for all disease categories was $0. Medical bills had the next highest cost, with a median of $83 and a mean of $628 for those with confirmed disseminated disease, a median of $83 and a mean of $389 for those with probable

disease, and a median of $42 and a mean of $314 for those with confirmed localized disease. All other cost components for all disease categories had median costs < $25 and mean costs < $80.

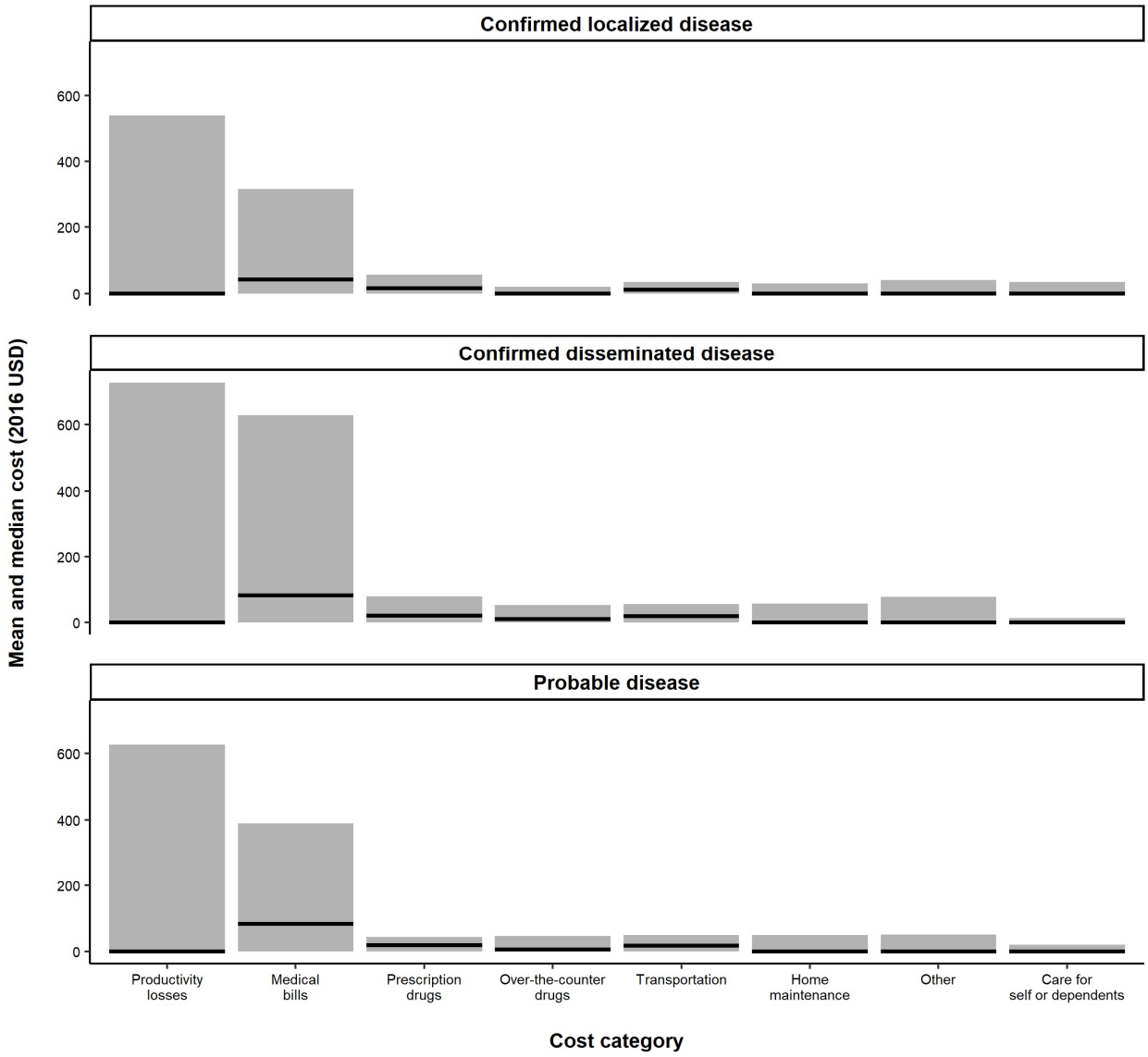

Figure 3.2 Mean and median out-of-pocket Lyme disease costs per patient, by disease and cost category

***** The gray bars indicate mean cost, and the black lines indicate median cost.

Nearly 10,000 CPT codes were collected to estimate direct medical costs (n = 9,679). The most common codes were for office visits (17%) and routine venipuncture (6%) (Appendix A, Table A.5). Overall, the direct medical cost of LD per patient ranged from $50 to $121,869, with a median of $478 and mean of $1,333 (Table 3.4). Participants with confirmed disseminated LD had the highest median and mean direct medical cost ($696 and $2,537, respectively), followed by those with probable disease ($612 and $1,804, respectively), then confirmed localized disease ($374 and $668, respectively).

Table 3.4 Direct medical cost of LD per patient, by disease category

		Direct medical cost per patient* (2016 USD)					
Disease category	**N**	**Median**	**Mean**	**Standard deviation**	**10th percentile**	**90th percentile**	**Range**
All	613	478	1,333	5,690	164	1,932	50 – 121,869
Confirmed localized	273	374	668	1,715	136	1,224	50 – 13,050
Confirmed disseminated	154	696	2,537	20,220	259	4,366	147 – 121,869
Probable	186	612	1,804	15,188	237	2,454	124 – 105,494

* Excludes CPT codes deemed unrelated to LD per physician subject matter expert; see Appendix A for list of excluded codes. The estimates for the overall population use the sample-weighted data except the range.

Overall, the total cost of LD per patient ranged from $54 to $122,766; the median was $690 and the mean was $2,032 (Table 3.5). Participants with confirmed disseminated LD had the highest median and mean total cost ($1,081 and $3,251, respectively), followed by those with probable disease ($940 and $2,620, respectively), then confirmed localized disease ($493 and $1,307, respectively). Appendix A, Table A.6 includes mean and median total costs per patient by demographic characteristic. Applying these per patient total costs to the total number of LD cases in the U.S. results

in an approximate aggregate cost to U.S. society of $800 million annually (Appendix A, Section A.2 and Table A.8).

Table 3.5 Total cost of LD per patient, by disease category

		Total cost per patient* (2016 USD)					
Disease category	**N**	**Median**	**Mean**	**Standard deviation**	**10th percentile**	**90th percentile**	**Range**
All	613	690	2,032	6,091	203	4,201	54 – 122,766
Confirmed localized	273	493	1,307	3,559	154	2,678	54 – 18,322
Confirmed disseminated	154	1,081	3,251	20,908	297	6,238	216 – 122,766
Probable	186	940	2,620	15,533	316	5,021	130 – 105,500

* Total cost includes patient out-of-pocket nonmedical costs, productivity losses, and direct medical costs. The estimates for the overall population use the sample-weighted data except the range.

In multivariable linear regression analysis, disease category, age, and state were associated with total cost per patient (Table 3.6; Appendix A, Table A.6). Participants with confirmed disseminated disease and probable disease had costs that were 120% and 59% higher, respectively, than those with confirmed localized disease ($p < 0.001$). Participants aged 18 – 45 and 46 – 65 years had costs that were 96% and 108% higher, respectively, than those aged < 18 years ($p < 0.001$); however, those aged > 65 years did not have significantly different costs. MN residents had 75% higher costs than CT residents, but MD and NY residents did not have significantly different costs than CT residents.

Table 3.6 Impact* on total cost of LD per patient due to disease category, age group, gender, and state (n = 613)

	Percent difference (%)	**Total cost difference (2016 USD)**	**95% CI for total cost difference (2016 USD)**

Baseline cost[**]	NA	305	206 – 451
Variable			
LD category			
Confirmed, localized (reference)			
Confirmed, disseminated	120	367	188 – 545
Probable	59	181	71 – 291
Age group (years)			
< 18 (reference)			
18 – 45	96	293	107 – 479
46 – 65	108	331	175 – 486
> 65	27	84	-28 – 195
Gender			
Female (reference)			
Male	11	35	-26 – 95
State			
CT (ref)			
MD	0	0	-76 – 76
MN	75	229	114 – 345
NY	-6	-19	-119 – 82

[*] Results from sample-weighted multivariable linear regression analysis. See Appendix A, Equation A.1 and Table A.7 for more model results.

[*]The model included independent variables of interest, i.e., disease category, age group, gender, and state, while controlling for insurance status, income, and study year. Adjusted $R^2 = 0.19$. Baseline cost represents a patient with confirmed localized LD, female, aged < 18 years, with residence in CT, without private insurance, with income < $60,000, and study year of 2014.

Discussion

We found patients had an average out-of-pocket cost of approximately $1,200 (median cost ≈ $240) and an average total cost of approximately $2,000 (median cost ≈ $700). In stratified analyses by disease category, those with confirmed disseminated and probable disease had approximately double or more the total cost per patient compared to those with confirmed localized disease, highlighting the importance of early and accurate diagnosis. Having disseminated or probable disease, being aged 18 – 65 years, and having residence in MN had the greatest impact on the total cost of LD. While median total costs are typically $1,000 or less for all disease categories, average costs are substantially higher, indicating that most patients have low costs, but some experience very high costs related to LD. Similarly, the low median number of provider

visits and hours of lost productivity suggest that illness with LD is manageable for most, but for a minority, it may be highly disruptive. With over 300,000 cases of LD each year, these costs represent a significant economic burden to U.S. society and underscore the need for effective prevention methods.

Classification of a reported case as probable means a clinician has diagnosed LD in a patient and there is laboratory evidence of infection. However, any reported symptoms are typically non-specific and do not meet clinical criteria for a confirmed case (i.e., EM, arthritis, carditis, or neurologic manifestations) [47]. Further, laboratory evidence of infection includes single-tier IgG immunoblot seropositivity, which might indicate past, rather than current, infection. As such, the increased costs for probable cases might result from higher healthcare utilization for disease unrelated to LD.

In a geographically-limited study of LD patients residing on the eastern shore of MD in 1998 – 2001, Zhang et al. reported mean and median total costs of $3,494 and $500 (2016 USD) per patient, respectively, attributable to LD [10]. However, their case definition differed from ours with inclusion of patients with early, late, and suspected disease, as well as those with tick bite and other related complaints, as identified using diagnosis codes in medical records. They reported mean and median total costs of $2,275 and $689 (2016 USD), respectively, for patients with clinically defined early disease, which are higher than what we found for confirmed, localized disease ($1,307 and $493, respectively). In regression analyses, Zhang et al. found that disease category and age, but not gender, were significantly associated with direct medical costs, similar to our findings for total cost. In another U.S. study using nationwide commercial insurance claims data to compare cases with matched controls in 2006 –

2010, Adrion et al. estimated an increase of $3,009 (2016 USD) in direct medical costs attributable to LD over a 12-month period [8]. This cost is higher than our overall mean direct medical cost ($1,333), likely due to study population differences, but it is similar to that found for our confirmed disseminated patients ($2,537). In a recent study in the Netherlands, Van den Wijngaard, et al. used a societal perspective to estimate a total cost of $137 for patients with EM only and $6,398 (2016 USD) for those with disseminated Lyme borreliosis [85]. These costs are lower and higher, respectively, compared to our results for confirmed localized ($1,307) and confirmed disseminated ($3,251) disease. These cost differences may result from different healthcare financing systems in the U.S. versus Europe or from variations in clinical manifestations resulting from infection with different *B. burgdorferi* sensu lato strains in the two continents [83-85].

This study has several strengths. Our study adds to the scarce literature on the economic burden of LD and provides a comprehensive estimate of the cost of LD, both to the patient and to society as a whole. Prospective collection of all patient out-of-pocket costs, including productivity losses, has not been done in previous studies. Further, these results provide estimates of the cost savings per LD case averted, which can be used in cost-benefit analyses of prevention interventions, such as a potential vaccine. Lastly, our regression results underscore that targeted messaging regarding increased awareness of disease risk and early diagnosis may aid in preventing disseminated disease and its associated high cost.

This study is also subject to several limitations. Our estimates may be affected by recall error, either by patients or providers, though we attempted to mitigate such error

by enrolling patients as close to disease onset as possible, by surveying them monthly to capture ongoing costs, and by requesting codes from providers for a date range instead of for individual visits. However, by requesting codes over a date range, some billing codes unrelated to LD (e.g., for other comorbidities) may have been included despite our excluding codes definitively unrelated to LD, potentially leading to overestimates. Information bias may have occurred in our measure of association between disease category and cost because those with milder disease may be more likely to forget some costs compared to those with more severe disease, with a potential bias away from null. Additionally, while the use of quota sampling to recruit reported cases was necessary to enroll patients near disease onset, this non-probability sampling method limits our ability to meet assumptions for calculating sampling error. Use of surveillance data to weight responses by disease category was intended to ensure representativeness by disease category. Nevertheless, in surveillance data, the number of confirmed localized cases are likely underreported and confirmed disseminated cases are likely overreported, so our overall cost may be overestimated [32, 122]. Finally, this study did not include costs related to mortality from LD, as no enrolled participants died. While very rare, mortality from Lyme carditis has been reported [108, 109], and these costs would greatly increase estimates of productivity losses.

While not necessarily a limitation, the generalizability of our results is limited to reported cases of LD in high incidence states [47]. These estimates may not represent the cost of diagnosed but unreported LD, and these estimates do include costs for suspected LD (e.g., consultation for tick bite, negative diagnostic tests), undiagnosed

LD, or non-acute LD (e.g., patients with post-treatment LD syndrome). These costs further increase the total economic burden attributable to LD and should be evaluated in future studies. Our estimates are likely generalizable to high incidence states in the northeastern, mid-Atlantic, and upper midwestern states, but may not reflect costs in states with emerging or low incidence LD.

In conclusion, LD represents a significant economic burden to individual patients and U.S. society. The aggregate cost of diagnosed LD could be upwards of $800 million annually, not including suspected, undiagnosed, or non-acute LD. These findings emphasize the importance of early and accurate diagnosis to reduce morbidity and associated costs. Future efforts should include cost-effectiveness analyses of current and future prevention methods, such as a vaccine, in addition to economic evaluations of unreported, suspected, and non-acute LD.

CHAPTER 4: EVALUATING PUBLIC ACCEPTABILITY OF A POTENTIAL LYME DISEASE VACCINE USING A POPULATION-BASED, CROSS-SECTIONAL SURVEY IN HIGH INCIDENCE AREAS OF THE UNITED STATES

Summary

Background

Lyme disease (LD) incidence is increasing, despite current prevention options. New LD vaccine candidates are in development that have the potential to substantially reduce disease incidence; however, investigation of the acceptability of a LD vaccine among potential consumers is needed prior to any vaccine coming to market. We conducted a population-based, cross-sectional study to estimate willingness to receive a potential LD vaccine and factors associated with willingness.

Methods

The web-based survey was administered to a random sample of Connecticut, Maryland, Minnesota, and New York residents June – July, 2018. Survey-weighted descriptive statistics were conducted to estimate the proportion willing to receive a LD vaccine. Multivariable, multinomial logistic regression models were used to quantify the association of sociodemographic characteristics and LD vaccine attitudes with willingness to receive a LD vaccine.

Results

The survey response rate was 6.3% (n = 3,313). We estimated that 64% of residents were willing to receive a LD vaccine, while 30% were uncertain and 7% were not willing. Those who were uncertain were more likely to be parents, adults 45 – 65 years of age,

non-white, have less than a bachelor's degree, or have safety concerns about a potential LD vaccine compared to those who were willing. Those who were unwilling were also more likely to be non-white, have less than a bachelor's degree, or have safety concerns about a potential LD vaccine, but they also would not be influenced by a positive recommendation from a HCP, have low confidence in vaccines in general, and have low perceived risk of contracting LD compared to those who were willing.

Discussion

Overall, willingness to receive a potential LD vaccine was high. Effective communication by clinicians regarding safety and other vaccine parameters to those groups who are uncertain about LD vaccination will be critical for increasing vaccine uptake and reducing LD incidence.

Introduction

Lyme disease (LD) is a multi-system illness caused by infection with *Borrelia burgdorferi*. These bacteria are transmitted to humans and animals by the bite of infected *Ixodes scapularis* ticks in northeastern, mid-Atlantic, and upper-midwestern regions of the United States (US)[1, 2]. Early symptoms of LD most often include a characteristic bull's-eye rash known as erythema migrans, as well as flu-like symptoms [29]. If left untreated, the disease can disseminate and lead to more severe manifestations, such as arthritis, meningitis, or carditis, the last of which can be fatal in rare cases. Most patients will experience a full recovery after antibiotic treatment, although a small proportion (~ 10%) may continue to experience symptoms related to disease sequelae [29, 37, 60, 123, 124].

In the US, there is a bimodal peak in LD incidence by age group, highest among children aged 5 – 10 years and adults aged 45 – 55 years, with a slight male predominance in most age groups [1]. Incidence has been increasing, with over 30,000 cases reported annually to the Centers for Disease Control and Prevention in the last decade [1]. However, recent studies have provided evidence that cases may be 10 – 12 fold underreported, with the true number estimated at over 300,000 annually [6, 7].

A safe and efficacious vaccine for LD called LYMErix was available for persons aged 15 – 70 years from 1998 until 2002 in the US [18, 19]. This vaccine conferred protection based on a recombinant outer surface protein A (rOspA) of *B. burgdorferi*. In 2002, it was voluntarily discontinued by the manufacturer, reportedly due to poor sales [20]. However, several factors have been highlighted as reasons contributing to low demand. Most importantly, it was not available for children under 15 years, one of the

highest risk age groups. Further, some have cited tepid and cumbersome recommendations by the Advisory Committee on Immunization Practices (ACIP) as a potential reason for low demand by clinicians and the public [17, 57]. Vocal opposition by some Lyme disease patient advocacy groups, based on unsubstantiated claims that the vaccine caused Lyme arthritis, is also thought to have played a role in LYMErix's withdrawal [50, 53-55]. The introduction and withdrawal of LYMErix also inauspiciously coincided with the then nascent anti-vaccination movement [55]. Since its withdrawal, the number of LD cases reported annually has nearly doubled, despite available personal and yard-based prevention methods [21, 48]. The inability of current measures to stem rising case numbers highlights the need for a prevention modality suitable for use at the population level, namely, a LD vaccine [125].

After nearly two decades without an effective prevention method, new LD vaccine candidates are in development, with initial results showing favorable safety and immunogenicity profiles and potential availability by 2024 [66-68]. While rising LD incidence would ostensibly result in increased demand for a vaccine, the controversial climate surrounding LD [45] and general vaccine hesitancy among some groups [70-73] necessitate further investigation of the acceptability of a LD vaccine among potential consumers prior to any vaccine coming to market. The primary objective of this study was to estimate what proportion of people living in states with a high incidence of LD would be willing to receive a vaccine that protects against LD if one were available. The secondary objective was to evaluate factors associated with willingness to receive a LD vaccine.

Methods

Study design and sampling

In the summer of 2018, we conducted a population-based, cross-sectional survey using address-based sampling of persons living in four states with high incidence of LD [126]. The target population included all residents of Connecticut, Maryland, Minnesota, and New York, excluding New York City. The sampling frame included all households with residential addresses listed in the U.S. Postal Service (USPS) database in these areas. We used a stratified, two-stage sampling design where the strata were counties from the above-mentioned states. The primary sampling unit was the household, while the unit of observation was the individual, with a single individual selected within the household. Addresses were purchased from a marketing company that receives updated information on a monthly basis directly from USPS based on change of address submissions. Household addresses were stratified according to county, and the number of addresses selected per county was allocated proportional to county population size. Households were randomly selected within counties. An individual within the household was selected as the one who had the most recent birthday, regardless of age, an established technique to approximate random sampling [127]. For minors selected, parents or guardians provided responses. Responses to the survey were made by individuals ≥ 18 years of age. Subsequently, the term “respondent” will refer to those about whom information was collected.

To estimate the proportion of residents willing to receive a potential LD vaccine, the sample size calculation parameters included a conservative estimate of 50% of participants responding “Yes” for willingness to receive a LD vaccine; $\alpha = 0.01$; an

acceptable margin of error of +/- 5%; and 2 clusters for multi-stage sampling [128]. These parameters resulted in a required sample size of 665 respondents per state (2,660 respondents total). Based on a 2016 survey using address-based sampling in Connecticut and Maryland [100], we anticipated a 5% response rate and, therefore, recruited 13,300 individuals per state (53,200 total) to obtain a sample representative of the populations in these states (including responses for both adults and children), in the absence of non-response.

Data collection

Recruitment, enrollment, and survey completion occurred during June – July 2018, with data collection corresponding with peak tickborne disease activity in these states. The survey invitation postcard was mailed to each randomly selected household; it summarized the study and explained which household resident should complete the survey (based on the most recent birthday) in English. The postcard also provided a web link, quick response (QR) barcode, and a unique access code to complete the online survey; alternatively, respondents could choose to complete the survey over the phone with study coordinators. A reminder was mailed two weeks following the original mailing, and the online surveys were open for approximately four weeks.

The following sociodemographic variables were collected from survey responses: age of the person about whom information was collected; age of the parent or guardian responding for the minor participant, if applicable; gender of the person about whom information was collected; gender of the parent or guardian responding for the minor participant, if applicable; race and ethnicity of the respondent; education of the respondent; number of adult household members; and number of minor household

members. An additional variable for metropolitan status (large central metropolitan area vs other) by county was created using the urban-rural classification scheme from the National Center for Health Statistics [129]. The main outcome variable was whether the respondent would be willing to receive a LD vaccine if one were available (or vaccinate the minor, if a parent respondent); the response options were “Yes”, “No”, and “Don’t know.” The following covariates were also collected from survey responses: how much LD vaccine safety concerns affect willingness to be vaccinated; how much cost affects willingness to be vaccinated; how much a positive recommendation for the LD vaccine from a healthcare provider (HCP) affects willingness to be vaccinated; history of LD diagnosis among household members; level of concern about getting LD; time spent in tick habitat; whether vaccines, in general, benefit people; primary source for LD information; and primary location for receiving vaccinations. Survey questions and response options are listed in Appendix B, Table B.1.

Analysis

The data were weighted to account for the unequal selection probabilities per respondent for the two-stage sampling design [127, 130]. We compared the sample distributions of age and gender to known population totals using chi-squared goodness-of-fit tests, and as necessary, conducted post-stratification according to county population distributions of age and gender to reduce sampling error and nonresponse error [130-133]. All analyses were conducted using the weighted, post-stratified dataset, and all analyses incorporated the sampling design into standard error and confidence interval computation and statements of inference.

To estimate what proportion of people in Connecticut, Maryland, Minnesota, and New York would be willing to receive a vaccine that protects against LD if one were available, summary statistics were computed for the three-level response for willingness to receive a vaccine. Additionally, descriptive analyses were conducted for the following independent variables: sociodemographic characteristics; LD history, attitudes, and practices; vaccine attitudes; primary sources of LD information; and primary location for receiving vaccines.

To evaluate factors associated with willingness to receive a LD vaccine, we stratified the outcome by the above mentioned independent variables, and Pearson chi-squared tests with Rao and Scott design-based adjustments were used to evaluate differences in the outcome across levels of each independent variable [134]. Because our outcome of willingness to be vaccinated has three, unordered levels, multinomial multivariable logistic regression models were used to quantify the association between LD vaccination responses and independent variables of interest. For each model, we used “Yes” responses to willingness to receive a vaccine as the reference group to which “No” and “Don’t know” responses were compared. The independent variables of interest included sociodemographic characteristics (i.e., gender, age category, state, race, and education), LD vaccine safety concerns, LD vaccine cost concerns, and positive recommendation for the LD vaccine from an HCP. The last three independent variables were dichotomized for analysis (Yes = “Some” or “A lot”; No = “Not at all” or “Don’t know”). Separate models were built for each independent variable of interest with a specific set of potential confounders identified *a priori* (Appendix B, Table B.2), and model diagnostics were conducted for each model fit. Multinomial logistic regression

model results are presented as unadjusted and adjusted odds ratios (ORs) and 95% confidence intervals (CIs).

Additionally, we conducted a sensitivity analysis to evaluate whether the odds ratios approximately estimated prevalence ratios (PRs). We conducted standard multivariable logistic regression by sub-setting the dataset first to “Yes” and “No” responses to willingness to be vaccinated and then “Yes” and “Don’t know” responses, using “Yes” as the reference level for each model and the same set of independent variables as the multinomial logistic regression models described above. We then compared resultant adjusted ORs and adjusted PRs (Appendix B, Table B.5).

We evaluated non-random missingness in our outcome variable related to non-response (i.e., selection bias) using Heckman-type selection models, also called generalized Tobit models [135-137]. Heckman models use two steps to first model the selection process using one or more independent selection variables and then the outcome equation (i.e., the regression equation for the outcome of interest). Results of the two-step process indicate whether selection bias is present based on the coefficient of the inverse Mill’s ratio; if so, a correction factor incorporating the coefficient of the inverse Mill’s ratio is applied to results.

Survey development, administration, data collection, and data management were conducted using the Research Electronic Data Capture (REDCap) software hosted at Yale University [138, 139]. R version 3.5.2 [116-121] was used for all analyses. This study was conducted through TickNET, a public health network composed of researchers at state health departments, universities, and the Centers for Disease Control and Prevention (CDC) who collaborate on tickborne disease research and

surveillance [110]. Research approval and waiver of documentation of informed consent were obtained from institutional review boards at CDC, Connecticut Department of Public Health, Maryland Department of Health, Minnesota Department of Health, New York State Department of Health, and Yale University. Respondents' participation in the survey indicated consent.

Results

The survey response rate was 6.3% (n = 3,313). Fifty-nine records were ineligible due to missing age data (n=38), the respondent not being the person in the household with the last birthday (n = 15), the adult respondent not being the one to make vaccination decisions for the selected minor (n = 1), or the respondent not answering the main outcome question regarding willingness to receive a LD vaccine (n = 5). An additional 48 records with missing gender information were removed prior to analysis because gender information was necessary for post-stratification. The resulting sample available for analysis was 3,206 records. The coefficient of the inverse Mill's ratio resulting from Heckman selection models indicated no evidence of significant selection bias (Appendix B, Table B.4).

Individuals in the sample were older with a higher proportion female compared to the source population; therefore, we post-stratified the data on age and gender as described above [130-133]. The following proportions of demographic characteristics were fixed by post-stratification: 54% of residents were female, 17% were aged ≥ 65 years, 33% were from New York, and 28% lived in a large central metropolitan area (Table 4.1). In weighted analysis, we estimated that 15% of residents were parents,

85% were white, and 65% had a bachelor's degree or higher (For brevity, CIs are reported in Table 4.1.).

For our outcome of interest, we estimated that 64% (n = 2098) of residents were willing to receive a LD vaccine, while 7% (n = 190) were not willing and 30% (n = 918) were uncertain (Table 4.1). Regarding LD history, attitudes, and practices, we estimated that 18% of residents experienced a past LD diagnosis in their household, and 86% expressed concern about a future LD diagnosis. An estimated 71% of residents spent time in tick habitat at least weekly. Nearly all residents (92%) used some type of LD prevention measure, while 70% were confident that available measures can prevent LD. The vast majority (94%) were confident that recommended vaccines benefit people. Regarding LD vaccine attitudes, the majority of residents had concerns about vaccine safety (71%) and cost (63%), and the majority (89%) indicated that a positive recommendation from an HCP for the LD vaccine would influence their willingness to be vaccinated. In stratified analyses, differences in willingness to be vaccinated were observed for all characteristics and were significant at $\alpha = 0.05$.

Table 4.1 Study population characteristics and willingness to receive a potential LD vaccine, weighted % (95% confidence interval)

		Willingness to receive a LD vaccine*		
Characteristic	**All****	**Yes**	**No**	**Don't Know**
		64 (62, 65)	7 (6, 8)	30 (29, 31)
Total, N = 3206		n = 2098	n = 190	n = 918
Demographics				
Gender**				
Female	54	54 (53, 54)	64 (59, 70)	54 (52, 56)
Male	46	46 (46, 47)	36 (30, 41)	46 (44, 48)

Age category* (years)**				
< 18	15	14 (13, 15)	13 (10, 16)	19 (17, 20)
18-44	33	36 (35, 37)	34 (29, 40)	28 (26, 30)
45-64	34	32 (31, 33)	39 (33, 45)	38 (36, 40)
65+	17	18 (18, 19)	14 (11, 17)	16 (14, 17)
State				
CT	20	21 (21, 22)	17 (12, 21)	16 (15, 18)
MD	27	27 (26, 28)	24 (19, 29)	29 (27, 31)
MN	20	20 (19, 21)	24 (20, 28)	18 (17, 20)
NY	33	32 (31, 33)	35 (29, 41)	37 (35, 39)
Race				
White	85 (84, 86)	87 (86, 88)	75 (69, 81)	81 (79, 83)
Non-white	15 (14, 16)	13 (12, 14)	25 (19, 31)	19 (17, 21)
Education				
Some college or less	35 (33, 36)	31 (29, 32)	50 (44, 56)	39 (37, 41)
Bachelor's degree or higher	65 (64, 67)	69 (68, 71)	50 (44, 56)	61 (59, 63)
Metropolitan status				
Large central metro area	28	28 (27, 29)	38 (33, 44)	26 (24, 28)
Other	72	72 (71, 73)	62 (56, 67)	74 (72, 76)
LD history, attitudes, and practices				
Past LD diagnosis in household				
Yes	18 (17, 19)	21 (20, 22)	14 (9, 19)	13 (12, 15)
No	82 (81, 83)	79 (78, 80)	86 (81, 91)	87 (85, 88)
Concern about future LD diagnosis				
Yes	86 (85, 86)	94 (93, 95)	56 (50, 62)	74 (72, 76)
No	14 (14, 15)	6 (5, 7)	44 (38, 50)	26 (24, 28)
Time spent in tick habitat				
At least weekly	71 (70, 73)	82 (80, 83)	51 (45, 57)	54 (52, 56)
Monthly or less	29 (27, 30)	18 (17, 20)	49 (43, 55)	46 (44, 48)
Current use of LD prevention measures				
Yes	92 (91, 93)	94 (93, 95)	87 (83, 91)	90 (88, 91)
No	8 (7, 9)	6 (5, 7)	13 (9, 17)	10 (9, 12)

Confidence in LD prevention measures				
Yes	70 (68, 71)	67 (65, 68)	81 (76, 85)	74 (71, 76)
No	30 (29, 32)	33 (32, 35)	19 (15, 24)	26 (24, 29)
Confidence in general vaccines				
Yes	94 (93, 95)	98 (97, 98)	69 (64, 74)	91 (89, 93)
No	6 (5, 7)	2 (2, 3)	31 (26, 36)	9 (7, 11)
LD vaccine attitudes				
LD vaccine safety concerns				
Yes	71 (70, 72)	68 (66, 69)	80 (75, 84)	75 (74, 77)
No	29 (28, 30)	32 (31, 34)	20 (16, 25)	25 (23, 26)
HCP influence on LD vaccination				
Yes	89 (88, 89)	93 (92, 94)	57 (52, 63)	87 (85, 89)
No	11 (11, 12)	7 (6, 8)	43 (37, 48)	13 (11, 15)
LD vaccine cost concerns				
Yes	63 (62, 65)	66 (65, 68)	34 (28, 40)	64 (62, 67)
No	37 (35, 38)	34 (32, 35)	66 (60, 72)	36 (33, 38)

*All comparisons made in stratified analyses using Pearson chi-squared tests with Rao and Scott design-based adjustments had resultant p values ≤ 0.001.

**County distributions of gender and age were used for post-stratification; as such, these point estimates for the overall sample are fixed at the population values and have no associated interval estimate. Because state and metropolitan status are based on county population totals, these point estimates are also fixed.

***Gender and age categories represent the potential vaccinee, i.e., adult respondents and the children for whom parents responded.

Overall, we estimated that the top sources of LD information for residents were health websites (29%, 95% CI: 28%, 30%), search engines (22%, 95% CI: 21%, 23%), and HCPs (21%, 95% CI: 20%, 22%) (Figure 4.1), with similar proportions for those who said “Yes” and “Don’t know” to potential LD vaccination (Appendix B, Figure B.1). Among those who said “No” to potential LD vaccination, a lower proportion (22%, 95% CI: 17%, 27%) cited health websites as a primary source of LD, and a higher proportion

cited search engines (25%, 95% CI: 19%, 31%) and social media (6%, 95% CI: 2%, 9%), compared to residents overall and those who said “Yes” and “Don’t know” to LD vaccination (Appendix B, Figure B.1).

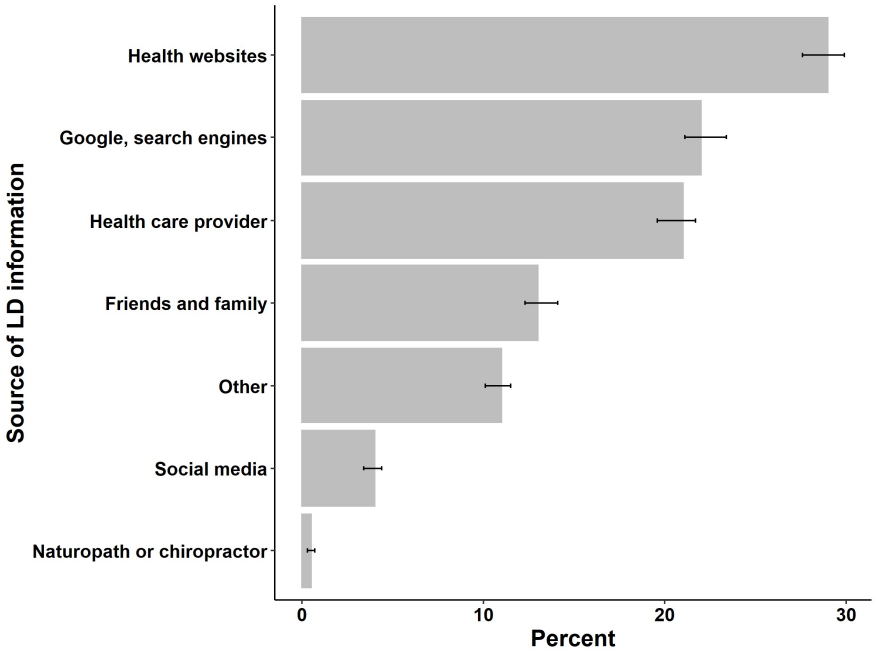

Figure 4.1 Residents’ primary source for LD information, weighted % and 95% confidence intervals*

*95% confidence interval are shown in the black bars.

Overall, the top three locations for receiving vaccinations were HCP offices, clinics, or hospitals (82%, 95% CI: 81%, 83%); pharmacies (12%, 95% CI: 11%, 12%); and workplaces (3%, 95% CI: 2%, 3%) (Figure 4.2). Proportions were similar for those who said “Yes” and “Don’t know” to potential LD vaccination, while a higher proportion of those who said “No” reported they “do not get vaccines” (14%, 95% CI: 10%, 18%) or that they “Don’t know” their primary location for receiving vaccination (5%, 95% CI: 4%,

6%), compared to residents overall and those who said “Yes” and “Don’t know” to LD vaccination (Appendix B, Figure B.2).

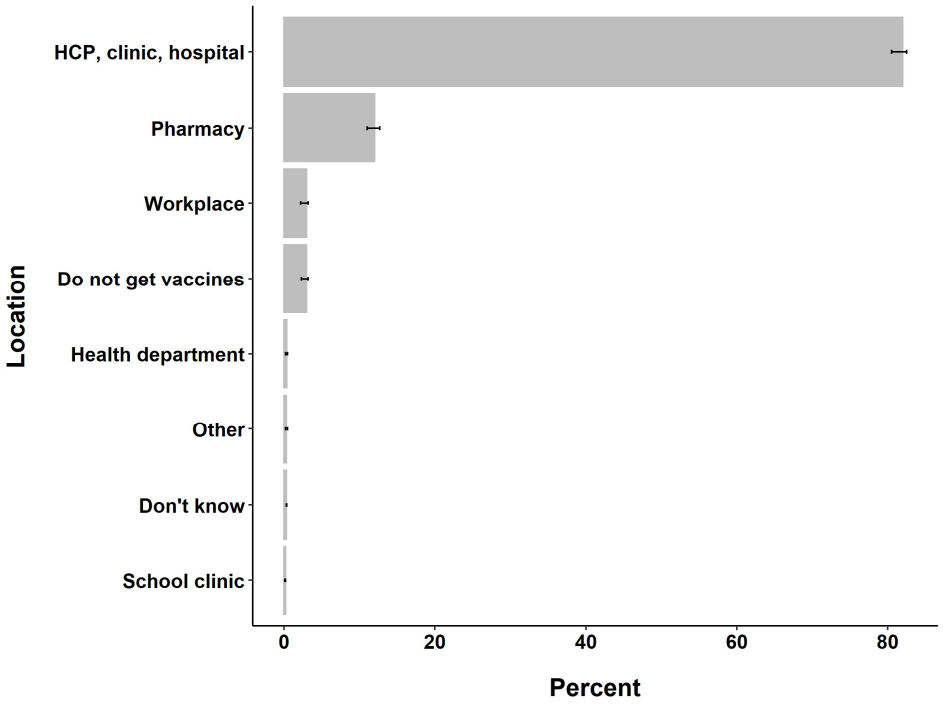

Figure 4.2 Residents’ primary location for receiving vaccination, weighted % and 95% confidence intervals

*95% confidence interval are shown in the black bars.

Table 4.2 shows the estimated unadjusted and adjusted ORs and 95% CIs resulting from survey-weighted, multivariable, multinomial logistic regression analysis. In terms of sociodemographic characteristics, the odds of parents of minors responding “Don’t know” (vs. “Yes”) to LD vaccination was 1.6 times that of the reference group, those 65 years and older (OR: 1.60, 95% CI: 1.06, 2.42). The odds of those aged 45 – 64 years responding “Don’t know” were also higher compared to those 65 years and older (OR: 1.40, 95% CI: 1.07, 1.85). Females had only slightly higher odds of

responding “No” (vs. “Yes”) to LD vaccination compared to males (OR: 1.55, 95% CI: 0.90, 2.68) and did not have higher odds of responding “Don’t know”. Those in Maryland and New York had higher odds of responding “Don’t know” to LD vaccination compared to those in Connecticut (aOR: 1.42, 95% CI: 1.01, 1.99 and aOR: 1.52, 95% CI: 1.05, 2.19, respectively). No differences were found among states for “No” responses. Non-white residents had higher odds of responding “No” to LD vaccination (aOR: 2.29, 95% CI: 1.21, 4.32) and “Don’t know” (aOR: 1.54, 95% CI: 1.10, 2.17) compared to white residents. Those with less than a bachelor’s degree had higher odds of responding “No” (aOR: 2.21, 95% CI: 1.28, 3.83) and “Don’t know” (aOR: 1.47, 95% CI: 1.13, 1.91) to LD vaccination compared to those with more education.

In terms of attitudes toward a LD vaccine, those with safety concerns had higher odds of responding “No” and “Don’t know” to LD vaccination (aOR: 2.62, 95% CI: 1.49, 4.6; aOR: 1.99, 95% CI: 1.42, 2.78, respectively) compared to those without safety concerns. Those who said HCP recommendation would not influence their willingness to be vaccinated had much higher odds of responding “No” (aOR: 5.21, 95% CI: 2.72, 10.00) but only slightly higher odds of responding “Don’t know” (aOR: 1.42, 95% CI: 0.94, 2.15). Finally, those with LD vaccine cost concerns had lower odds of responding “No” to LD vaccination (aOR: 0.36, 95% CI: 0.20, 0.64) compared to those without cost concerns.

Table 4.2 Unadjusted and adjusted odds ratios for LD vaccination responses using multinomial logistic regression

	LD vaccination responses (ref. = Yes)			
	No		Don't Know	
Variable	**OR (95% CI)**	**aOR (95% CI)**	**OR (95% CI)**	**aOR (95% CI)**
Vaccinee age category*				
(ref. = 65 + years)				
<18	1.19 (0.38, 3.68)	NA	1.60 (1.06, 2.42)	NA
18 – 44	1.23 (0.69, 2.19)	NA	0.91 (0.66, 1.26)	NA
45 – 64	1.59 (0.88, 2.85)	NA	1.40 (1.07, 1.85)	NA
Gender*				
(ref. = Male)				
Female	1.55 (0.90, 2.68)	NA	1.00 (0.77, 1.31)	NA
State[1]				
(ref. = Connecticut)				
Maryland	1.13 (0.60, 2.13)	1.16 (0.61, 2.19)	1.40 (0.99, 1.98)	1.42 (1.01, 1.99)
Minnesota	1.54 (0.77, 3.07)	1.51 (0.76, 3.00)	1.20 (0.83, 1.73)	1.19 (0.82, 1.73)
New York	1.41 (0.79, 2.50)	1.41 (0.80, 2.48)	1.52 (1.05, 2.20)	1.52 (1.05, 2.19)
Race[2]				
(ref. = White)				
Non-white	2.24 (1.18, 4.26)	2.29 (1.21, 4.32)	1.55 (1.10, 2.18)	1.54 (1.10, 2.17)
Education[3]				
(ref. = ≥ Bachelor's degree)				
< Bachelor's degree	2.29 (1.35, 3.88)	2.21 (1.28, 3.83)	1.45 (1.12, 1.87)	1.47 (1.13, 1.91)
LD vaccine safety concerns[4]				
(ref. = No)				
Yes	1.86 (1.12, 3.1)	2.62 (1.49, 4.60)	1.48 (1.07, 2.03)	1.99 (1.42, 2.78)
HCP influence on LD vaccination[5]				
(ref. = Yes)				
No	9.32 (5.43, 16.01)	5.21 (2.72, 10.00)	1.92 (1.30, 2.84)	1.42 (0.94, 2.15)

LD vaccine cost concerns[6]				
(ref. = No)				
Yes	0.26 (0.16, 0.43)	0.36 (0.20, 0.64)	0.92 (0.74, 1.16)	1.07 (0.82, 1.39)

[*] Unadjusted models only; no potential confounders were included in these models.
[1]State model adjusted for age category and education.
[2]Race model adjusted for metro status.
[3]Education model adjusted for age category, gender, state, race, and metro status.
[4]LD vaccine safety concerns model adjusted for age category, gender, education, HCP recommendation, past LD diagnosis in household, concern about future LD diagnosis, time spent in tick habitat, current use of LD prevention measures, general confidence in vaccines.
[5]HCP influence on LD vaccination model adjusted for age category, gender, education, past LD diagnosis in household, concern about future LD diagnosis, time spent in tick habitat, general confidence in vaccines.
[6]LD vaccine cost concerns model adjusted for age category, gender, state, education, HCP recommendation, concern about future LD diagnosis, time spent in tick habitat, current use of LD prevention measures, general confidence in vaccines.

In our sensitivity analysis using standard logistic regression to compare adjusted ORs and PRs, we found the two measures of association to be comparable (Appendix B, Table B.5). For the rarer “No” response to willingness to be vaccinated, the ORs and PRs were within a tenth of each other for all variables except education, LD vaccine safety concerns, and HCP influence on vaccination. For the less rare “Don’t know” responses, ORs and PRs were within 0.5 of each other.

Discussion

We estimate that over 60% of residents living in areas with a high incidence of Lyme disease would be willing to receive a LD vaccine if one were available. Approximately 30% of residents were unsure about their willingness to be vaccinated, and they were more likely to be parents making decisions for their children, adults 45 – 65 years of age, non-white, have less than a bachelor’s degree, or have concerns about the safety of a potential LD vaccine. Targeting vaccine communications to these groups, especially those in the age groups at highest risk for LD, may increase uptake of a LD

vaccine. Less than 10% of residents indicated that they were not willing to be vaccinated. They were also more likely to be non-white, have less than a bachelor's degree, or have concerns about the safety of a potential LD vaccine, but they also would not be influenced by a positive recommendation from a HCP, have low confidence in vaccines in general, and have low perceived risk of contracting LD. Targeted outreach may be unlikely to change these groups' willingness to receive a LD vaccine. Alternatively, these groups may have low perceived risk of LD because of truly being at low risk of LD (e.g., those living in more urban areas who do not spend time outdoors in tick habitat), and they may not benefit from LD vaccination.

A 2002 study among parents in Nassau County, New York evaluated whether parents would request the LYMErix vaccine for their children, if and when it became available. The vast majority said they would "definitely" (23%) or "likely" (65%) request it, followed by those "unlikely" (9%) to request it and those who would not (3%)[93]. While this response scale differs from that in our study, these results are similar to ours, with the majority willing to be vaccinated and few declining. Another study evaluated a LYMErix vaccination program among New York State Department of Health employees at risk for occupational tick exposure. While only 16% of employees chose to be vaccinated, the majority of non-recipients reported safety as a major concern, as seen in our results [94].

Prior to the present study there has been little research on acceptability of a potential new LD vaccine, though a 2016 convenience sample survey conducted in Connecticut and Maryland counties with a high incidence of LD found that the majority of respondents were likely to receive a potential LD vaccine, with 49% "very likely", 35%

“somewhat likely”, 8% “somewhat unlikely”, and 7% “very unlikely” [100]. Similarly, a nationwide population-based survey conducted in 2014 and 2015 found that 65% of respondents in high incidence states would be “likely” to receive a vaccine [101]. Additionally, a qualitative research study conducted in 2018 using focus groups of those at high risk for LD showed that 57% would be “very likely” to receive a LD vaccine (Devchand et al, submitted). Again, while the response scales of these studies differ from the present study, our estimates of potential vaccine uptake are concordant.

Demographic disparities in vaccination coverage are common and complex for both compulsory childhood vaccines and for recommended, non-compulsory vaccines for adults and children [70, 71, 90] [97-99]. Our finding that those who are non-white or those with lower education are more likely to respond “No” and “Don’t know” to LD vaccination contrasts somewhat with studies on childhood vaccines. In Arizona, non-medical exemption rates (i.e., vaccine refusals) among kindergarteners were higher in schools with a higher proportion of white children and a lower proportion of free lunches (as a proxy for income) [70]. In a nationwide survey, more white parents reported being unsure about or refusing childhood vaccinations versus other racial groups [71]. However, another nationwide survey found demographic differences when comparing under-vaccinated children with unvaccinated children; under-vaccinated children tended to be black, have a mother without a college degree, and have lower household income while unvaccinated children tended to be white, have a mother with a college degree, and have higher household income [90]. However, our survey was not parent-specific, and our sample includes only a small proportion of parent respondents. Our results for a voluntary LD vaccine are likely more comparable to annual reports of coverage for

recommended, non-compulsory vaccines for adults. Annually, these reports show higher coverage generally for whites compared with most other racial groups [97, 98]. Racial minorities are at risk for LD [140], and vaccine communications should focus on these groups in endemic areas.

Vaccine safety concerns are often cited as reasons for delaying or refusing vaccinations generally among both parents and adults, and these concerns were also an important factor in LYMErix vaccination decisions, despite it being proven to be safe [71-73, 90-94]. Our results show that safety will also be an important consideration in future LD vaccination decisions. A new LD vaccine may spawn additional safety concerns given that the waning demand for LYMErix was due, in part, to safety concerns, albeit unfounded. However, current vaccine candidates do not include the alleged, arthritis-causing epitope present in the LYMErix vaccine, which may assuage concerns for some [141]. Further, many studies, including this one, have shown that a positive recommendation for vaccination from a HCP has a significant influence on the vaccination decision and may increase uptake [92, 142, 143]. While other factors such as efficacy, convenience, and LD risk, among others, will undoubtedly play a role in uptake of a potential LD vaccine, effectively communicating its safety profile will be critical, and HCPs may be the best communicators of this information to the public [144]. As such, it will be important for public health practitioners to work with HCPs to develop messaging and other tools for communicating about a LD vaccine with patients.

These results must be interpreted in the context of several potential limitations. While we anticipated and accounted for a low response rate in our sample size calculations, such large non-response may affect the validity of our estimate of vaccine

uptake due to non-response error. For example, it is possible that those who do not perceive themselves to be at risk for LD had low interest in the survey and chose not to respond. These non-respondents may be likely to decline LD vaccination due to their perceived low risk, thereby causing an overestimate of the proportion who would receive a LD vaccine in our sample, compared to the target population. However, post-stratification was intended to mitigate this non-response error. Further, Heckman selection model results did not reveal significant selection bias. In terms of information bias, most survey questions, including the willingness to be vaccinated outcome and independent variables of interest, concerned respondents' opinions, making recall or misclassification error unlikely. However, given the hypothetical nature of the survey questions, the estimate of intention to receive a LD vaccine may change as more information on vaccine parameters becomes available or may differ from actual vaccine uptake. For example, results were mixed for studies evaluating the correlation between intention to receive a vaccine and actual uptake during the 2009-2010 influenza A/H1N1 pandemic in the United States [145-147]. Lastly, while these results are generalizable to the populations of participating states, excluding residents of New York City, these results may or may not be generalizable to other states with a high incidence of LD. However, the states in this study represent a range of endemicity, from fully endemic in Connecticut to focally endemic in parts of Minnesota and New York; therefore, results are likely applicable to other endemic states, such as Massachusetts and Wisconsin, but may not apply to states where LD is emerging, such as Michigan and West Virginia.

In anticipation of a new LD vaccine coming to market, future studies should further evaluate parent-specific vaccine concerns, given that children are at high risk for

LD and may benefit most from the vaccine. Additional evaluations of vaccine acceptability will also be needed once safety, efficacy, dosing, and immunogenicity data is available for a new vaccine. Our estimate of potential vaccine uptake provides important information for ACIP recommendations and may be used in economic evaluations of a potential vaccine. Lastly, our characterization of the factors affecting willingness to receive a potential LD vaccine can inform future communication and education efforts with clinicians and the public to increase awareness and uptake of a vaccine.

Conclusions

LD incidence is increasing, despite current prevention options. A new LD vaccine could substantially reduce disease incidence if vaccine uptake is high. The majority of residents in four high incidence states would be willing to receive a LD vaccine if one were available. Effective communication by clinicians regarding safety, efficacy, and other vaccine parameters to those demographic groups who are uncertain about LD vaccination will be critical for increasing vaccine uptake and reducing LD incidence.

CHAPTER 5: COST-BENEFIT ANALYSIS OF VACCINATING A POPULATION AGAINST LYME DISEASE IN HIGH INCIDENCE AREAS OF THE UNITED STATES

Summary

Introduction

An estimated 300,000 cases of Lyme disease occur in the United States annually, resulting in significant disease and cost burdens. New Lyme disease vaccines are currently in development, which have the potential to substantially reduce disease incidence, but the economic benefit of these vaccine candidates is unknown.

Methods

We conducted a cost-benefit analysis to estimate the net cost of vaccination against Lyme disease. We used a decision-analytic model to compare a vaccination strategy to no vaccination among 100,000 individuals living in high incidence areas over a three-year time horizon. Vaccine and disease probabilities and costs were estimated from the literature as well as from primary research. Deterministic sensitivity analyses were conducted. Model outputs included cases averted, the net cost of the vaccination strategy, cost per case averted, and net cost per vaccinee.

Results

In the base-case analysis, we estimated that 2,160 cases would be averted during a three-year period for a 100,000-person cohort residing in an area with an incidence of 0.01. The net cost of the vaccination strategy was $12,510,475, which translates to a cost per case averted of $9,301 and a net cost per vaccinee of $156 over a three-year period. The net cost per vaccinee was most sensitive to changes in disease incidence

and vaccine price, with a $0 net cost resulting from a vaccine price of $45 at an incidence of 0.01 or a vaccine price of $476 at an incidence of 0.08.

Conclusions

Many counties in endemic states have annual incidence greater than 0.01, and while the price of a potential vaccine is currently unknown, it is possible that an eventual vaccine could be cost saving. This analysis should be repeated when price and performance parameters for a Lyme disease vaccine are available. Results can inform recommendations for the use of a vaccine in the United States, when available.

Introduction

Lyme disease (LD) is a bacterial illness caused by infection with *Borrelia burgdorferi*, and more rarely, *B. mayonii*, in the United States (U.S.). It is primarily transmitted by the bite of infected *Ixodes scapularis* ticks in the northeastern, mid-Atlantic, and upper-midwestern states [3, 4]. Cases of LD are increasing as the range of *I. scapularis* expands from historical foci and as human development intensifies in tick habitat [1, 5]. This multi-system disease is the most commonly reported vector-borne disease in the U.S. [1, 2], with bimodal incidence highest among children aged 5-10 years and adults aged 45-55 years [1]. Annually, over 30,000 cases are reported to the Centers for Disease Control and Prevention (CDC), but recent studies have provided evidence that the true number of cases is estimated to be over 300,000 each year in the U.S. [6, 7]. In recent years, 95% of cases were reported from 14 states: Connecticut, Delaware, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont, Virginia, and Wisconsin [1]. Though cases are concentrated geographically, this disease burden represents considerable direct and indirect costs to U.S. society [8](Aim 1, Chapter 3). The inability of currently available prevention measures to stem rising LD incidence highlights the need for a prevention modality suitable for use at the population level, such as a vaccine [17].

An LD vaccine called LYMErix was available 1998 – 2002 in the U.S. until it was voluntarily discontinued by the manufacturer due to low demand caused by a number of factors unrelated to its positive safety and efficacy profiles [18-20]. Since then, the number of LD cases reported annually has nearly doubled [21]. After almost two decades without an effective prevention method, a new vaccine candidate called VLA15

[22-25] is being developed by the French biotech company, Valneva, in partnership with Pfizer [63-65]. This recombinant OspA-based vaccine candidate is being evaluated as a three-dose series for use in the general population, including children aged two years and older. It is designed to protect against the primary LD-causing strains found in both the U.S. and Europe. Randomized, observer-blind, placebo-controlled Phase II trials were completed in 2020 in LD endemic areas of the U.S. and Europe, with results showing both a favorable safety profile and high immunogenicity across all tested age groups. If successful, VLA15 may be licensed for use as early as 2024. In addition, a passive vaccination approach using a single monoclonal antibody administered annually is also in development [66-68]. This product, called Lyme pre-exposure prophylaxis (Lyme PrEP), is being developed by MassBiologics, a non-profit vaccine manufacturer overseen by the University of Massachusetts Medical School. MassBiologics plans to initiate Phase 1 trials in 2020 with potential availability in 2022 [66].

Three cost-effectiveness analyses were conducted for the LYMErix vaccine from 1999 – 2002 [60-62], comparing a vaccination strategy with a no vaccination strategy. Results included incremental cost-effectiveness ratios ranging from $9,309 to $11,346 (2020 USD) per LD case averted at an incidence rate of 0.01 [69]. When these cost-effectiveness analyses were conducted, incidence rates close to 0.01 occurred only in a few counties in the northeastern U.S., which limited the overall economic benefit of the vaccine. With the number of reported cases currently growing and recent studies estimating true cases at approximately 10 – 12 fold higher [6, 7], there are now many more areas of the U.S. where incidence meets or exceeds 0.01, warranting an updated economic evaluation for a potential, new LD vaccine.

With recently available data on the direct and indirect costs per case of LD (Aim 1, Chapter 3), we conducted a cost-benefit analysis comparing the costs and monetary benefits of a vaccination strategy with those of the current status quo (i.e., no vaccine strategy) using the societal perspective. Specifically, the primary objective of this project was to estimate the net cost of vaccination per vaccinee. The secondary objective was to identify variables that have the greatest impact on the net costs of vaccination. These estimates can be used to inform national recommendations by the Advisory Committee on Immunization Practices (ACIP) for the use of a LD vaccine, when available.

Methods

The Model

We developed a decision-analytic model to assess the net costs or savings associated with a vaccination strategy compared to no vaccination. This approach is particularly appropriate for acute, non-communicable diseases occurring over a short, fixed time horizon, such as LD [107]. The decision tree used for the model is composed of branches and nodes, which are classified as either decision, chance, or terminal nodes. The structure of the decision-analytic model for this analysis included two main branches for the vaccination strategy; within the vaccination strategy, an individual chooses at the decision node whether to receive vaccination (Figure 5.1; see “Data” section below for associated probabilities for each node). The no vaccination strategy is not shown but is identical to the lower branch (“Vaccine not effective”) of the vaccination strategy wherein an individual chooses not to receive vaccination.

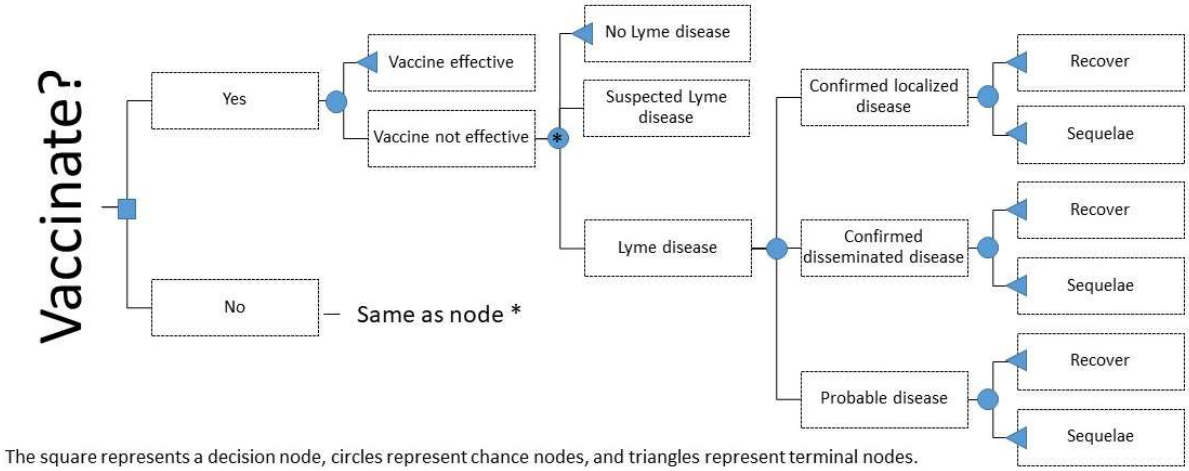

Figure 5.1 Decision analysis tree used to model the costs and benefits of a Lyme disease vaccination strategy

The vaccination strategy assumed use of a hypothetical Osp-A based, multi-valent, sub-unit Lyme disease vaccine requiring three doses (i.e., VLA15), using available data on VLA15's performance parameters when possible [65]. The decision-analytic model was used to simulate a static cohort of 100,000 individuals living in LD endemic areas with an incidence of approximately 0.01 prior to vaccine introduction. We assumed that an individual's vaccination decision in year one would be the same for subsequent years (i.e., those who were not vaccinated in year 1 remained unvaccinated). Therefore, for the vaccination strategy, the costs for the vaccine and its administration were included only in year 1. For the no vaccination strategy, all parameters were repeated annually.

Reinfection with LD has been well documented [148]. Further, incidence in endemic areas is generally stable from year to year [1]. For these reasons, the model utilized a one-year cycle length wherein an individual's risk for reinfection if not

vaccinated or if the vaccine was not effective is assumed to be the same annually. Duration of immunity after two years post-vaccination was not evaluated for LYMErix before its withdrawal [51, 52], and data on duration of immunity is not yet available for VLA15. For our model, we assumed that duration of immunity following vaccination would last at least three years based on the most optimistic duration of immunity from the LYMErix vaccine and assuming that the higher dose of vaccine used with VLA15 compared to LYMErix would result in immunity at least as long [50, 61, 65]. Therefore, we chose a 3-year analytic time horizon for our model. Because it is currently unknown whether booster vaccinations will be needed for an eventual vaccine, booster dosing was not included in the model.

Model Outputs

The model outputs included the number of overall LD cases averted by the vaccination strategy compared to the no vaccination strategy; total cost of the vaccination strategy; the cost per case of LD averted; the net cost (or savings) of the vaccination strategy; and the net cost (or savings) per person vaccinated. The formulas for these outputs are listed in Table 5.1. All cost outputs were discounted at a 3.4% annual discount rate and given as their net present value [149].

Table 5.1 Lyme disease vaccine decision-analytic model outputs and formulas

Output	Formula
Lyme disease cases averted with vaccination strategy	Cases in no vaccination strategy **–** cases in vaccination strategy
Cost of vaccination strategy	Sum of costs of vaccination and illness in vaccination strategy
Cost per case averted with vaccination strategy	(Cost of vaccination strategy **–** Cost of no vaccination strategy*) **/** (Cases in vaccination strategy **–** Cases in no vaccination strategy)
Net cost (or savings) of vaccination strategy	(Cost of vaccination strategy **–** Cost of no vaccination strategy*) **–** (Benefit of vaccination strategy **–** Benefit of no vaccination strategy*)

Net cost (or savings) per vaccinee	(Cost of vaccination strategy **–** Cost of no vaccination strategy*) **–** (Benefit of vaccination strategy **–** Benefit of no vaccination strategy*) **/** number vaccinated in vaccination strategy

*The no vaccination strategy represents the status quo. As such, the cost of the no vaccination strategy as well as the benefit of the no vaccination strategy equals $0.

Data

The probability and cost variables used in the model are shown in Tables 5.2 and 5.3, respectively, and were estimated from the literature (see references in Table 5.2), Aim 1 (Chapter 3), and Aim 2 (Chapter 4). For each variable, we assigned a best estimate for use in the base-case analysis, as well as a clinically plausible range to use in deterministic sensitivity analyses.

Table 5.2 Base-case probability estimates and plausible ranges

Variable	Estimate	Range	Reference
Vaccination			
Efficacy	0.9	0.7 – 0.99	[51, 52, 64, 65]
Uptake	0.8	0.64 – 0.94	Aim 2 (Ch. 4)
Lyme disease			
Incidence, endemic states	0.01	0.001 – 0.08	[1, 6, 7, 150]
Confirmed, localized Lyme disease	0.55	0.50 – 0.9	[1, 21]
Confirmed, disseminated Lyme disease	0.21	0.1 – 0.3	[1, 21]
Probable Lyme disease	0.24	0.1 – 0.5	[1, 21]
Sequelae			
Confirmed, localized Lyme disease	0.03	0.00 – 0.07	[37, 60, 62, 123]
Confirmed, disseminated Lyme disease	0.26	0.18 – 0.28	[60, 62, 123]
Probable Lyme disease	0.14	0.10 – 0.18	[60, 62, 123]
Suspected Lyme disease (i.e., tested, non-Lyme disease)			
Incidence, suspected Lyme disease	0.061	0.057 – 0.063	[7]
Incidence, suspected Lyme disease if vaccinated	0.012	0.011 – 0.013	[7]

Vaccine parameters

Instead of assuming that 100% of our hypothetical cohort would receive vaccination in the vaccination strategy, we used an estimate of uptake derived from Aim 2 to reflect a more realistic scenario. In Aim 2, we estimated that, of those living in

endemic areas, 63.6% would be willing to receive vaccination against LD, 29.6% were uncertain, and 6.7% were not willing. For the present model, we assumed that a portion of those who were uncertain would ultimately choose vaccination; therefore, our base-case estimate of the probability of vaccine uptake was 0.80, with a lower bound of 0.64 and an upper bound of 0.94.

In our model, we estimated that the base-case probability for vaccine efficacy was 0.9 based on the most recent data released from VLA15's second Phase II trial [65]. This trial found that seroconversion rates among those vaccinated exceeded 90% across all six *B. burgdorferi* serotypes for all ages tested (18 – 65 years). Generally speaking, seroconversion signifies protection against infection in most scenarios [151]. Phase III clinical trials for LYMErix and ImmuLyme, a similar OspA vaccine candidate that was never licensed, demonstrated vaccine efficacy ranging from 49 – 68% for two doses and 76 – 77% for three doses [51, 52]. However, the dose for the previous vaccines was much lower than the current candidate (30 μg of OspA for LYMErix vs. 135 μg or 180 μg for VLA15) and different dosing schedules were used. Therefore, we chose a lower bound of 0.7 to approximate efficacy with reduced compliance of only 2/3 doses of VLA15, or in the event that vaccine efficacy for VLA15 is eventually shown to be similar to that of LYMErix. We assumed an upper bound of 0.99 under a scenario of an optimal dosing and administration schedule. We did not account for adverse events related to vaccination in our model because no significant adverse events were reported in either Phase II trial for VLA15.

Clinical parameters

The annual risk for infection with LD is derived from incidence rates based on reported cases in highly endemic states; these numbers are then multiplied by 10 to account for the rate of underreporting for LD and approximate true incidence [6, 7]. For clinical outcomes, we used surveillance data to estimate probabilities associated with confirmed localized disease (i.e., presence of erythema migrans or early disease), confirmed disseminated disease (i.e., cardiac, neurologic, and/or rheumatologic symptoms resulting from disseminated infection), and probable disease. The probable disease category includes those with a physician diagnosis of LD and laboratory evidence of infection but no accompanying clinical information. This category may include some individuals without true LD (e.g., those with past infection) whose symptoms and associated costs are nevertheless attributed to LD. Probabilities for these three categories are derived from the average proportion of confirmed cases reported 2008 – 2017, multiplied by the proportion of reported erythema migrans (for confirmed localized disease) or the proportion of reported non-erythema migrans symptoms (for confirmed disseminated disease), respectively, for the same time period [1, 21]. The probability associated with a probable disease outcome was derived from the average proportion of probable cases reported 2008 – 2017 [1, 21].

Estimates of the probabilities of sequelae, defined as persistent symptoms for six months or more after confirmed LD [29], were derived from the literature. We assumed the base-case probability of sequelae resulting from localized disease to be 0.05 (range 0 – 0.07) [37] and sequelae resulting from disseminated disease to be 0.26 (range 0.18 – 0.28); the latter was derived by averaging probabilities for specific manifestations

(e.g., cardiac, neurologic, or arthritic) [60-62]. Sequelae resulting from probable disease was estimated to be an average of localized and disseminated disease parameters (0.14, range 0.09 – 0.18).

We defined suspected LD cases as those who were tested for LD, and as such, incurred testing costs but did not have evidence of current *B. burgdorferi* infection. Probabilities for suspected LD were derived from Hinckley et al. 2014 [7]. This study estimated that 88% (range 81.5 – 90%) of diagnostic tests conducted for LD by four large commercial laboratories were for non-infected individuals. We multiplied the total number of specimens (2,432,396, used as proxies for individuals) tested by these laboratories by the proportion non-infected (0.88) and the proportion of specimens from four endemic states (0.31), resulting in an estimate of 663,558 (range 614,570 – 678,666) suspected LD cases in these states (Connecticut, Maryland, Minnesota, and New York). These four states represent 36% of all reported LD cases; applied to an annual, nationwide total of 300,000 cases, these four states, therefore, account for 108,000 cases. We then calculated the ratio of suspected LD cases (663,558) to true LD cases (108,000) to get a multiplier of 6.14. This multiplier was applied to the incidence rate in endemic areas (0.01) for a resulting base-case suspected LD incidence rate of 0.0614 (range 0.0569 – 0.0628), which was used in the no vaccine strategy. For the vaccine strategy, we assumed that this rate would decrease by 80% among those vaccinated, resulting in a base-case estimate of 0.0123 (range 0.0114 – 0.0126).

Costs

The cost-benefit analysis was conducted from a societal perspective, including all direct and indirect costs of vaccine administration and illness, regardless of who is responsible for these costs. The costs of the vaccination strategy represented the sum of the costs of vaccination (vaccine and its administration) and the costs associated with LD cases that occurred in the vaccination strategy. The benefits of the vaccination strategy are equivalent to the cost of LD cases averted due to vaccination. All costs included in the model were adjusted for inflation to 2020 U.S. dollars using the medical care component of the consumer price index [113]. The base-case estimates, plausible ranges, and references for the cost variables are given in Table 5.3.

Table 5.3 Base-case cost estimates and plausible ranges

Variable	Estimate	Range	Reference
Costs (USD 2020)			
Vaccination series and administration	213	28 – 684	[59]
Confirmed, localized Lyme disease	1,461	173 – 2,994	Aim 1 (Ch. 2)
Confirmed, disseminated Lyme disease	3,634	332 – 6,973	Aim 1 (Ch. 2)
Probable Lyme disease	2,929	353 – 5,613	Aim 1 (Ch. 2)
Sequelae	17,295	7,728 – 23,322	[62, 123, 124]
Diagnostic testing for suspected Lyme disease	322	237 – 400	[7]

The base-case estimate of the cost of the three-dose vaccination series was derived from the Centers for Disease Control and Prevention's (CDC) Vaccine Price List, updated September 2020 [59]. Vaccines for adults and children were selected for which three doses are required. The CDC cost per dose and private sector cost per dose were averaged per vaccine, then multiplied by three to get an average series cost per vaccine. Our base-case vaccine series cost was estimated as the average series cost from all vaccines selected from the Vaccine Price List. Our series cost range was based on the minimum and maximum series costs derived from the Vaccine Price List.

We did not include costs associated with vaccine side effects as no serious adverse events have been reported for VLA15, as described above.

The cost estimates for LD cases by confirmed localized, confirmed disseminated, and probable disease were derived from Aim 1 (See Chapter 3 for details on methodology. See Appendix C, Table C.1 for summary statistics of costs by disease category.). The costs by disease category include direct costs for medical care for LD as well as indirect costs for LD, including productivity losses and non-medical costs incurred by the patient (e.g., transportation costs to receive medical care for LD). For this analysis, the mean cost per person by disease category was used in the base-case analysis, with the 10^{th} and 90^{th} percentiles used for the plausible range (Table 5.3; Appendix C, Table C.1). The cost of disease sequelae was derived from the literature [62, 123, 124]; we averaged the estimates for arthritic, cardiac, and neurologic sequelae for a single base-case cost estimate and plausible range.

The cost of suspected LD was derived from Hinckley et al. 2014, similar to the derivations for the probability of suspected LD [7]. Hinckley et al. (2014) estimated the total cost of testing ($492M in 2008 USD); we multiplied this by the proportion of all negative tests (0.88) and the proportion in four endemic states (0.31). We then divided this cost by the number of individuals with suspected LD (663,558) for an average per-person cost of testing. This cost was added to an average office consultation cost and routine venipuncture cost for a base-case estimate of $322 per person (range $237 – 400; 2020 USD).

Sensitivity Analysis

Deterministic sensitivity analyses were conducted to evaluate uncertainty in results and determine which variables have the greatest impact on the net cost per vaccinee, defined as the variables resulting in the greatest range between the minimum and maximum change in the net result [106]. In one-way sensitivity analyses, LD incidence, vaccine efficacy, clinical probabilities, and cost estimates were each varied over their plausible ranges to estimate changes in model outputs. The two most influential variables were evaluated in a two-way sensitivity analysis, and threshold analysis was conducted to determine the values at which these two variables resulted in a $0 net cost (i.e., the point at which the result changes from net cost to net savings) [106]. Lastly, we conducted an analysis of extremes, sometimes referred to as "worst/best case analysis" [106]. With this method, the extreme estimates from the plausible ranges of all model parameters are fixed under two scenarios, one that favors and one that does not favor vaccination (e.g., a low cost, high effectiveness scenario or a high cost, low effectiveness scenario, respectively). Herein, we have termed these "optimistic scenario" and "pessimistic scenario," respectively (Appendix C, Table C.2).

Results

In the base-case analysis, we estimated that 2,160 cases of LD would be averted during a three-year period for every 100,000 persons (i.e., 80,000 persons vaccinated per the vaccine uptake parameter) living in an endemic area with an incidence of 0.01 (Table 5.4). The net cost of the vaccination strategy in the base-case analysis was $12,510,475, which translates to a cost per case averted of $9,301 and a net cost per vaccinee of $156 over a three-year period.

In the optimistic scenario, when all vaccine parameters were set to their extremes favoring vaccination (Appendix C, Table C.2), we estimated that 22,334 cases of LD would be averted during a three-year period (Table 5.4). In this scenario, the net *savings* of the vaccination strategy was $131,788,122, which results in a cost per case averted of $616 and net *savings* per vaccinee of $1,402. In the pessimistic scenario, when all vaccine parameters were set to their extremes that do not favor vaccination (Appendix C, Table C.2), we estimated that 134 cases of LD would be averted during a three-year period. In this scenario, the net cost of the vaccination strategy was $42,507,925, which results in a cost per case averted of $316,848 and a net cost per vaccinee of $664.

Table 5.4 Base-case, optimistic, and pessimistic scenarios for a Lyme disease vaccination strategy compared to a no vaccination strategy among a 100,000-person cohort

Strategy	Cost (USD 2020)	Cases	Cases averted	Cost per case averted (USD 2020)	Net cost of strategy (USD 2020)	Net cost per vaccinee (USD 2020)
Base-case scenario						
No vaccine	16,096,564	3,000	NA	NA	NA	NA
Vaccine	20,089,797	840	2,160	9,301	12,510,475	156
Optimistic scenario						
No vaccine	163,466,390	24,000	NA	NA	NA	NA
Vaccine	13,751,460	1,666	22,334	616	-131,788,122	-1,402
Pessimistic scenario						
No vaccine	3,988,705	300	NA	NA	NA	NA
Vaccine	42,584,410	166	134	316,848	42,507,925	664

In one-way sensitivity analyses, the cost of the vaccine (plausible range $28 – 684) had the greatest effect on the main outcome, ranging from a net savings of $17 to a net cost of $597 per vaccinee (Figure 5.2). Increasing vaccine cost had the greatest potential to increase the net cost per vaccinee of all parameters. Endemic incidence (plausible range 0.001 – 0.08) had the second greatest effect on the net cost per vaccinee, ranging from a net savings of $248 to a net cost of $208. Increasing incidence

had the greatest potential for net savings per vaccinee of all parameters. In an additional sensitivity analysis using the minimum and maximum costs per disease category found in Aim 1 (Chapter 3), vaccine price and disease incidence still had the greatest impact on net cost per vaccinee, but the cost of disease also had a large effect on results, with increasing probable disease and confirmed disseminated disease cost resulting in net savings per vaccinee (see Appendix C, Table C.1 and Figure C.1).

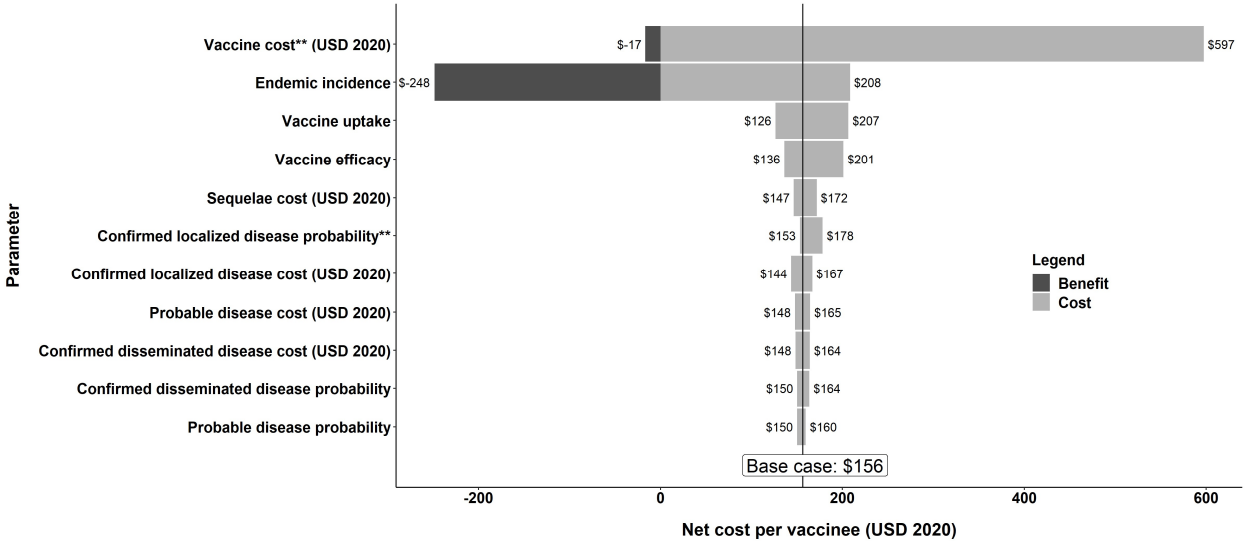

Figure 5.2 Impact of select model parameters on the net cost per Lyme disease vaccinee resulting from one-way sensitivity analyses*

*Probabilities for suspect Lyme disease (LD), cost of suspect LD, and probabilities for sequelae had a negligible impact on the net cost per vaccinee and were not included in the plot.
**Vaccine cost and confirmed localized disease probability have a positive relationship with net cost per vaccinee. All other parameters have a negative relationship with net cost per vaccinee.

In a two-way sensitivity analysis varying the parameters with the greatest impact in one-way sensitivity analyses, vaccine price and LD incidence, we found that at the lower bound incidence of 0.001, there were no net savings per vaccinee at any vaccine price (Figure 5.3; Appendix C, Figure C.2). At the base-case incidence of 0.01, there is

a potential for net savings per vaccinee at lower vaccine costs, and the breakeven vaccine price was $45 for a $0 net cost per vaccinee. At the upper bound incidence of 0.08, there is a potential for net savings per vaccinee up to a vaccine price of $476, which is the breakeven price for a $0 net cost per vaccinee.

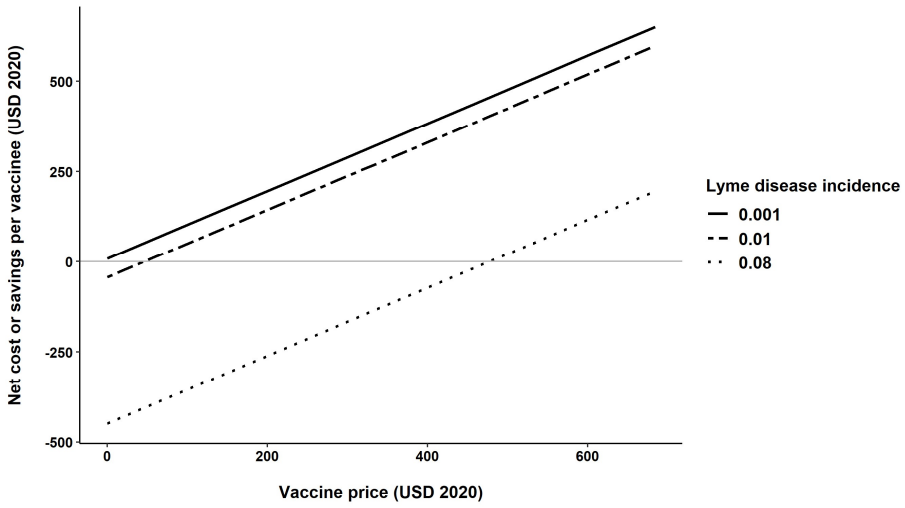

Figure 5.3. Net cost per vaccinee in two-way sensitivity analysis of Lyme disease vaccine price and Lyme disease incidence

Discussion

In this cost-benefit analysis, a LD vaccination strategy among a hypothetical cohort of 100,000 individuals living in endemic areas resulted in over 2100 cases averted during a three-year time period in our base-case scenario. The net cost of the vaccination strategy was $12.5M and the net cost per vaccinee was approximately $150, corresponding to a net cost per vaccinee per year of approximately $50. Vaccine price and LD incidence had the greatest influence on model results. At an incidence of 0.01, the vaccination strategy became cost-saving at a vaccine price of $45 per person. When a rate of 10 – 12 fold underreporting of LD cases is taken into account [6, 7],

many counties have annual incidence greater than 0.01, increasing the likelihood that a LD vaccine could be cost saving, particularly if the eventual vaccine price is < $200 (Appendix C, Figure C.1).

Several cost-effectiveness analyses were conducted for the previously available LYMErix vaccine, and these findings may be compared to our results for cost per case averted of $9,301 at an incidence of 0.01, vaccine price of $213, and other base-case estimates of parameters (Table 5.2). Meltzer et al. estimated a cost per case averted of $10,143 (USD 2020) annually with a vaccination cost of $100 per year at an incidence of 0.01 [60]. Shadick et al. estimated a cost per case averted of $11,346 (USD 2020) with a vaccination cost of $150 at an incidence of 0.01 [62]. Hsia et al. estimated a cost per case averted of $9,309 (USD 2020) with a vaccination cost of $621, which included the cost of a booster vaccination at 3 years [61]. All three studies concluded that LD incidence was the most important factor in determining cost-effectiveness for a LD vaccine and that at > 0.01 incidence, a LD vaccine was potentially cost-effective, but that individual risk should be taken into account when recommending the LYMErix vaccine. These findings are comparable to our cost-effectiveness results, though important differences in probability and cost estimates for model parameters should be noted. These cost-effectiveness analyses assumed universal vaccination of the cohorts used in their models, while we included an estimate of vaccine uptake (0.8) derived from Aim 2 (Chapter 4). Further, these studies estimated vaccine efficacy at 0.76 – 0.85 based on the data available for LYMErix at the time. Our higher base-case estimate of 0.9 vaccine efficacy is derived from interim clinical trial data for VLA15 and assumes full compliance for the three-shot series [65, 152]. These studies used probabilities and cost

for disease and sequelae based on clinical outcomes by symptom category (neurologic, cardiac, and arthritis), while our study categorized disease based on surveillance data for confirmed localized disease, confirmed disseminated disease, and probable disease. Finally, these studies did not have data available on the total cost of LD per person, and all but Meltzer et al. used direct costs only for the treatment of LD. Our use of the total cost of LD per person from the societal perspective from Aim 1 included all direct and indirect costs associated with LD. This difference allowed us to monetize the benefit of a case averted and go beyond estimating cost-effectiveness to estimating the net cost or savings of a LD vaccine.

Currently, cost-benefit analyses for other LD prevention methods do not exist, such as for residential acaricide treatments, residential rodent-targeted bait boxes, or permethrin treated clothing. While the annual cost per person for these interventions may be comparable to the cost of a LD vaccine [Niesobecki et al, in press], the effectiveness of these interventions in terms of cases averted remains unknown. Recent studies have evaluated residents' willingness to pay to avoid risk of contracting LD (i.e., avoidance of habitat with ticks infected with *B. burgdorferi*) as evidenced by substituting away from outdoor recreation in areas with LD risk or by their willingness to travel further to lower-risk recreational areas [153, 154]. Berry et al. estimated an average of 9.41 hours annually are substituted away from outdoor activity due to LD risk at an estimated cost of $210 per person (USD 2020) annually, significantly higher than the estimated $50 net cost of LD vaccination per person annually found in the present study. Slunge estimated that residents in Sweden were willing to pay $30 (USD 2020) more per recreational trip in the form of traveling further to avoid areas with many ticks

and risk for Lyme borreliosis. Assuming a similar willingness to pay in the U.S. and that people take at least two outdoor recreation trips per year, willingness to pay to travel further to reduce risk of LD is greater than the $50 net cost of vaccination per person annually. However, Slunge also found that the willingness to pay to avoid ticks was lower among persons vaccinated against tick-borne encephalitis, suggesting there may be an additional benefit of vaccination in the form of increased leisure time spent outdoors in endemic areas [153].

While many vaccinations are consistently cost-saving, such as routine childhood vaccinations [155], there are recommended immunizations that generate a net cost depending on disease incidence, target population, vaccination strategy, and other factors. For example, influenza vaccinations may generate a net cost depending on the match between the circulating strain and available vaccine [156, 157]. Vaccination against tick-borne encephalitis among French troops in the Balkans resulted in a net cost, primarily due to low incidence of the disease, despite its associated high morbidity and mortality [158]. In addition, economic analyses of meningococcal vaccines have shown that costs usually outweigh the benefits, yet it remains recommended for those at risk due to associated high morbidity and mortality, even with adequate treatment [159, 160]. Similarly, setting priorities for vaccination against LD will likely not be based solely on economic considerations but on the relative risks of certain groups for serious complications, the overall burden of disease in the U.S., and the lack of effective prevention alternatives, among other factors.

Every attempt was made to select representative estimates for the probabilities and costs used in our model, however these findings are valid only insofar as the

parameters and assumptions included in the model are valid. Because this project uses primary data from Aims 1 (disease cost) and 2 (vaccine uptake), it is subject to the limitations for these projects described in previous chapters (chapters 3 and 4). In addition, the vaccination costs used in the model are considered marginal costs and do not account for development of or upgrades to the basic infrastructure necessary for a vaccine program; thus, general administrative costs may be underestimated [161, 162]. While we did not include costs associated with vaccine side effects because no serious adverse events have been reported in the most recent Phase II trials for VLA15, subsequent, larger Phase III trials may reveal risk for serious adverse events which should be included in future cost-benefit analyses and would influence results away from cost savings. Further, we did not include the cost of productivity losses associated with death due to LD as this outcome is exceedingly rare; however, inclusion of this cost would influence results toward cost savings. Vaccination against LD will not prevent infections with other pathogens transmitted by *I.scapularis* ticks such as *Anaplasma phagocytophilum*, *Babesia microti*, Powassan virus, and *B. miyamotoi*. While these diseases are much less common than LD, vaccination may cause people to reduce their usual measures for preventing *I. scapularis* tick bites and increase risk for these other diseases, thereby creating an additional cost associated with LD vaccination. For the purposes of this analysis, we assumed current prevention behaviors would continue to be employed with the availability of a LD vaccine. Regarding probabilities used for disease categories, these were derived from surveillance data, with likely overreporting of rarer, disseminated disease and underreporting of more common, early localized disease occurring [122]. However, the plausible ranges for these probabilities account

for these potential inaccuracies, and disease probabilities did not have a large impact on the net cost per vaccinee in sensitivity analyses. Lastly, as a new LD vaccine is not currently licensed and available, there are uncertainties surrounding vaccine efficacy, vaccine effectiveness, duration of immunity, and dosing schedule. If boosters are required with VLA15, this will drive up the net cost per vaccinee and require future analysis over a longer time horizon. In addition, if vaccinees receive only one or two of the required doses, this will reduce vaccine efficacy and increase the net cost per vaccinee. As more definite data for these parameters become available, the model can be modified to incorporate these changes. The model may also be easily adjusted for economic evaluations of other future vaccines or vaccine-like candidates, such as Lyme PrEP.

Conclusions

LD incidence is increasing, despite current prevention options, but a new LD vaccine could substantially reduce disease incidence. While our base-case analysis did not find a hypothetical LD vaccine to be cost-saving from a societal perspective, those living in endemic areas may be willing to pay out of pocket for the net cost of $150 per vaccinee estimated from our analysis for at least three years of protection. Our sensitivity analysis showed that the net cost (or savings) was very sensitive to vaccine price and LD incidence. Because many counties in LD endemic states have annual incidence greater than our base-case estimate of 0.01, and because the price of a potential vaccine is currently unknown, there is potential that an eventual vaccine could be cost-saving. This analysis should be conducted in the future when exact performance parameters for a vaccine or vaccine-like preventive is available.

CHAPTER 6: CONCLUSIONS

Summary

The body of work described in this dissertation provides critical information for public health considerations for a potential Lyme disease (LD) vaccine in the United States (U.S.). Specifically, this research provides new information on the economic burden of LD, the acceptability of a potential LD vaccine by the public, and the net cost of a potential vaccination program. We found that most LD patients have low costs, but some experience very high costs related to LD; further, the total economic burden of diagnosed LD in the U.S. could be upwards of $800 million annually, a significant societal cost. We also found that acceptance of a LD vaccine among potential consumers was high, with over 60% willing to receive vaccination, approximately 30% uncertain, and less than 10% unwilling. Lastly, using these cost and vaccine acceptability results, we estimated that a vaccination program in areas with a high incidence of LD could generate a net cost of approximately $150 per vaccinee over three years of vaccine effectiveness; however, a vaccination program could potentially be cost-saving depending on the eventual price of a LD vaccine and disease incidence. With currently available prevention measures failing to decrease LD incidence, new vaccine candidates have the potential to make a substantial impact on the morbidity and economic burden of LD in the U.S.

Individual project conclusions and next steps

Aim 1: The Economic Burden of Reported Lyme Disease in High Incidence Areas of the United States

In a prospective, cost of illness study conducted in Connecticut, Maryland, Minnesota, and New York, we found patients had an average out-of-pocket cost of approximately $1,340 (median cost ≈ $270) and an average total cost of approximately $2,270 (median cost ≈ $770) (2020 USD). In stratified analyses by disease category, those with confirmed disseminated and probable disease had approximately double or more the total cost per patient compared to those with confirmed localized disease, highlighting the importance of early and accurate diagnosis. Having disseminated or probable disease, being aged 18 – 65 years, and having residence in Minnesota had the greatest impact on the total cost of LD. While median total costs were typically $1,000 or less for all disease categories, average costs were substantially higher, indicating that most patients have low costs, but some experience very high costs related to LD. Similarly, the low median number of provider visits and hours of lost productivity suggest that illness with LD is manageable for most, but for a minority, it may be highly disruptive. With over 300,000 cases of LD diagnosed each year, the aggregate cost of diagnosed LD could be upwards of $800 million (2020 USD) annually, not including suspected, undiagnosed, or non-acute LD. These costs represent a significant economic burden to U.S. society and underscore the need for effective prevention methods. Future efforts should include use of these results in economic evaluations of current and future prevention methods, such as a vaccine. In addition, more research is needed to determine the cost of unreported, suspected, and non-acute

LD for an even more comprehensive estimate of the economic burden attributable to LD in the U.S.

Aim 2: Evaluating public acceptability of a potential Lyme disease vaccine using a population-based, cross-sectional survey in high incidence areas in the U.S.

From the results of a population-based, cross-sectional survey conducted in Connecticut, Maryland, Minnesota, and New York, we estimated that over 60% of residents in states with a high incidence of Lyme disease would be willing to receive vaccination if a LD vaccine were available. Approximately 30% of residents were unsure about their willingness to receive LD vaccination, and they were more likely to be parents making decisions for their children, adults 45 – 65 years of age, non-white, have less than a bachelor's degree, or have concerns about the safety of a potential LD vaccine. Targeting vaccine communications to these groups, especially those in the age groups at highest risk for LD, may increase uptake of a LD vaccine. Less than 10% of residents indicated that they were not willing to receive LD vaccination. They were also more likely to be non-white, have less than a bachelor's degree, or have concerns about the safety of a potential LD vaccine, but they also would not be influenced by a positive recommendation from a HCP, have low confidence in vaccines in general, and have low perceived risk of contracting LD. Targeted outreach may be unlikely to change these groups' willingness to receive LD vaccination. Effective communication by clinicians regarding safety, efficacy, and other vaccine parameters to those demographic groups who are uncertain about LD vaccination will be critical for increasing vaccine uptake. Next steps should include conducting a larger study among parents of minors to further elucidate factors contributing to LD vaccine hesitancy, as children are one of the groups

at highest risk for LD. Further, vaccine acceptability studies should be conducted among clinicians providing primary care to patients living in endemic areas. These results will allow for targeted messaging among consumers and clinicians to increase vaccine awareness and acceptability, and will also aid in the development of communication tools to assist clinicians in discussing the LD vaccine with patients.

Aim 3: Cost-benefit analysis of a strategy to vaccinate a population against Lyme disease in high incidence areas of the U.S.

In this cost-benefit analysis, a LD vaccination strategy among a hypothetical cohort of 100,000 individuals living in endemic areas resulted in over 2,100 cases averted during a three-year time period in the base-case scenario, which included an LD incidence of 0.01 and a vaccine price of approximately $200. The net cost of the vaccination strategy was $12.5M and the net cost per vaccinee was approximately $150, corresponding to a net cost per vaccinee per year of approximately $50. Individuals living in endemic areas may be willing to pay $150 out of pocket for at least three years of protection. Vaccine price and LD incidence had the greatest influence on model results. At an incidence of 0.01, the vaccination strategy became cost-saving at a vaccine price of $45 per person. When a rate of 10 – 12-fold underreporting of LD cases is taken into account, many counties have annual incidence greater than 0.01, increasing the likelihood that a LD vaccine could be cost saving, particularly if the eventual vaccine price is < $200. This analysis should be conducted in the future when exact performance parameters of a vaccine are known, such as efficacy, duration of immunity, dosing schedule, price, and frequency of adverse effects. To aid in future resource allocation decisions, the decision-analytic model used for the present analysis

may be adjusted as needed for a new vaccine, such as VLA15; a vaccine-like preventive, such as Lyme PrEP; or even for a non-vaccine LD intervention. Additional economic studies should be conducted to determine how much potential consumers would be willing to pay for a LD vaccine to further enhance understanding of public acceptability of a vaccine and aid decision-makers in vaccine financing decisions.

Overall contribution and impact

The Advisory Committee on Immunization Practices (ACIP) is hosted by the Centers for Disease Control and Prevention (CDC) but is comprised of immunization experts from academia, professional organizations, clinical practice, industry, and public health. This committee meets several times a year to make national recommendations for the use of licensed vaccines based on factors such as disease burden, public acceptance, public health impact, cost, vaccine supply, and other considerations beyond the safety and efficacy data used for FDA approval [58]. These recommendations become CDC policy upon publication in the *Morbidity and Mortality Weekly Report* and are the principal guide for clinicians in vaccination decisions for individual patients. The primary results from all three Aims provide important, complementary information that may be considered by the ACIP in making recommendations for a new LD vaccine, when available. Specifically, these results show the need for, potential public demand for, and economic benefit of a new LD vaccine. Further, these results include much more information than was available to the ACIP in 1998 when the committee made what many regard as lukewarm recommendations for the formerly available LD vaccine, LYMErix [17, 50, 57]. It is possible that the current, robust collection of findings will result in stronger

recommendations for a new LD vaccine for those living in any state with a high incidence of LD (i.e., Connecticut, Delaware, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont, Virginia, and Wisconsin), for those living in counties in other states where LD is emerging, and potentially for those planning to travel to these areas [1].

The results from the cost of illness study described in Aim 1 (Chapter 3) add to the small but growing body of literature on the economic burden of LD in the U.S. A major strength of this study over previous ones is its prospective collection of patient out-of-pocket costs, including productivity losses, thereby providing a comprehensive estimate of the cost of LD, both to the patient and to society as a whole. These results illustrate the economic burden of LD in the U.S., but can also be used in economic evaluations of a vaccine and non-vaccine LD interventions. The LD vaccine acceptability study (Aim 2, Chapter 4) generated some of the first estimates of uptake for a past or future vaccine in the U.S. These results also provide a critical variable in the cost-benefit analysis, allowing for a more realistic estimate of the cost or benefit of a vaccination program. The cost-benefit analysis (Aim 3, Chapter 5) is the first of its kind for a LD vaccine, as previous economic evaluations of the formerly available LYMErix vaccine did not have comprehensive cost of illness data available and were thus limited to cost-effectiveness analyses. While cost-effectiveness results allow for a comparison of the cost of different interventions for the same health outcome, the results of a cost-benefit analysis allow for a comparison of the net cost of the intervention of interest to any other intervention, whether for the same or a different health outcome, or alternatively, for a health outcome vs. a non-health outcome. For example, the federal

government may use the results from Aim 3 in resource allocation decisions regarding vaccination programs for LD vs. dengue; or, it may compare the net cost of a LD vaccination program to an environmental intervention.

While the impacts of our primary results described above are directly relevant to ACIP considerations for a potential vaccine, the findings from the secondary objectives of this suite of research also have important public health implications for improving the prevention and control of LD. The cost of illness results in Aim 1 highlight patient characteristics associated with higher costs, which can be used to improve economic efficiency in the clinical management of LD. The characterization of factors associated with willingness to receive a LD vaccine in Aim 2 will allow for more targeted communications among the public and clinicians about a new vaccine to prevent some of the challenges that led to the demise of the LYMErix vaccine. Lastly, because we found that the results of the cost-benefit analysis were very sensitive to disease incidence, the model could be transformed into a decision tool for use by state and local public health practitioners to generate net cost results based on local incidence at different, potentially subsidized, vaccine prices.

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APPENDIX A: SUPPLEMENTAL MATERIALS FOR CHAPTER 3, THE ECONOMIC BURDEN OF REPORTED LYME DISEASE IN HIGH INCIDENCE AREAS OF THE UNITED STATES

Table A.1 Participating counties from Maryland and New York

State	County
Maryland	Anne Arundel
	Baltimore
	Calvert
	Carroll
	Cecil
	Frederick
	Harford
	Howard
	Montgomery
New York	Albany
	Rensselaer
	Columbia
	Greene
	Saratoga
	Schoharie
	Schnectady
	Washington
	Fulton
	Montgomery
	Ostego
	Delaware
	Dutchess
	Ulster

Section A.1 Detailed description of cost calculations for out-of-pocket patient costs and direct medical costs

To estimate the out-of-pocket costs per patient, we summed self-reported medical costs, non-medical costs, cost of productivity losses, and other related costs over all surveys. For non-medical costs related to travel for clinician, pharmacy, or lab visits, the self-reported roundtrip mileage per visit was multiplied by the standard mileage rate from the Internal Revenue Service for the respective year [163]. To calculate cost estimates for productivity losses, self-reported hours missed from work for adult patients or parents of pediatric patients were multiplied by the hourly earnings by age and sex derived from Grosse et al. 2019 [164], which uses the human capital approach to estimate annual market and non-market productivity from the U.S. Census Bureau's American Community Survey and American Time Use Survey.

We calculated the direct medical cost per patient by summing the mean cost per CPT code collected for each patient. Mean cost for each CPT code collected for participants with private insurance was extracted from IBM® MarketScan® Research Databases, which include national medical claims data for privately insured persons up to age 65 and their dependents. Costs for CPT codes collected for non-privately insured participants were extracted from the Physician Fee Schedule National Payment Amount File from the Centers for Medicare and Medicaid Services (CMS) [112]. We did not collect billing codes from pharmacies or laboratories. Therefore, we extracted the mean cost of the recommended antibiotics for LD by state and study year from MarketScan® drug cost data and added this cost to each participant's total direct medical cost [165-169]. Because laboratory evidence of infection is required to meet criteria for confirmed disseminated or probable disease [47], we added the cost of the recommended two-

tiered LD diagnostic testing to the total direct medical cost for all participants in these disease categories who did not already have these CPT codes documented. We excluded from analysis participants for whom CPT code collection was incomplete due to provider nonresponse to code collection requests. We also excluded individual CPT codes deemed unrelated to LD, per consultation with an infectious disease physician, that were collected coincidentally from providers (Table A.4).

Table A.2 Characteristics of the subset of participants with complete out-of-pocket and direct medical costs data, N = 613

Characteristic		N	Unweighted %	Weighted %
Disease category	Confirmed localized	273	44.5	54.4
	Confirmed disseminated	154	25.1	20.2
	Probable	186	30.3	25.4
Age group (years)	< 18	173	28.2	27.7
	18 – 45	96	15.7	15.7
	46 – 65	228	37.2	37
	> 65	116	18.9	19.5
Gender	Female	262	42.7	43.0
	Male	351	57.3	57.0
Race	Non-white	45	7.3	7.1
	White	568	92.7	92.9
State	CT	128	20.9	19.3
	MD	203	33.1	33.6
	MN	191	31.2	31.1
	NY	91	14.8	15.9
Income[1]	≤ $60,000	160	28.7	28.4
	> $60,000	398	71.3	71.6
Insurance	Private	438	28.5	28.5
	Other	175	71.5	71.5
Median clinician visits (range)		2 (1 - 33)	NA	NA
Median surveys (range)		3 (1 - 12)	NA	NA

[1] Participants were not required to provide information on income; n = 558

Equation A.1 Multivariable linear regression model equation

We used a multivariable linear regression model to estimate the relative impact of our independent variables of interest on the total societal cost of Lyme disease (LD) per patient. As is typical for healthcare cost data, the distribution of total cost was highly skewed, resulting in heteroskedasticity of the residuals in the model [115]. Therefore, we transformed total cost per patient using natural logarithms and conducted sampling-weighted least squares regression. The basic equation is as follows:

$$\log(Y_i) = \beta_0 + \beta^T X_i + \epsilon_i$$

where Y_i, is the dependent variable, the total societal cost of LD for patient i; X_i is a vector of covariates; and ϵ_i is a mean-zero random error. The equation is written as follows for our specific vector of covariates (i.e., independent variables of interest and potential confounders):

$$\log(Y_i) = \beta_0 + \beta_1 \text{Disease category}_i + \beta_2 \text{Age group}_i + \beta_3 \text{Gender}_i + \beta_4 \text{State}_i +$$

$$\beta_5 \text{Insurance status}_i + \beta_6 \text{Income}_i + \beta_7 \text{Study year}_i + \epsilon_i$$

Baseline costs come from the intercept term, β_0, which represents a patient with confirmed localized Lyme disease, female, aged < 18 years, with residence in CT, without private insurance, with income < $60,000, and study year of 2014. Resulting beta coefficients were back transformed by exponentiation, interpreted as the multiplicative difference in the geometric mean of the total cost of Lyme disease for a 1-unit difference in the independent variable of interest after adjusting for confounders. We calculated the percent difference in cost from baseline for each level of each independent variable, excluding reference (i.e., baseline) levels (Percent difference = (Exp(coefficient) – 1) * 100). These additional costs were added or subtracted to the baseline costs for each independent variable of interest (see Chapter 3, Table 3.5 and Table A.7 for results).

Table A.3 Mean and median out-of-pocket Lyme disease costs per patient, by disease and cost category, 2016 USD*

Cost category	Confirmed localized disease		Confirmed disseminated disease		Probable disease	
	Median (95% CI)	Mean (95% CI)	Median (95% CI)	Mean (95% CI)	Median (95% CI)	Mean (95% CI)
Productivity losses	0 (0, 0)	540 (368, 712)	0 (0, 0)	727 (359, 1095)	0 (0, 0)	627 (429, 824)
Medical bills	42 (31, 52)	314 (201, 426)	83 (61, 145)	628 (408, 848)	83 (62, 99)	389 (264, 514)
Prescription medicine	16 (11, 21)	56 (32, 80)	21 (17, 21)	79 (54, 105)	19 (16, 21)	44 (34, 54)
Over-the-counter medicine	0 (0, 4)	20 (13, 27)	10 (7, 10)	53 (28, 78)	5 (2, 8)	47 (21, 72)
Transportation	11 (10, 12)	34 (16, 52)	20 (17, 23)	55 (37, 74)	18 (14, 20)	49 (30, 69)
Home maintenance	0 (0, 0)	31 (7, 55)	0 (0, 0)	58 (12, 103)	0 (0, 0)	50 (4, 97)
Other	0 (0, 0)	40 (23, 58)	0 (0, 0)	78 (37, 118)	0 (0, 0)	51 (27, 75)
Care for self/dependents	0 (0, 0)	35 (0, 91)	0 (0, 0)	14 (0, 28)	0 (0, 0)	20 (0, 42)

* This table is a complement to the information displayed in Chapter 3, Figure 3.2. All calculations use the sample-weighted data.

Table A.4 List of CPT codes removed from analyses, code description, frequency, mean cost per code (n = 30)*

CPT CODE	CODE DESCRIPTION	N	MEAN COST (2016 USD)
11406	Removal of growth (4.0 centimeters) of the trunk, arms, or legs	1	1152
11606	Removal of malignant growth (over 4.0 centimeters) of the trunk, arms, or legs	1	1240
36475	Destruction of insufficient vein of arm or leg, accessed through the skin	1	3021
37609	Tying or biopsy of temporal artery (side of skull)	1	1844
42821	Removal of tonsils and adenoid glands patient age 12 or over	1	1946
42830	Removal of adenoids patient younger than age 12	1	1854
43238	Ultrasound guided needle aspiration or biopsies of esophagus using an endoscope	1	1664
45378	Diagnostic examination of large bowel using an endoscope	4	752
45380	Biopsy of large bowel using an endoscope	1	1131
45385	Removal of polyps or growths of large bowel using an endoscope	2	2911
47562	Removal of gallbladder using an endoscope	1	4062
55700	Biopsy of prostate gland	1	679
59510	Cesarean delivery with pre- and post-delivery care	1	2893
62311	Injections of substances into lower or sacral spine	3	565
64490	Injections of upper or middle spine facet joint using imaging guidance	1	788
64491	Injections of upper or middle spine facet joint using imaging guidance	1	531
64492	Injections of upper or middle spine facet joint using imaging guidance	1	502
64635	Destruction of lower or sacral spinal facet joint nerves using imaging guidance	1	1155
64636	Destruction of lower or sacral spinal facet joint nerves with imaging guidance	1	801
66984	Removal of cataract with insertion of lens	3	2415
69436	Incision of eardrum with insertion of eardrum tube under general anesthesia	1	1802
78582	Lung ventilation & perfusion imaging	1	598
92928	Catheter insertion of stents in major coronary artery or branch, accessed through the skin	1	3530
95810	Sleep monitoring of patient (6 years or older) in sleep lab	1	1535
C1725	Catheter, transluminal angioplasty, non-laser (may include guidance, infusion/perfusion capability)	2	2182
C1874	Stent, coated/covered, with delivery system	1	5411
C9600	Percutaneous transcatheter placement of drug eluting intracoronary stent(s), with coronary angioplasty when performed; single major coronary artery or branch	1	12616
G0202	Screening mammography digital	14	490
G0206	Diagnostic mammography digital	3	523
J0133	Injection, acyclovir, 5 mg	1	824

* An infectious disease physician with subject matter expertise in Lyme disease deemed these CPT codes to be unrelated to Lyme disease; 54 instances with these 30 codes recorded were deleted from the dataset prior to all analyses.

Table A.5 Twenty-five most frequently reported CPT codes, code description, and summary statistics

CPT code	Code description	N	Proportion	MarketScan mean, median reimbursement (USD 2016)	CMS mean, median reimbursement (USD 2016)
99213	Established office visit	970	0.1	100.55, 85.14	75.04, 74.70
99214	Established patient office or other outpatient, visit typically 25 minutes	707	0.07	144.43,120.56	112.68,115.18
36415	Routine venipuncture	579	0.06	8.40, 3.89	3.00, 3.00
Q9967	LOCM 300-399mg/ml iodine,1ml	344	0.04	336.87,165.17	152.19,165.17
86617	Confirmation test for antibody to Borrelia burgdorferi (Lyme disease bacteria)	308	0.03	64.58, 32.82	28.49, 28.49
85025	Complete blood cell count (red cells, white blood cell, platelets), automated test	287	0.03	26.57, 18.03	14.30, 14.30
86618	Analysis for antibody Borrelia burgdorferi (Lyme disease bacteria)	273	0.03	42.44, 33.62	31.32, 31.32
J3490	Unclassified drugs	180	0.02	489.57, 28.90	37.95, 28.90
97110	Therapeutic exercises	166	0.02	64.88, 49.72	33.17, 32.36
J1642	Injection, heparin sodium, (heparin lock flush), per 10 units	130	0.01	248.86, 24.21	24.21, 24.21
80053	Blood test, comprehensive group of blood chemicals	105	0.01	40.06, 14.87	19.43, 19.43
97112	Neuromuscular reeducation	102	0.01	44.74, 25.22	34.03, 33.71
86140	Measurement C-reactive protein for detection of infection or inflammation	96	0.01	21.47, 9.49	9.52, 9.52
98940	Chiropractic manipulative treatment, 1-2 spinal regions	88	0.01	38.20, 28.00	29.52, 29.43
80048	Blood test, basic group of blood chemicals	87	0.01	33.53, 18.90	15.55, 15.55
J0696	Injection, ceftriaxone sodium, per 250 mg	85	0.01	165.44, 32.76	44.70, 32.76
A9585	Injection, gadobutrol, 0.1 ml	83	0.01	228.98, 90.00	90.01, 90.00
99212	Established patient office or other outpatient visit, typically 10 minutes	82	0.01	68.39, 51.74	45.35, 45.11
90471	Administration of 1 vaccine	78	0.01	26.87, 24.47	26.56, 25.52
99203	New patient office or other outpatient visit, typically 30 minutes	77	0.01	138.31,109.00	112.28,116.07
85652	Red blood cell sedimentation rate, to detect inflammation	76	0.01	10.53, 4.73	4.97, 4.97
93000	Routine EKG using at least 12 leads including interpretation and report	75	0.01	47.41, 38.79	17.95, 18.34
87880	Strep test (Streptococcus, group A)	70	0.01	20.26, 17.31	22.05, 22.05
99284	Emergency department visit, problem of high severity	70	0.01	532.25,411.12	119.94,120.87
85027	Complete blood cell count (red cells, white blood cell, platelets), automated test	65	0.01	23.06, 13.97	11.90, 11.90

Table A.6 Total cost of LD per patient, by demographic characteristic, N = 613

Characteristic		N	Mean (2016 USD)	Median (2016 USD)
Disease category	Confirmed localized	273	1307	493
	Confirmed disseminated	154	3251	1081
	Probable	186	2620	940
Age group (years)	< 18	173	1550	503
	18 – 45	96	2100	960
	46 – 65	228	2421	1136
	> 65	116	1926	521
Gender	Female	262	1417	646
	Male	351	2497	741
Race	Non-white	45	2188	774
	White	568	2021	685
State	CT	128	3307	621
	MD	203	1493	604
	MN	191	2112	1124
	NY	91	1470	434
Income[1]	≤ $60,000	160	2159	685
	> $60,000	398	2088	696
Insurance	Private	438	2295	807
	Other	175	1376	578

[1] Participants were not required to provide information on income; n = 558

Table A.7 Multivariable linear regression results[1] (n = 613)

Variable	Coefficient	Standard error of coefficient	Exp(coefficient)[2]	Percent difference (%)	Cost difference (2016 USD)	95% CI for cost difference (2016 USD)	P value
Baseline (Intercept)[4]	5.72	0.20	305.08	NA	NA	206.28 – 451.20	< 0.001
Confirmed disseminated	0.79	0.11	2.20	120	366.58	188.12 – 545.04	< 0.001
Probable	0.47	0.10	1.59	59	181.13	70.84 – 291.42	< 0.001
18 – 45 years	0.67	0.15	1.96	96	292.99	107.11 – 478.88	< 0.001
46 – 65 years	0.73	0.11	2.08	108	330.79	175.08 – 486.50	< 0.001
> 65 years	0.24	0.17	1.27	27	83.65	-27.51 – 194.81	0.15
Male	0.11	0.09	1.11	11	34.56	-25.67 – 94.8	0.24
MD	0.00	0.13	1.00	0	-0.01	-75.98 – 75.97	1.00
MN	0.56	0.13	1.75	75	229.44	113.85 – 345.03	< 0.001
NY	-0.06	0.17	0.94	-6	-18.52	-118.96 – 81.91	0.72
Privately insured	0.24	0.15	1.27	27	82.53	-23.22 – 188.28	0.11
> $60,000 income	-0.06	0.12	0.94	-6	-18.52	-90.11 – 53.08	0.61
Study year 2015	-0.07	0.10	0.93	-7	-21.35	306.05 – 427.11	0.48
Study year 2016	0.50	0.50	1.65	65	197.52	-306.37 – 668.64	0.32

[1]The model included independent variables of interest, i.e., disease category, age group, gender, and state, while controlling for insurance status, income, and study year. Reference levels are not shown but are described in Table 3.5 of Chapter 3. Adjusted $R^2 = 0.19$.

[2] Beta coefficients were back transformed by exponentiation, interpreted as the multiplicative difference in the geometric mean of the total cost of Lyme disease for a 1-unit difference in the independent variable of interest after adjusting for confounders.

[3]Percent difference = (Exp(coefficient) – 1) * 100; this represents the percent change in cost from baseline for each level of each variable, excluding reference (i.e., baseline) levels.

[4]Baseline cost (i.e., e^{β_0}) represents a patient with confirmed localized Lyme disease, female, aged < 18 years, with residence in CT, without private insurance, with income < $60,000, and study year of 2014.

Section A.2 Description of calculations for extrapolation of total cost per patient to annual, aggregate total societal cost in the U.S.

In 2016, 36,429 cases of LD were reported via surveillance. Previous research has demonstrated that surveillance cases numbers are likely 8 – 12 fold underreported [6, 7]. If we assume a 10-fold increase in reported case numbers, we estimate that in 2016 there were approximately 364,290 cases in the U.S. The table below shows total cases broken down by confirmed localized, confirmed disseminated, and probable disease per the proportions found in surveillance data. To estimate the total aggregate cost of LD to U.S. society, case numbers by disease category are multiplied by the mean total cost per patient estimated from this study for an aggregate cost per disease category. When summed, the total cost of LD in the U.S. annually is approximately $734,878,574 (2016 USD). In 2020 USD, this cost is $788,615,003 using the Consumer Price Index (CPI) for all consumers and $818,510,585 when using the CPI for medical care [170].

Table A.8 Inputs for extrapolation of total cost per patient to aggregate total cost to U.S.

Lyme disease category	Estimated proportion of total cases	Total cases	Mean total cost per patient (2016 USD)	Total aggregate cost (2016 USD)
Confirmed localized	0.55	199315	1,307	257,108,596
Confirmed disseminated	0.21	76744	3,251	248,704,426
Probable	0.24	88231	2,620	229,065,552
			TOTAL (2016 USD)	734,878,574
			TOTAL (2020 USD) *	788,615,003
			TOTAL (2020 USD, medical CPI)**	818,510,585

*Converted to 2020 USD using Consumer Price Index, "All items in U.S. city average, all urban consumers, not seasonally adjusted" (CPI-U, Series ID: CUUR0000SA0). 2016 annual average CPI and 2020 first half of year average CPI used. Data extracted from https://data.bls.gov/pdq/SurveyOutputServlet on 9/30/2020.

**Converted to 2020 USD using Consumer Price Index, "Medical care in U.S. city average, all urban consumers, not seasonally adjusted" (CPI-U Medical care, Series ID: CUUR0000SAM). 2016 annual average CPI and 2020 first half of year average CPI used. Data extracted from https://data.bls.gov/pdq/SurveyOutputServlet on 9/30/2020.

APPENDIX B: SUPPLEMENTAL MATERIAL FOR CHAPTER 4, EVALUATING PUBLIC ACCEPTABILITY OF A POTENTIAL LYME DISEASE VACCINE USING A POPULATION-BASED, CROSS-SECTIONAL SURVEY IN HIGH INCIDENCE AREAS OF THE UNITED STATES

Table B.1 Select vaccine acceptability survey questions and response options*

Question	Response options
If a Lyme disease vaccine were available, would you get vaccinated?	Yes No Don't know/not sure
How concerned are you about the safety of a Lyme disease vaccine?	Not at all concerned Somewhat concerned Very concerned Don't know/not sure
How much would the cost of a Lyme disease vaccine affect your decision to get vaccinated?	Not at all Some A lot Don't know/not sure
How much would a positive recommendation from your doctor affect your decision to get vaccinated?	Not at all Some A lot Don't know/not sure
Has anyone in your household ever been diagnosed with LD by a health care professional?	Yes No Not sure
How concerned are you about getting LD in the future?	Not at all concerned Somewhat concerned Very concerned Don't know/not sure
In the months April-October, do you spend time in or near places where ticks could get on you (for example, wooded or brushy areas, whether in your yard, other yards, or recreational areas)?	Yes, daily Yes, weekly Yes, monthly Yes, less than once a month No Don't know/not sure
Which of the following measures do you take to prevent ticks from getting on you? (Check all that apply)	Apply insect repellent Check for ticks Use special clothing Use sprays in your yard Other measures None of these
How confident are you that these measures can prevent LD?	Very confident Somewhat confident Not at all confident Don't know/not sure
Where do you most often get information about Lyme disease? (choose one)	Doctor, nurse, or other medical professional Naturopath or chiropractor Friends or family members Google or other internet search engines

	Health websites Social media sites Other
How confident are you that recommended vaccines benefit people?	Very confident Somewhat confident Not at all confident Don't know/not sure
Where do you usually get vaccines? (choose one)	Doctor's office, clinic, or hospital Pharmacy or drug store Health department Workplace School clinic Other Don't know I do not get vaccines
**** Questions for the parent survey were identical, but phrased with the child as vaccinee (e.g., "If a LD vaccine were available, would you vaccinate your child?")***	

Table B.2 Confounders identified a priori and adjusted for in multinomial logistic regression models

	Confounders											
Model	**Vaccinee age category**	**Gender**	**State**	**Race**	**Education**	**Metro status**	**Provider recommend-ation**	**Past LD diagnosis in household**	**Concern about future LD diagnosis**	**Time spent in tick habitat**	**Current use of LD prevention measures**	**General confidence in vaccines**
Vaccinee age category*												
Gender*												
State	X				X							
Race						X						
Education	X	X	X	X		X						
LD vaccine safety concerns	X	X			X		X	X	X	X	X	X
HCP influence on LD vaccination	X	X			X			X	X	X	X	X
LD vaccine cost concerns	X	X			X			X	X	X		X

*Unadjusted models

Table B.3 Observed and weighted respondent characteristics, N = 3206

Characteristic	N	Unweighted %	Weighted % (95% CI) *
Demographics			
Gender**			
Female	1878	59	54
Male	1328	41	46
Age category (years)**			
< 18	246	8	15
18-44	772	24	33
45-64	1225	38	34
65+	963	30	17
State			
Connecticut	679	21	20
Maryland	808	25	27
Minnesota	998	31	20
New York	721	23	33
Race			
White	2852	90	85 (84, 86)
Non-white	322	10	15 (14, 16)
Education			
Some college or less	1248	39	35 (33, 36)
Bachelor's degree or higher	1941	61	65 (64, 67)
Metropolitan status			
Large central metropolitan area	674	21	28
Other	2532	79	72
LD history, attitudes, and practices			
Past LD diagnosis in household			
Yes	640	20	18 (17, 19)
No	2563	80	82 (81, 83)
Concern about future LD diagnosis			
Yes	2813	88	86 (85, 86)
No	391	12	14 (14, 15)
Spend time in tick habitat			
At least weekly	2376	74	71 (70, 73)
Monthly or less	828	26	29 (27, 30)
Currently use LD prevention measures			
Yes	2948	92	92 (91, 93)
No	258	8	8 (7, 9)
Confidence in LD prevention measures			

Yes	2041	70	70 (68, 71)
No	896	30	30 (29, 32)
Confidence in general vaccines			
Yes	3022	94	94 (93, 95)
No	182	6	6 (5, 7)
LD vaccine attitudes			
Willing to receive LD vaccine			
Yes	2098	65	64 (62, 65)
No	190	6	7 (6, 8)
Don't know	918	29	30 (28, 31)
LD vaccine safety concerns			
Yes	2257	70	71 (70, 72)
No	948	30	29 (28, 30)
HCP influence on LD vaccination			
Yes	2858	89	89 (88, 89)
No	348	11	11 (11, 12)
LD vaccine cost concerns			
Yes	2036	64	63 (62, 65)
No	1168	36	37 (35, 38)

[*] County distributions of gender and age were used for post-stratification; as such, these point estimates are fixed at the population values and have no associated interval estimate. Because state and metropolitan status are based on county population totals, these point estimates are also fixed.
[**]Gender and age categories represent the potential vaccinee, i.e., adult respondents and the children for whom parents responded.

Section B.1 Heckman-type selection models

We evaluated non-random missingness in our outcome variable, willingness to receive a LD vaccine, in relation to non-response (i.e., selection bias) using Heckman-type selection models, also called generalized Tobit models [135-137]. Heckman-type selection models correct for selection bias when nonparticipation is determined both by observed and by unobserved factors. Performance depends on the availability of selection variables that determine survey participation but do not independently affect the outcome of interest. Heckman models use two steps to first model the selection process using one or more independent selection variables and then model the outcome equation (i.e., the regression equation for the outcome of interest). The key feature of Heckman-type selection models is that a correlation between the unobserved error terms in the selection equation and outcome equation is estimated (r). The coefficient of the inverse Mill's ratio represents the covariance between the error terms, and has an associated p-value. These results of the two-step process indicate whether selection bias is present and, if so, a correction factor can be applied to results.

We chose two selection variables, presence of children in the household and household member count, under the assumption that these variables were predictive of participation in the survey, but unrelated to the outcome, willingness to receive a LD

vaccine. For example, those with children in the household and/or higher numbers of household members may not have time to participate in a voluntary survey. All variables in the selection equation must be available for all sampled individuals, regardless of participation. Independent variables for all sampled households were purchased from the marketing firm from which addresses were purchased. The selection equation included the following:

Selection ~ endemicity + property type + household income + presence of children in household + household member count

The outcome equation includes the independent variables from the selection equation, excluding the selection variables. The outcome equation included the following:

Vaccine decision ~ endemicity + property type + household income

Table B.4 shows the results of the Heckman-type selection models using the two-step process. Of note, r = 0.7 and the coefficient of the inverse Mill's ratio is 0.4305 (p = 0.5307), meaning that the data are consistent with no selection bias (i.e., the null hypothesis that the errors are uncorrelated cannot be rejected).

These results are limited by the fact that only variables available for the entire sample could be used in the evaluation. Further, the accuracy of these variables typically used for marketing research are questionable, plus some records were missing observations for these variables. Lastly, our assumption that the selection variables, presence of children in household and household member count, are unrelated to the willingness to vaccinate outcome is somewhat tenuous. For example, because children are one of the groups at highest risk for LD, parents with children in the household may be more likely to participate in a survey about a LD vaccine and also express willingness to vaccinate their children.

Table B.4 Results of Heckman-type selection models

	Dependent variable: Willingness to receive LD vaccine (0= No/DK; 1 = Yes)
Terms	Coefficient (95% CI)
Endemicity:	-0.0223
Non-endemic	(-0.1285, 0.0840)
Property type:	0.0690
Single family dwelling unit	(-0.0825, 0.2206)
Household income:	0.0709
> $70K	(-0.0868, 0.2286)

Constant	-0.2494
	(-2.4066, 1.9078)
Observations	34,667
R^2	0.0006
Adjusted R^2	-0.0009
Log Likelihood	
Akaike Inf. Crit.	
rho	0.6958
Inverse Mills Ratio	0.4305 (0.5307)

[1]The selection equation for the Heckman selection model used presence of children and household member count as selection variables, i.e., instrumental variables
Note: *p**p***p<0.01

Table B.5 Comparison of adjusted odds ratios (aORs) from multinomial logistic regression (MLR) and aORs and adjusted prevalence ratios (aPRs) from standard logistic regression (SLR)

	LD vaccination responses (ref. = Yes)					
	No			Don't Know		
Variable	**MLR aOR (95% CI)**	**SLR aOR (95% CI)**	**SLR aPR (95% CI)**	**MLR aOR (95% CI)**	**SLR aOR (95% CI)**	**SLR aPR (95% CI)**
Vaccinee age category* (ref. = 65 + years)						
<18	1.19 (0.38, 3.68)	1.11 (0.86, 1.42)	1.10 (0.88, 1.37)	1.60 (1.06, 2.42)	1.60 (1.35, 1.91)	1.37 (1.22, 1.53)
18 – 44	1.23 (0.69, 2.19)	1.16 (0.91, 1.48)	1.14 (0.92, 1.43)	0.91 (0.66, 1.26)	0.93 (0.81, 1.08)	0.95 (0.86, 1.06)
45 – 64	1.59 (0.88, 2.85)	1.45 (1.11, 1.90)	1.40 (1.10, 1.78)	1.40 (1.07, 1.85)	1.37 (1.19, 1.57)	1.24 (1.12, 1.36)
Gender* (ref. = Male)						
Female	1.55 (0.90, 2.68)	1.48 (1.21, 1.82)	1.43 (1.19, 1.71)	1.00 (0.77, 1.31)	1.00 (0.90, 1.12)	1.00 (0.93, 1.08)
State[1] (ref. = Connecticut)						
Maryland	1.16 (0.61, 2.19)	0.99 (0.71, 1.39)	0.99 (0.73, 1.34)	1.42 (1.01, 1.99)	1.35 (1.13, 1.62)	1.23 (1.09, 1.39)
Minnesota	1.51 (0.76, 3.00)	1.39 (1.03, 1.87)	1.34 (1.03, 1.75)	1.19 (0.82, 1.73)	1.17 (0.98, 1.4)	1.12 (0.99, 1.27)
New York	1.41 (0.80, 2.48)	1.48 (1.08, 2.03)	1.41 (1.07, 1.87)	1.52 (1.05, 2.19)	1.47 (1.25, 1.73)	1.3 (1.16, 1.45)
Race[2] (ref. = White)						
Non-white	2.29 (1.21, 4.32)	2.2 (1.70, 2.84)	1.98 (1.60, 2.46)	1.54 (1.10, 2.17)	1.59 (1.35, 1.88)	1.35 (1.22, 1.49)
Education[3] (ref. = ≥ Bachelor's degree)						
< Bachelor's degree	2.21 (1.28, 3.83)	1.91 (1.55, 2.37)	1.75 (1.45, 2.12)	1.47 (1.13, 1.91)	1.45 (1.30, 1.62)	1.28 (1.19, 1.37)
LD vaccine safety concerns[4] (ref. = No)						
Yes	2.62 (1.49, 4.60)	3.02 (2.26, 4.03)	1.99 (1.61, 2.46)	1.99 (1.42, 2.78)	1.99 (1.74, 2.28)	1.48 (1.36, 1.60)
HCP influence on LD vaccination[5] (ref. = Yes)						
No	5.21 (2.72, 10.00)	5.12 (3.92, 6.70)	2.77 (2.29, 3.35)	1.42 (0.94, 2.15)	1.37 (1.09, 1.71)	1.22 (1.10, 1.36)
LD vaccine cost concerns[6] (ref. = No)						
Yes	0.36 (0.20, 0.64)	0.48 (0.37, 0.62)	0.56 (0.46, 0.68)	1.07 (0.82, 1.39)	1.04 (0.91, 1.19)	1.02 (0.94, 1.10)

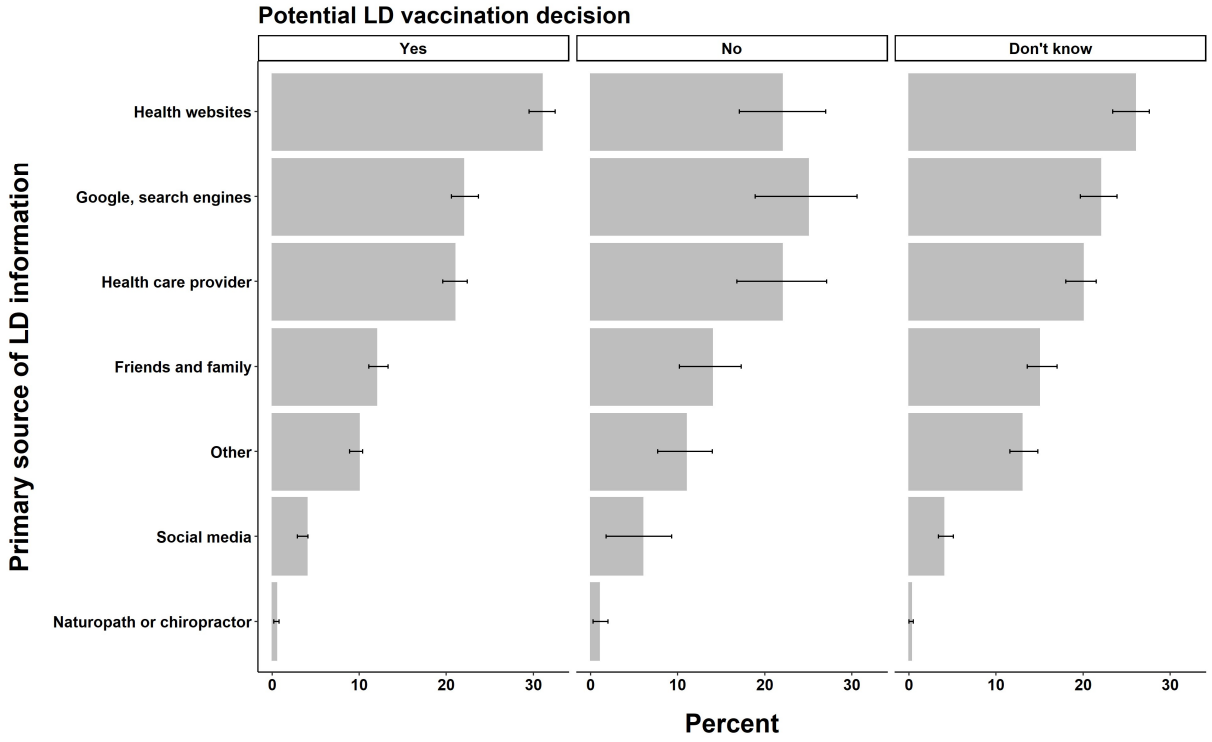

Figure B.1. Respondents' primary source for LD information, by potential LD vaccination decision, weighted % and 95% confidence intervals*

*95% confidence interval shown in the black bars

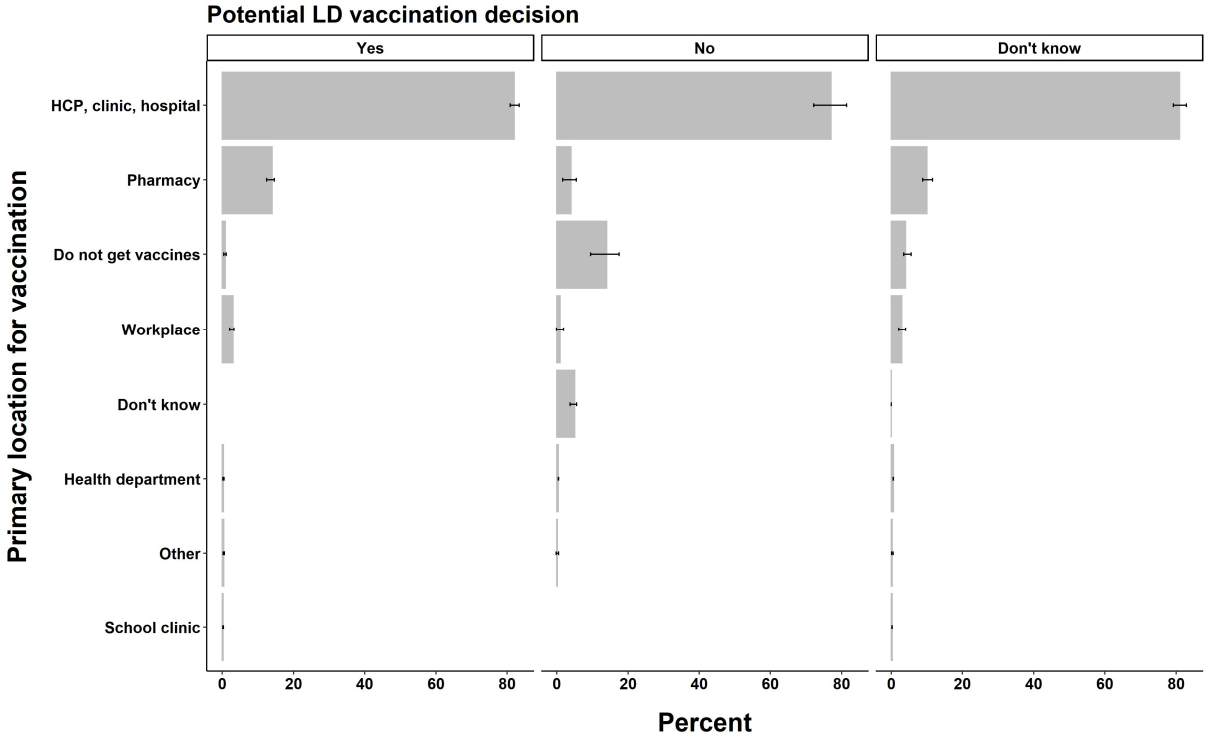

Figure B.2. Respondents' primary location for receiving vaccination, by potential LD vaccination decision, weighted % and 95% confidence intervals*

*95% confidence interval shown in the black bars

APPENDIX C: SUPPLEMENTAL MATERIAL FOR CHAPTER 5, COST-BENEFIT ANALYSIS OF VACCINATING A POPULATION AGAINST LYME DISEASE IN HIGH INCIDENCE AREAS OF THE UNITED STATES

Table C.1 Total cost of Lyme disease per patient, by disease category (from Aim 1, Chapter 3)

	Total cost per patient* (2020 USD)								
Disease category	**N**	**Median**	**Mean**	**Standard deviation**	**10th percentile**	**25th percentile**	**75th percentile**	**90th percentile**	**Range**
All	613	771	2,272	6,809	227	380	1,779	4,696	60 – 137,228
Confirmed localized	273	551	1,461	3,978	173	280	1,487	2,994	60 – 20,480
Confirmed disseminated	154	1,208	3,634	2,3371	332	596	2,680	6,973	241 – 137,228
Probable	186	1,051	2,929	17,363	353	580	1,957	5,613	145 – 117,928

* Total cost includes patient out-of-pocket nonmedical costs, productivity losses, and direct medical costs. The estimates for the overall population use the sample-weighted data except the range.

Table C.2 Model parameter values for optimistic and pessimistic scenarios

	Optimistic scenario value	Pessimistic scenario value
Probability variables		
Vaccination		
Efficacy	0.99	0.7
Uptake	0.94	0.64
Lyme disease		
Incidence, endemic states	0.08	0.001
Confirmed, localized disease	0.55	0.55
Confirmed, disseminated disease	0.21	0.21
Probable disease	0.24	0.24
Sequelae		
Confirmed, localized disease	0.07	0.00
Confirmed, disseminated disease	0.28	0.18
Probable disease	0.18	0.10
Suspected Lyme disease (i.e., tested, non-Lyme disease)		
Incidence, suspected LD	0.063	0.057
Incidence, suspected LD if vaccinated	0.011	0.013
Costs (USD 2020)		
Vaccination		
Vaccination series and administration	28	684
Lyme disease		
Confirmed, localized disease	2,994	173
Confirmed, disseminated disease	6,973	332
Probable disease	5,613	353
Sequelae		
Sequelae	23,322	7,728
Suspected Lyme disease (i.e., tested, non-Lyme disease)		
Diagnostic testing for suspected LD	400	237

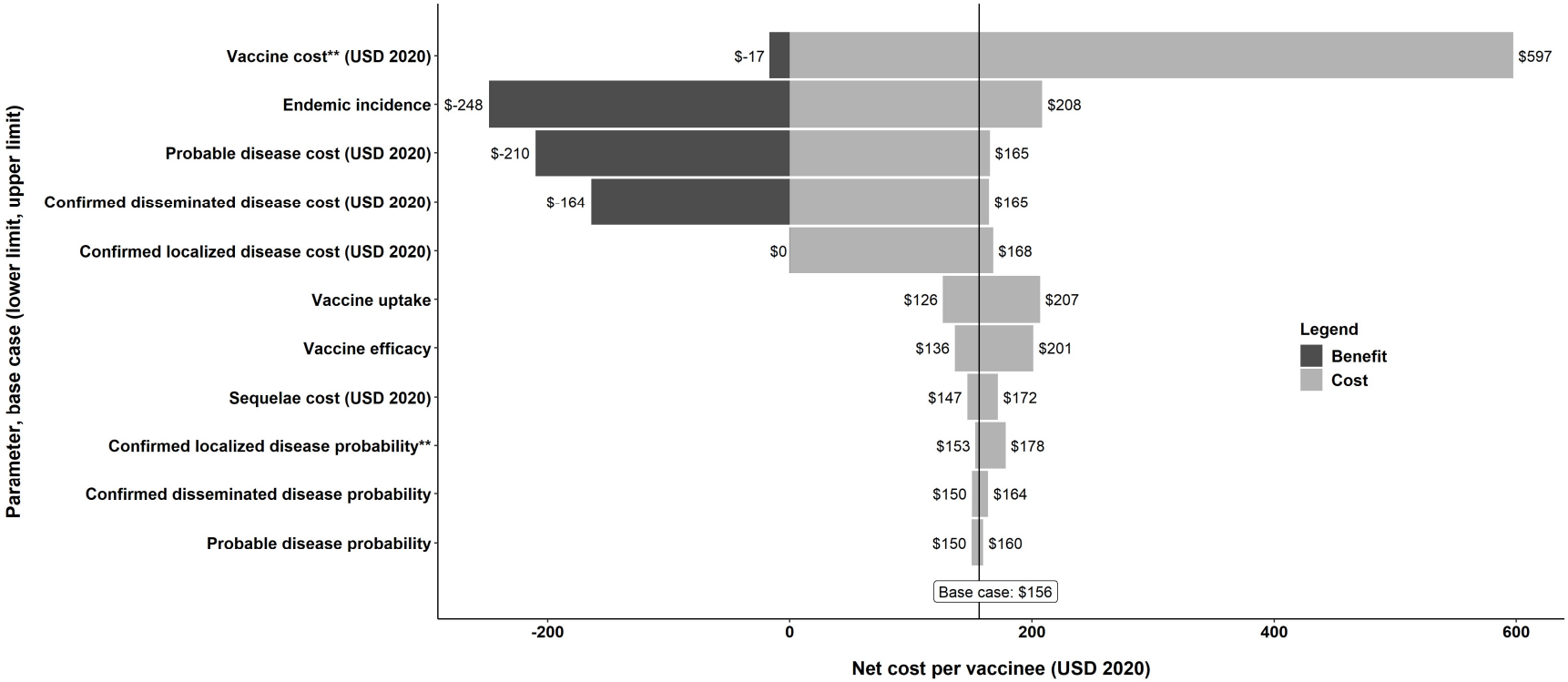

Figure C.1 Impact of select model parameters on the net cost per vaccinee resulting from one-way sensitivity analyses using minimum and maximum cost per Lyme disease category*

*See Appendix Table C.1 for the range of costs for confirmed localized, confirmed disseminated, and probable disease. Probabilities for suspect LD, cost of suspect LD, and probabilities for sequelae had a negligible impact on the net cost per vaccinee and were not included in the plot.
**Vaccine cost and confirmed localized disease probability have a positive relationship with net cost per vaccinee. All other parameters have a negative relationship with net cost per vaccinee.

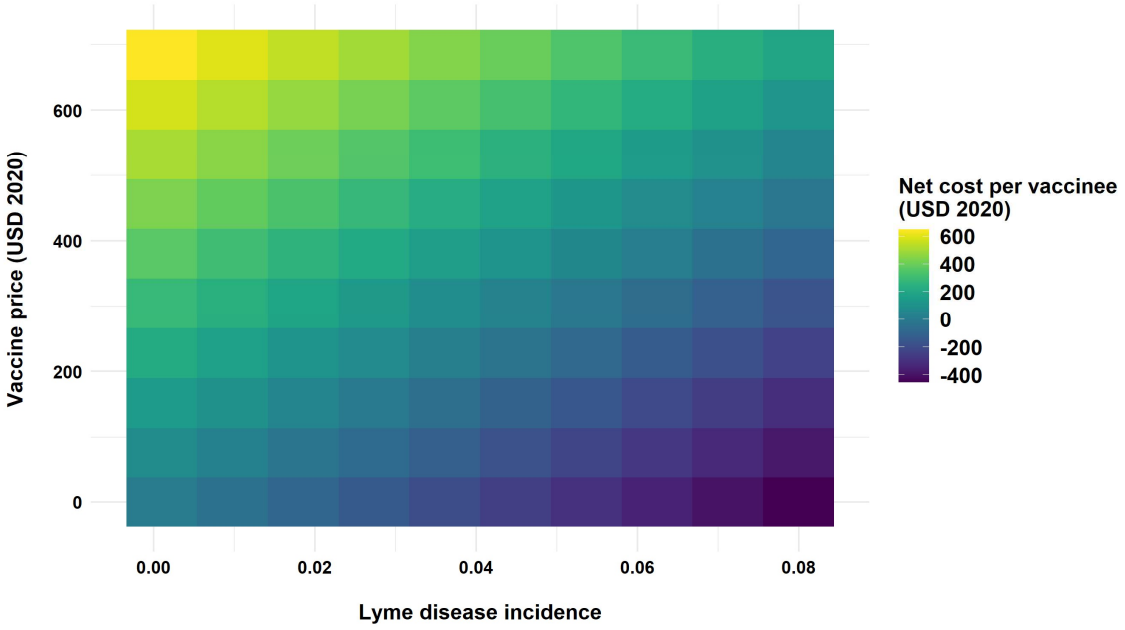

Figure C.2 Impact of vaccine price and Lyme disease incidence on the net cost per vaccinee